WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

VOLUME 78
IONIZING RADIATION, PART 2: SOME INTERNALLY DEPOSITED RADIONUCLIDES

2001
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F R A N C E

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ON THE

EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Ionizing Radiation, Part 2: Some Internally Deposited Radionuclides

VOLUME 78

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

14–21 June 2000

2001

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, life-style factors and biological and physical agents, as well as those in specific occupations.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed.

The lists of IARC evaluations are regularly updated and are available on Internet: http://monographs.iarc.fr/

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NOTE TO THE READER

The term ‘carcinogenic risk’ in the *IARC Monographs* series is taken to mean the probability that exposure to an agent will lead to cancer in humans.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.

IARC WORKING GROUP ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS: IONIZING RADIATION, PART 2, SOME INTERNALLY DEPOSITED RADIONUCLIDES

Lyon, 14–21 June 2000

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PREAMBLE

IARC MONOGRAPHS PROGRAMME ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. The *Monographs* programme has since been expanded to include consideration of exposures to complex mixtures of chemicals (which occur, for example, in some occupations and as a result of human habits) and of exposures to other agents, such as radiation and viruses. With Supplement 6 (IARC, 1987a), the title of the series was modified from *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* to *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, in order to reflect the widened scope of the programme.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs series*. Those criteria were subsequently updated by further ad-hoc working groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987b, 1988, 1991a; Vainio *et al.*, 1992).

2. OBJECTIVE AND SCOPE

The objective of the programme is to prepare, with the help of international working groups of experts, and to publish in the form of monographs, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* may also indicate where additional research efforts are needed.

The *Monographs* represent the first step in carcinogenic risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that certain exposures could alter the incidence of cancer in humans. The second step is quantitative risk estimation. Detailed, quantitative evaluations of epidemiological data may be made in the *Monographs*, but without extrapolation beyond the range of the data available. Quantitative extrapolation from experimental data to the human situation is not undertaken.

The term ‘carcinogen’ is used in these monographs to denote an exposure that is capable of increasing the incidence of malignant neoplasms; the induction of benign neoplasms may in some circumstances (see p. 19) contribute to the judgement that the exposure is carcinogenic. The terms ‘neoplasm’ and ‘tumour’ are used interchangeably.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991a; Vainio *et al.*, 1992; see also pp. 25–27).

The *Monographs* may assist national and international authorities in making risk assessments and in formulating decisions concerning any necessary preventive measures. The evaluations of IARC working groups are scientific, qualitative judgements about the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which regulatory measures may be based. Other components of regulatory decisions vary from one situation to another and from country to country, responding to different socioeconomic and national priorities. **Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments and/or other international organizations.**

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of a wide range of human exposures. A survey of users in 1988 indicated that the *Monographs* are consulted by various agencies in 57 countries. About 3000 copies of each volume are printed, for distribution to governments, regulatory bodies and interested scientists. The Monographs are also available from IARC*Press* in Lyon and via the Distribution and Sales Service of the World Health Organization in Geneva.

3. SELECTION OF TOPICS FOR MONOGRAPHS

Topics are selected on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some evidence or suspicion of carcinogenicity. The term ‘agent’ is used to include individual chemical compounds, groups of related chemical compounds, physical agents (such as radiation) and biological factors (such as viruses). Exposures to mixtures of agents may occur in occupational exposures and as a result of personal and cultural habits (like smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. The IARC information bulletins on agents being tested for carcinogenicity (IARC, 1973–1996) and directories of on-going research in cancer epidemiology (IARC, 1976–1996) often indicate exposures that may be scheduled for future meetings. Ad-hoc working groups convened by IARC in 1984, 1989, 1991, 1993 and 1998 gave recommendations as to which agents should be evaluated in the IARC Monographs series (IARC, 1984, 1989, 1991b, 1993, 1998a,b).

As significant new data on subjects on which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. DATA FOR MONOGRAPHS

The *Monographs* do not necessarily cite all the literature concerning the subject of an evaluation. Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to biological and epidemiological data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed by the working groups. In certain instances, government agency reports that have undergone peer review and are widely available are considered. Exceptions may be made on an ad-hoc basis to include unpublished reports that are in their final form and publicly available, if their inclusion is considered pertinent to making a final evaluation (see pp. 25–27). In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, unpublished sources of information may be used.

5. THE WORKING GROUP

Reviews and evaluations are formulated by a working group of experts. The tasks of the group are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanism of action; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans.

Working Group participants who contributed to the considerations and evaluations within a particular volume are listed, with their addresses, at the beginning of each publication. Each participant who is a member of a working group serves as an individual scientist and not as a representative of any organization, government or industry. In addition, nominees of national and international agencies and industrial associations may be invited as observers.

6. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, the topics of the monographs are announced and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by the Carcinogen Identification and Evaluation Unit of IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as MEDLINE and TOXLINE.

For chemicals and some complex mixtures, the major collection of data and the preparation of first drafts of the sections on chemical and physical properties, on analysis,

on production and use and on occurrence are carried out under a separate contract funded by the United States National Cancer Institute. Representatives from industrial associations may assist in the preparation of sections on production and use. Information on production and trade is obtained from governmental and trade publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available because their publication could disclose confidential information. Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants, or is used by IARC staff, to prepare sections for the first drafts of monographs. The first drafts are compiled by IARC staff and sent before the meeting to all participants of the Working Group for review.

The Working Group meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, edited and prepared for publication. The aim is to publish monographs within six months of the Working Group meeting.

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study, directly impinging on its interpretation, should be brought to the attention of the reader, a comment is given in square brackets.

7. EXPOSURE DATA

Sections that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are included at the beginning of each monograph.

Most monographs on individual chemicals, groups of chemicals or complex mixtures include sections on chemical and physical data, on analysis, on production and use and on occurrence. In monographs on, for example, physical agents, occupational exposures and cultural habits, other sections may be included, such as: historical perspectives, description of an industry or habit, chemistry of the complex mixture or taxonomy. Monographs on biological agents have sections on structure and biology, methods of detection, epidemiology of infection and clinical disease other than cancer.

For chemical exposures, the Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name and the IUPAC Systematic Name are recorded; other synonyms are given, but the list is not necessarily comprehensive. For biological agents,

taxonomy and structure are described, and the degree of variability is given, when applicable.

Information on chemical and physical properties and, in particular, data relevant to identification, occurrence and biological activity are included. For biological agents, mode of replication, life cycle, target cells, persistence and latency and host response are given. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

The purpose of the section on analysis or detection is to give the reader an overview of current methods, with emphasis on those widely used for regulatory purposes. Methods for monitoring human exposure are also given, when available. No critical evaluation or recommendation of any of the methods is meant or implied. The IARC published a series of volumes, *Environmental Carcinogens: Methods of Analysis and Exposure Measurement* (IARC, 1978–93), that describe validated methods for analysing a wide variety of chemicals and mixtures. For biological agents, methods of detection and exposure assessment are described, including their sensitivity, specificity and reproducibility.

The dates of first synthesis and of first commercial production of a chemical or mixture are provided; for agents which do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided. In addition, methods of synthesis used in past and present commercial production and different methods of production which may give rise to different impurities are described.

Data on production, international trade and uses are obtained for representative regions, which usually include Europe, Japan and the United States of America. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice, nor does it imply judgement as to their therapeutic efficacy.

Information on the occurrence of an agent or mixture in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. In the case of mixtures, industries, occupations or processes, information is given about all agents present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with time and place. For biological agents, the epidemiology of infection is described.

Statements concerning regulations and guidelines (e.g., pesticide registrations, maximal levels permitted in foods, occupational exposure limits) are included for some countries as indications of potential exposures, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccines and therapy, are described.

8. STUDIES OF CANCER IN HUMANS

(*a*) *Types of studies considered*

Three types of epidemiological studies of cancer contribute to the assessment of carcinogenicity in humans—cohort studies, case–control studies and correlation (or ecological) studies. Rarely, results from randomized trials may be available. Case series and case reports of cancer in humans may also be reviewed.

Cohort and case–control studies relate the exposures under study to the occurrence of cancer in individuals and provide an estimate of relative risk (ratio of incidence or mortality in those exposed to incidence or mortality in those not exposed) as the main measure of association.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent, mixture or exposure circumstance under study. Because individual exposure is not documented, however, a causal relationship is less easy to infer from correlation studies than from cohort and case–control studies. Case reports generally arise from a suspicion, based on clinical experience, that the concurrence of two events—that is, a particular exposure and occurrence of a cancer—has happened rather more frequently than would be expected by chance. Case reports usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure. The uncertainties surrounding interpretation of case reports and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, relevant case reports or correlation studies may add materially to the judgement that a causal relationship is present.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed by working groups. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(*b*) *Quality of studies considered*

The Monographs are not intended to summarize all published studies. Those that are judged to be inadequate or irrelevant to the evaluation are generally omitted. They may be mentioned briefly, particularly when the information is considered to be a useful supplement to that in other reports or when they provide the only data available. Their

inclusion does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of the study description.

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. By 'bias' is meant the operation of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between disease and an agent, mixture or exposure circumstance. By 'confounding' is meant a situation in which the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. In evaluating the extent to which these factors have been minimized in an individual study, working groups consider a number of aspects of design and analysis as described in the report of the study. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken account in the study design and analysis of other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may be more appropriate than those with national rates. Internal comparisons of disease frequency among individuals at different levels of exposure should also have been made in the study.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. The methods used should preferably have been the generally accepted techniques that have been refined since the mid-1970s. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(*c*) *Inferences about mechanism of action*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure and time since exposure ceased, are reviewed and summarized when available. The analysis of temporal relationships can be useful in formulating models of carcinogenesis. In particular, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although at best they allow only indirect inferences about the mechanism of action. Special attention is given to measurements of biological markers of carcinogen exposure or action, such as DNA or protein adducts, as well as markers of early steps in the carcinogenic process, such as proto-oncogene mutation, when these are incorporated into epidemiological studies focused on cancer incidence or mortality. Such measurements may allow inferences to be made about putative mechanisms of action (IARC, 1991a; Vainio *et al.*, 1992).

(*d*) *Criteria for causality*

After the individual epidemiological studies of cancer have been summarized and the quality assessed, a judgement is made concerning the strength of evidence that the agent, mixture or exposure circumstance in question is carcinogenic for humans. In making its judgement, the Working Group considers several criteria for causality. A strong association (a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that relative risks of small magnitude do not imply lack of causality and may be important if the disease is common. Associations that are replicated in several studies of the same design or using different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in amount of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound. When suspicion of carcinogenicity arises largely from a single study, these data are not combined with those from later studies in any subsequent reassessment of the strength of the evidence.

If the risk of the disease in question increases with the amount of exposure, this is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship. Demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Although a carcinogen may act upon more than one target, the specificity of an association (an increased occurrence of cancer at one anatomical site or of one morphological type) adds plausibility to a causal relationship, particularly when excess cancer occurrence is limited to one morphological type within the same organ.

Although rarely available, results from randomized trials showing different rates among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, the judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first of all that the studies giving rise to it meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should be consistent with a relative risk of unity for any observed level of exposure and, when considered together, should provide a pooled estimate of relative risk which is at or near unity and has a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency for the relative risk of cancer to increase with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained in this way from several epidemiological studies can apply only to the type(s) of cancer studied and to dose levels and intervals between first exposure and observation of disease that are the same as or less than those observed in all the studies. Experience with human cancer indicates that, in some cases, the period from first exposure to the development of clinical cancer is seldom less than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

9. STUDIES OF CANCER IN EXPERIMENTAL ANIMALS

All known human carcinogens that have been studied adequately in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (aflatoxins, 4-aminobiphenyl, azathioprine, betel quid with tobacco, bischloromethyl ether and chloromethyl methyl ether (technical grade), chlorambucil, chlornaphazine, ciclosporin, coal-tar pitches, coal-tars, combined oral contraceptives, cyclophosphamide, diethylstilboestrol, melphalan, 8-methoxypsoralen plus ultraviolet A radiation, mustard gas, myleran, 2-naphthylamine, nonsteroidal estrogens, estrogen replacement therapy/steroidal estrogens, solar radiation, thiotepa and vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans, nevertheless, **in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is *sufficient evidence* (see p. 24) of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans**. The possibility that a given agent may cause cancer through a species-specific mechanism which does not operate in humans (see p. 27) should also be taken into consideration.

The nature and extent of impurities or contaminants present in the chemical or mixture being evaluated are given when available. Animal strain, sex, numbers per group, age at start of treatment and survival are reported.

Other types of studies summarized include: experiments in which the agent or mixture was administered in conjunction with known carcinogens or factors that modify carcinogenic effects; studies in which the end-point was not cancer but a defined precancerous lesion; and experiments on the carcinogenicity of known metabolites and derivatives.

For experimental studies of mixtures, consideration is given to the possibility of changes in the physicochemical properties of the test substance during collection, storage, extraction, concentration and delivery. Chemical and toxicological interactions of the components of mixtures may result in nonlinear dose–response relationships.

An assessment is made as to the relevance to human exposure of samples tested in experimental animals, which may involve consideration of: (i) physical and chemical characteristics, (ii) constituent substances that indicate the presence of a class of substances, (iii) the results of tests for genetic and related effects, including studies on DNA adduct formation, proto-oncogene mutation and expression and suppressor gene inactivation. The relevance of results obtained, for example, with animal viruses analogous to the virus being evaluated in the monograph must also be considered. They may provide biological and mechanistic information relevant to the understanding of the process of carcinogenesis in humans and may strengthen the plausibility of a conclusion that the biological agent under evaluation is carcinogenic in humans.

(*a*) *Qualitative aspects*

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route and schedule of exposure, species, strain, sex, age, duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

As mentioned earlier (p. 11), the *Monographs* are not intended to summarize all published studies. Those studies in experimental animals that are inadequate (e.g., too short a duration, too few animals, poor survival; see below) or are judged irrelevant to the evaluation are generally omitted. Guidelines for conducting adequate long-term carcinogenicity experiments have been outlined (e.g. Montesano *et al.*, 1986).

Considerations of importance to the Working Group in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was adequately monitored, particularly in inhalation experiments; (iii) whether the doses and duration of treatment were appropriate and whether the survival of treated animals was similar to that of controls; (iv) whether there were adequate numbers of animals per group; (v) whether animals of each sex were used; (vi) whether animals were allocated randomly to groups; (vii) whether the duration of observation was adequate; and (viii) whether the data were adequately reported. If available, recent data on the incidence of specific tumours in historical controls, as

well as in concurrent controls, should be taken into account in the evaluation of tumour response.

When benign tumours occur together with and originate from the same cell type in an organ or tissue as malignant tumours in a particular study and appear to represent a stage in the progression to malignancy, it may be valid to combine them in assessing tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be pre-neoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent or mixture induces only benign neoplasms that appear to be end-points that do not readily progress to malignancy, it should nevertheless be suspected of being a carcinogen and requires further investigation.

(*b*) *Quantitative aspects*

The probability that tumours will occur may depend on the species, sex, strain and age of the animal, the dose of the carcinogen and the route and length of exposure. Evidence of an increased incidence of neoplasms with increased level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Both DNA damage and increased cell division are important aspects of carcinogenesis, and cell proliferation is a strong determinant of dose–response relationships for some carcinogens (Cohen & Ellwein, 1990). Since many chemicals require metabolic activation before being converted into their reactive intermediates, both metabolic and pharmacokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship, as could saturation of processes such as DNA repair (Hoel *et al.*, 1983; Gart *et al.*, 1986).

(*c*) *Statistical analysis of long-term experiments in animals*

Factors considered by the Working Group include the adequacy of the information given for each treatment group: (i) the number of animals studied and the number examined histologically, (ii) the number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986). When there is no difference in survival between control and treatment groups, the Working Group usually compares the proportions of animals developing each tumour type in each of the groups. Otherwise, consideration is given as to whether or not appropriate adjustments have been made for differences in survival. These adjustments can include: comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour is discovered), in the case where most differences in survival occur before tumours appear; life-table methods, when tumours are visible or when they may be considered ‘fatal’ because mortality rapidly follows tumour development; and the Mantel-Haenszel test or logistic regression,

when occult tumours do not affect the animals' risk of dying but are 'incidental' findings at autopsy.

In practice, classifying tumours as fatal or incidental may be difficult. Several survival-adjusted methods have been developed that do not require this distinction (Gart *et al.*, 1986), although they have not been fully evaluated.

10. OTHER DATA RELEVANT TO AN EVALUATION OF CARCINOGENICITY AND ITS MECHANISMS

In coming to an overall evaluation of carcinogenicity in humans (see pp. 25–27), the Working Group also considers related data. The nature of the information selected for the summary depends on the agent being considered.

For chemicals and complex mixtures of chemicals such as those in some occupational situations or involving cultural habits (e.g. tobacco smoking), the other data considered to be relevant are divided into those on absorption, distribution, metabolism and excretion; toxic effects; reproductive and developmental effects; and genetic and related effects.

Concise information is given on absorption, distribution (including placental transfer) and excretion in both humans and experimental animals. Kinetic factors that may affect the dose–response relationship, such as saturation of uptake, protein binding, metabolic activation, detoxification and DNA repair processes, are mentioned. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data on humans and on animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be of particular importance for extrapolation between species. Data are given on acute and chronic toxic effects (other than cancer), such as organ toxicity, increased cell proliferation, immunotoxicity and endocrine effects. The presence and toxicological significance of cellular receptors is described. Effects on reproduction, teratogenicity, fetotoxicity and embryotoxicity are also summarized briefly.

Tests of genetic and related effects are described in view of the relevance of gene mutation and chromosomal damage to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, where necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests on p. 18. The available data are interpreted critically by phylogenetic group according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations, aneuploidy and cell transformation. The concentrations employed are given, and mention is made of whether use of an exogenous metabolic system *in vitro* affected the test result. These data are given as listings of test systems, data and references. The Genetic and Related Effects data presented in the *Monographs* are also available in the form of Graphic Activity Profiles (GAP) prepared in collaboration with the United States Environmental Protection Agency (EPA) (see also

Waters *et al.*, 1987) using software for personal computers that are Microsoft Windows® compatible. The EPA/IARC GAP software and database may be downloaded free of charge from *www.epa.gov/gapdb*.

Positive results in tests using prokaryotes, lower eukaryotes, plants, insects and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information about the types of genetic effect produced and about the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g., gene mutations and chromosomal aberrations), while others are to a greater or lesser degree associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour-promoting activity and for cell transformation may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. A critical appraisal of these tests has been published (Montesano *et al.*, 1986).

Genetic or other activity manifest in experimental mammals and humans is regarded as being of greater relevance than that in other organisms. The demonstration that an agent or mixture can induce gene and chromosomal mutations in whole mammals indicates that it may have carcinogenic activity, although this activity may not be detectably expressed in any or all species. Relative potency in tests for mutagenicity and related effects is not a reliable indicator of carcinogenic potency. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence to rule out carcinogenicity of agents or mixtures that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative proliferation, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may lead to misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986).

When available, data relevant to mechanisms of carcinogenesis that do not involve structural changes at the level of the gene are also described.

The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is evaluated by the same criteria as are applied to epidemiological studies of cancer.

Structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent are also described.

For biological agents—viruses, bacteria and parasites—other data relevant to carcinogenicity include descriptions of the pathology of infection, molecular biology (integration and expression of viruses, and any genetic alterations seen in human tumours) and other observations, which might include cellular and tissue responses to infection, immune response and the presence of tumour markers.

11. SUMMARY OF DATA REPORTED

In this section, the relevant epidemiological and experimental data are summarized. Only reports, other than in abstract form, that meet the criteria outlined on p. 11 are considered for evaluating carcinogenicity. Inadequate studies are generally not summarized: such studies are usually identified by a square-bracketed comment in the preceding text.

(*a*) *Exposure*

Human exposure to chemicals and complex mixtures is summarized on the basis of elements such as production, use, occurrence in the environment and determinations in human tissues and body fluids. Quantitative data are given when available. Exposure to biological agents is described in terms of transmission and prevalence of infection.

(*b*) *Carcinogenicity in humans*

Results of epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized.

(*c*) *Carcinogenicity in experimental animals*

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species and route of administration, it is stated whether an increased incidence of neoplasms or preneoplastic lesions was observed, and the tumour sites are indicated. If the agent or mixture produced tumours after prenatal exposure or in single-dose experiments, this is also indicated. Negative findings are also summarized. Dose–response and other quantitative data may be given when available.

(*d*) *Other data relevant to an evaluation of carcinogenicity and its mechanisms*

Data on biological effects in humans that are of particular relevance are summarized. These may include toxicological, kinetic and metabolic considerations and evidence of DNA binding, persistence of DNA lesions or genetic damage in exposed humans. Toxicological information, such as that on cytotoxicity and regeneration, receptor binding and hormonal and immunological effects, and data on kinetics and metabolism in experimental animals are given when considered relevant to the possible mechanism of the carcinogenic action of the agent. The results of tests for genetic and related effects are summarized for whole mammals, cultured mammalian cells and nonmammalian systems.

When available, comparisons of such data for humans and for animals, and particularly animals that have developed cancer, are described.

Structure–activity relationships are mentioned when relevant.

For the agent, mixture or exposure circumstance being evaluated, the available data on end-points or other phenomena relevant to mechanisms of carcinogenesis from studies in humans, experimental animals and tissue and cell test systems are summarized within one or more of the following descriptive dimensions:

(i) Evidence of genotoxicity (structural changes at the level of the gene): for example, structure–activity considerations, adduct formation, mutagenicity (effect on specific genes), chromosomal mutation/aneuploidy

(ii) Evidence of effects on the expression of relevant genes (functional changes at the intracellular level): for example, alterations to the structure or quantity of the product of a proto-oncogene or tumour-suppressor gene, alterations to metabolic activation/inactivation/DNA repair

(iii) Evidence of relevant effects on cell behaviour (morphological or behavioural changes at the cellular or tissue level): for example, induction of mitogenesis, compensatory cell proliferation, preneoplasia and hyperplasia, survival of premalignant or malignant cells (immortalization, immunosuppression), effects on metastatic potential

(iv) Evidence from dose and time relationships of carcinogenic effects and interactions between agents: for example, early/late stage, as inferred from epidemiological studies; initiation/promotion/progression/malignant conversion, as defined in animal carcinogenicity experiments; toxicokinetics

These dimensions are not mutually exclusive, and an agent may fall within more than one of them. Thus, for example, the action of an agent on the expression of relevant genes could be summarized under both the first and second dimensions, even if it were known with reasonable certainty that those effects resulted from genotoxicity.

12. EVALUATION

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent, mixture or exposure circumstance to a higher or lower category than a strict interpretation of these criteria would indicate.

(*a*) *Degrees of evidence for carcinogenicity in humans and in experimental animals and supporting evidence*

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency) nor to the mechanisms involved. A classification may change as new information becomes available.

An evaluation of degree of evidence, whether for a single agent or a mixture, is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of degree of evidence.

(i) *Carcinogenicity in humans*

The applicability of an evaluation of the carcinogenicity of a mixture, process, occupation or industry on the basis of evidence from epidemiological studies depends on the

variability over time and place of the mixtures, processes, occupations and industries. The Working Group seeks to identify the specific exposure, process or activity which is considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, conditions and levels of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

(ii) *Carcinogenicity in experimental animals*

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and levels of exposure studied.

(*b*) *Other data relevant to the evaluation of carcinogenicity and its mechanisms*

Other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is then described. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and pharmacokinetics, physicochemical parameters and analogous biological agents.

Data relevant to mechanisms of the carcinogenic action are also evaluated. The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is assessed, using terms such as weak, moderate or strong. Then, the Working Group assesses if that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans come from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(*c*) *Overall evaluation*

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity to humans of an agent, mixture or circumstance of exposure.

An evaluation may be made for a group of chemical compounds that have been evaluated by the Working Group. In addition, when supporting data indicate that other, related compounds for which there is no direct evidence of capacity to induce cancer in humans or in animals may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of compounds if the strength of the evidence warrants it.

The agent, mixture or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture or exposure circumstance is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1 —The agent (mixture) is carcinogenic to humans.
The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

Group 2A—The agent (mixture) is probably carcinogenic to humans.
The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans, *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

Group 2B—The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3—The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents, mixtures and exposure circumstances for which the *evidence of carcinogenicity* is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents (mixtures) for which the *evidence of carcinogenicity* is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4—The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

References

Breslow, N.E. & Day, N.E. (1980) *Statistical Methods in Cancer Research*, Vol. 1, *The Analysis of Case–Control Studies* (IARC Scientific Publications No. 32), Lyon, IARC*Press*

Breslow, N.E. & Day, N.E. (1987) *Statistical Methods in Cancer Research*, Vol. 2, *The Design and Analysis of Cohort Studies* (IARC Scientific Publications No. 82), Lyon, IARC*Press*

Cohen, S.M. & Ellwein, L.B. (1990) Cell proliferation in carcinogenesis. *Science*, **249**, 1007–1011

Gart, J.J., Krewski, D., Lee, P.N., Tarone, R.E. & Wahrendorf, J. (1986) *Statistical Methods in Cancer Research*, Vol. 3, *The Design and Analysis of Long-term Animal Experiments* (IARC Scientific Publications No. 79), Lyon, IARC*Press*

Hoel, D.G., Kaplan, N.L. & Anderson, M.W. (1983) Implication of nonlinear kinetics on risk estimation in carcinogenesis. *Science*, **219**, 1032–1037

Huff, J.E., Eustis, S.L. & Haseman, J.K. (1989) Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metastasis Rev.*, **8**, 1–21

IARC (1973–1996) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity/Directory of Agents Being Tested for Carcinogenicity*, Numbers 1–17, Lyon, IARC*Press*

IARC (1976–1996), Lyon, IARC*Press*

Directory of On-going Research in Cancer Epidemiology 1976. Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1977 (IARC Scientific Publications No. 17). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1978 (IARC Scientific Publications No. 26). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1979 (IARC Scientific Publications No. 28). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1980 (IARC Scientific Publications No. 35). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1981 (IARC Scientific Publications No. 38). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1982 (IARC Scientific Publications No. 46). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1983 (IARC Scientific Publications No. 50). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1984 (IARC Scientific Publications No. 62). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1985 (IARC Scientific Publications No. 69). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1986 (IARC Scientific Publications No. 80). Edited by C.S. Muir & G. Wagner

Directory of On-going Research in Cancer Epidemiology 1987 (IARC Scientific Publications No. 86). Edited by D.M. Parkin & J. Wahrendorf

Directory of On-going Research in Cancer Epidemiology 1988 (IARC Scientific Publications No. 93). Edited by M. Coleman & J. Wahrendorf

Directory of On-going Research in Cancer Epidemiology 1989/90 (IARC Scientific Publications No. 101). Edited by M. Coleman & J. Wahrendorf

Directory of On-going Research in Cancer Epidemiology 1991 (IARC Scientific Publications No.110). Edited by M. Coleman & J. Wahrendorf

Directory of On-going Research in Cancer Epidemiology 1992 (IARC Scientific Publications No. 117). Edited by M. Coleman, J. Wahrendorf & E. Démaret

Directory of On-going Research in Cancer Epidemiology 1994 (IARC Scientific Publications No. 130). Edited by R. Sankaranarayanan, J. Wahrendorf & E. Démaret

Directory of On-going Research in Cancer Epidemiology 1996 (IARC Scientific Publications No. 137). Edited by R. Sankaranarayanan, J. Wahrendorf & E. Démaret

IARC (1977) *IARC Monographs Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Preamble (IARC intern. tech. Rep. No. 77/002)

IARC (1978) *Chemicals with* Sufficient Evidence *of Carcinogenicity in Experimental Animals*—IARC Monographs *Volumes 1–17* (IARC intern. tech. Rep. No. 78/003)

IARC (1978–1993) *Environmental Carcinogens. Methods of Analysis and Exposure Measurement*, Lyon, IARC*Press*

Vol. 1. Analysis of Volatile Nitrosamines in Food (IARC Scientific Publications No. 18). Edited by R. Preussmann, M. Castegnaro, E.A. Walker & A.E. Wasserman (1978)

Vol. 2. Methods for the Measurement of Vinyl Chloride in Poly(vinyl chloride), Air, Water and Foodstuffs (IARC Scientific Publications No. 22). Edited by D.C.M. Squirrell & W. Thain (1978)

Vol. 3. Analysis of Polycyclic Aromatic Hydrocarbons in Environmental Samples (IARC Scientific Publications No. 29). Edited by M. Castegnaro, P. Bogovski, H. Kunte & E.A. Walker (1979)

Vol. 4. Some Aromatic Amines and Azo Dyes in the General and Industrial Environment (IARC Scientific Publications No. 40). Edited by L. Fishbein, M. Castegnaro, I.K. O'Neill & H. Bartsch (1981)

Vol. 5. Some Mycotoxins (IARC Scientific Publications No. 44). Edited by L. Stoloff, M. Castegnaro, P. Scott, I.K. O'Neill & H. Bartsch (1983)

Vol. 6. N-Nitroso Compounds (IARC Scientific Publications No. 45). Edited by R. Preussmann, I.K. O'Neill, G. Eisenbrand, B. Spiegelhalder & H. Bartsch (1983)

Vol. 7. Some Volatile Halogenated Hydrocarbons (IARC Scientific Publications No. 68). Edited by L. Fishbein & I.K. O'Neill (1985)

Vol. 8. Some Metals: As, Be, Cd, Cr, Ni, Pb, Se, Zn (IARC Scientific Publications No. 71). Edited by I.K. O'Neill, P. Schuller & L. Fishbein (1986)

Vol. 9. Passive Smoking (IARC Scientific Publications No. 81). Edited by I.K. O'Neill, K.D. Brunnemann, B. Dodet & D. Hoffmann (1987)

*Vol. 10. Benzene and Alkylated Benzenes (*IARC Scientific Publications No. 85). Edited by L. Fishbein & I.K. O'Neill (1988)

Vol. 11. Polychlorinated Dioxins and Dibenzofurans (IARC Scientific Publications No. 108). Edited by C. Rappe, H.R. Buser, B. Dodet & I.K. O'Neill (1991)

Vol. 12. Indoor Air (IARC Scientific Publications No. 109). Edited by B. Seifert, H. van de Wiel, B. Dodet & I.K. O'Neill (1993)

IARC (1979) *Criteria to Select Chemicals for* IARC Monographs (IARC intern. tech. Rep. No. 79/003)

IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 4, *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans* (IARC Monographs, Volumes 1 to 29), Lyon, IARC*Press*

IARC (1983) *Approaches to Classifying Chemical Carcinogens According to Mechanism of Action* (IARC intern. tech. Rep. No. 83/001)

IARC (1984) *Chemicals and Exposures to Complex Mixtures Recommended for Evaluation in IARC Monographs and Chemicals and Complex Mixtures Recommended for Long-term Carcinogenicity Testing* (IARC intern. tech. Rep. No. 84/002)

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 6, *Genetic and Related Effects: An Updating of Selected* IARC Monographs *from Volumes 1 to 42*, Lyon, IARC*Press*

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, IARC*Press*

IARC (1988) *Report of an IARC Working Group to Review the Approaches and Processes Used to Evaluate the Carcinogenicity of Mixtures and Groups of Chemicals* (IARC intern. tech. Rep. No. 88/002)

IARC (1989) *Chemicals, Groups of Chemicals, Mixtures and Exposure Circumstances to be Evaluated in Future IARC Monographs, Report of an ad hoc Working Group* (IARC intern. tech. Rep. No. 89/004)

IARC (1991a) *A Consensus Report of an IARC Monographs Working Group on the Use of Mechanisms of Carcinogenesis in Risk Identification* (IARC intern. tech. Rep. No. 91/002)

IARC (1991b) *Report of an ad-hoc* IARC Monographs *Advisory Group on Viruses and Other Biological Agents Such as Parasites* (IARC intern. tech. Rep. No. 91/001)

IARC (1993) *Chemicals, Groups of Chemicals, Complex Mixtures, Physical and Biological Agents and Exposure Circumstances to be Evaluated in Future* IARC Monographs, *Report of an ad-hoc Working Group* (IARC intern. Rep. No. 93/005)

IARC (1998a) *Report of an ad-hoc* IARC Monographs *Advisory Group on Physical Agents* (IARC Internal Report No. 98/002)

IARC (1998b) *Report of an ad-hoc* IARC Monographs *Advisory Group on Priorities for Future Evaluations* (IARC Internal Report No. 98/004)

McGregor, D.B., Rice, J.M. & Venitt, S., eds (1999) *The Use of Short and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation* (IARC Scientific Publications No. 146), Lyon, IARC*Press*

Montesano, R., Bartsch, H., Vainio, H., Wilbourn, J. & Yamasaki, H., eds (1986) *Long-term and Short-term Assays for Carcinogenesis—A Critical Appraisal* (IARC Scientific Publications No. 83), Lyon, IARC*Press*

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parish, S., Peto, J., Richards, S. & Wahrendorf, J. (1980) Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 2, *Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal*, Lyon, IARC*Press*, pp. 311–426

Tomatis, L., Aitio, A., Wilbourn, J. & Shuker, L. (1989) Human carcinogens so far identified. *Jpn. J. Cancer Res.*, **80**, 795–807

Vainio, H., Magee, P.N., McGregor, D.B. & McMichael, A.J., eds (1992) *Mechanisms of Carcinogenesis in Risk Identification* (IARC Scientific Publications No. 116), Lyon, IARC*Press*

Vainio, H., Wilbourn, J.D., Sasco, A.J., Partensky, C., Gaudin, N., Heseltine, E. & Eragne, I. (1995) Identification of human carcinogenic risk in IARC Monographs. *Bull. Cancer,* **82**, 339–348 (in French)

Waters, M.D., Stack, H.F., Brady, A.L., Lohman, P.H.M., Haroun, L. & Vainio, H. (1987) Appendix 1. Activity profiles for genetic and related tests. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 6, *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42*, Lyon, IARC*Press*, pp. 687–696

Wilbourn, J., Haroun, L., Heseltine, E., Kaldor, J., Partensky, C. & Vainio, H. (1986) Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs Programme. *Carcinogenesis*, **7**, 1853–1863

GENERAL REMARKS

1. Internal irradiation

1.1 *General aspects*

Radiation sources can be either external to the body, such as medical X-rays, or internal. The latter can result from the ingestion, inhalation, dermal absorption or injection of radionuclides. The effects of radiation are directly related to the dose that an organ receives, and any difference between the effects of external and internal sources is in large part related to the distribution of dose within and among body organs. Volume 75 of the *Monographs* (IARC, 2000) addressed the carcinogenic potential of external X-rays, γ-rays and neutrons in exposed populations; at least for X-rays and γ-rays, the effects are reasonably well known, and the carcinogenic risks have been quantified. Internal sources of radiation are more difficult to evaluate because of problems in determining the distribution of doses in tissues and organs. The dose received from external sources depends on the parts of the body that were irradiated, whereas the distribution of dose from internal sources can be affected by biological processes and metabolism. For example, radioactive iodine concentrates in the thyroid gland, and no other organs receive doses of any comparable magnitude.

Table 1 lists epidemiological studies of populations exposed to external and internal sources of radiation. The external sources include direct exposure to ionizing radiation from the atomic bombs exploded over Hiroshima and Nagasaki, radiotherapy for malignant and benign conditions, medical diagnostic procedures such as repeated chest X-ray fluoroscopies, occupational exposure such as received by radiologists and external exposure related to reactor accidents, such as that of Chernobyl clean-up workers. The distinction between external and internal sources is not complete in all cases. Brachytherapy, for example, involves the insertion of encapsulated radioactive materials such as radium within body cavities and thus could be considered an 'internal' source, but for the purposes of this monograph it is considered to be external and is not covered. Nuclear industry workers could inhale or ingest small amounts of radionuclides during their occupational exposure in addition to receiving external γ-rays.

Internal sources of radiation include radioactive fall-out from nuclear weapons tests or the Chernobyl accident, radiotherapy for malignant conditions such as ^{131}I to

Table 1. Sources of external and internal exposure to radiation, with examples of exposed populations

Type of exposure	Source	Examples of populations exposed
External	Atomic bombs	Japanese bomb survivors Marshall Islanders
	Radiotherapy for neoplastic disease	Patients with: Cervical cancer Childhood cancer Retinoblastoma Breast cancer Endometrial cancer Hodgkin disease Bone-marrow transplants
	Radiotherapy for benign conditions	Patients with: Ankylosing spondylitis Benign gynaecological disorders Peptic ulcer Breast disease Tinea capitis Thymus enlargement Tonsil enlargement Haemangioma
	Diagnostic procedures	Pregnant women (X-rays) Patients with: Tuberculosis (fluoroscopic X-rays) Scoliosis (X-rays)
	Occupation	Radiologists, technologists, nuclear workers
	Reactor accident	Workers in the Chernobyl nuclear power plant, clean-up workers and neighbouring populations
Internal	Atomic bombs	Marshall Islanders
	Radiotherapy	Patients with: Bone disease (^{224}Ra) Hyperthyroidism (^{131}I) Polycythaemia vera (^{32}P)
	Diagnostic procedures	Patients undergoing: Angiography (Thorotrast; ^{232}Th) Thyroid uptake and scans (^{131}I)
	Occupation	Radium-dial painters (^{226}Ra and ^{228}Ra) Underground miners (radon and progeny) Plutonium workers

Table 1 (contd)

Type of exposure	Source	Examples of populations exposed
Internal (contd)	Reactor accident	Workers in the Chernobyl nuclear power plant, clean-up workers and neighbouring populations
	Environmental contamination	Inhabitants of the Techa River area
	Radon	House dwellers
	Monoazite sands	Inhabitants of India and Brazil

From UNSCEAR (1994); Boice *et al*. (1996); IARC (2000); UNSCEAR (2000)

treat thyroid cancer, radiotherapy for non-neoplastic conditions such as ^{224}Ra to treat bone tuberculosis and ankylosing spondylitis, diagnostic radiographic procedures such as cerebral angiography with Thorotrast (^{232}Th), occupational exposure such as that to plutonium of workers at the Mayak military plant in the Russian Federation, and environmental contamination such as that of the Techa River, also in the Russian Federation.

Ionizing radiation interacts randomly with atoms in cells and can alter molecular structure, the most important alteration being damage to DNA that is either unrepaired or is accurately or inaccurately repaired. These alterations can be amplified by biological processes to result in observable effects. The biological effects, however, depend not only on the total absorbed dose but also on the local density of ionization. Linear energy transfer (LET), defined in section 3.2, is a measure of the energy loss per unit distance travelled and depends on the velocity, charge, energy and mass of a charged particle or other secondary charged particles (electrons) from neutrons, or of secondary X-rays or γ-rays. High-LET radiations such as α-particles (helium nuclei) release energy in short tracks (< 100 μm) of dense ionizations. They are not penetrating and can be stopped in the outer layers of skin. Low-LET radiations such as β-particles (electrons), X-rays or γ-rays, are more sparsely ionizing, on average, although there is some clustering of low-energy secondary electrons. The depth of penetration of β-particles can vary from a few micrometres up to several millimetres, depending on their energy. X-rays and γ-rays are generally much more penetrating and are attenuated exponentially, as they occasionally interact to produce secondary electrons as they pass through tissue.

In experimental studies, the induction of many cancers by low-LET radiation appears to follow a sigmoidal relationship with dose, risk per unit dose being somewhat lower at low doses and high doses owing to repair and cell killing, respectively. The induction of cancer by exposure to high-LET radiation (particularly neutrons) often appears to follow a more linear dose–response relationship. Protraction and

fractionation of doses tend to decrease the risk for cancer after exposure to low-LET radiation but not high-LET radiation, possibly because of a reduction in the competing effect of cell killing (UNSCEAR, 1993).

The relative biological effectiveness (RBE) of radiation characterizes its ability to have a specific level of effect (e.g. frequency of chromosomal aberration, cell death or neoplastic transformation) when compared with a standard, usually X-rays or γ-rays. A RBE of 20 for α-particles at an absorbed dose of 0.1 Gy, for example, would imply that the level of biological effect from 0.1 Gy of α-particles is the same as that from 2 Gy of γ-rays. For the purposes of radiation protection, the International Commission on Radiological Protection (ICRP) has defined the equivalent dose and effective dose, both expressed in units of sievert (Sv), which include specified radiation and tissue weighting factors. The radiation weighting factor for α-particles is specified as 20 and that for β-particles, γ-rays and X-rays as 1 (ICRP, 1991; IARC, 2000).

Another difference between external and internal sources of radiation is the duration of exposure: an internal source might stay in the body for a long time and irradiate tissues. Once the external exposure is over, however, there is no longer delivery of ionizing radiation within body cells. Internal sources can remain in the body for many years. For example, ingested ^{226}Ra is incorporated into bone and for all practical purposes affects tissues in the body continually. Some radionuclides, such as ^{99m}Tc, have shorter half-lives, so that the radiation dose is delivered within a period of hours after exposure.

The difficulties in determining or quantifying the effects of internal sources also include the problem of non-uniform distribution of dose in organs and tissues. For example, the risk for thyroid cancers in humans due to incorporated ^{131}I would result from absorption of β-particle energy not in the colloid of the thyroid but rather in the radiation-sensitive follicular cells, which are at risk for cancer development.

1.2 *Nomenclature*

(*a*) *Radiation dose*

The *absorbed dose* is defined as the radiation energy absorbed per unit mass of an organ or tissue and is expressed in grays (Gy); 1 Gy is equal to 1 J/kg.

The *equivalent dose* (H) takes account of different types of radiation and differences in ionization densities: to calculate the equivalent dose, the average absorbed dose in an organ or tissue is multiplied by a radiation weighting factor w_R. The radiation weighting factors currently recommended by ICRP (1991) are listed in Table 2. The equivalent dose is expressed in sieverts (Sv); 1 Sv is equal to 1 J/kg.

The *effective dose* (E) takes into account variations in equivalent dose among radiosensitive organs and tissues and is calculated by multiplying the equivalent dose by a tissue-weighting factor w_T. The effective dose gives a measure of the impact of radiation irrespective of how the dose was received. This approach allows effective doses from internal and external sources to be aggregated and correlates well with the

Table 2. Radiation weighting factors

Type and energy range	Radiation weighting factor
Photons, all energies	1
Electrons and muons[a], all energies[b]	1
Neutrons, energy:	
< 10 keV	5
10–100 keV	10
> 0.1–2 MeV	20
> 2–20 MeV	10
> 20 MeV	5
Protons, other than recoil protons, energy > 2 MeV	5
α-Particles, fission fragments, heavy nuclei	20

From ICRP (1991); all values relate to the radiation incident on the body or, for internal sources, emitted from the source.

[a] One of the elementary particles, a member of a category of light-weight particles called leptons which also include electrons and neutrinos

[b] Excluding Auger electrons (280–2100 eV) emitted from nuclei bound to DNA, which are ejected after excitation by an incident electron beam

total of the stochastic effects. The tissue weighting factors currently recommended by ICRP (1991) are listed in Table 3. The effective dose is expressed in sieverts (Sv).

The *committed effective dose* is defined as the time integral of the effective dose rate over a period of 50 years for an adult and from the time of intake to age 70 years for children.

The *total effective dose*, $E(t)$, during any time, t, from external and internal sources of radiation is given by:

$$E(t) = H_p(d) + \sum_j e_{j,inh}(50) \times I_{j,inh} + \sum_j e_{j,ing}(50) \times I_{j,ing}$$

where $H_p(d)$ is the personal dose equivalent from external radiation during time t at a depth d in the body, normally 10 mm for penetrating radiation; $e_{j,inh}(50)$ and $e_{j,ing}(50)$ are the committed effective doses per unit activity intake by inhalation and ingestion, respectively, from radionuclide j, integrated over 50 years; and $I_{j,inh}$ and $I_{j,ing}$ are the intake of radionuclide j by inhalation and ingestion, respectively, during time t (UNSCEAR, 2000).

(*b*) *Radiation dose and exposure to radon and its decay products: working-level month*

Potential α energy is used as a quantity to describe the amount of short-lived decay products of ^{220}Rn (also known as thoron) and ^{222}Rn (known as radon) in air and the ensuing exposure by inhalation. It is defined as the total α energy (in J) emitted during the decay of ^{220}Rn or ^{222}Rn to ^{208}Pb or ^{210}Pb, respectively. The total α energy

Table 3. Tissue weighting factors

Tissue or organ	Tissue weighting factor
Gonads	0.20
Bone marrow (active)	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Oesophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surface	0.01
Remainder[a]	0.05

From ICRP (1991). The values were derived on the basis of data for a reference population of equal numbers of males and females and a wide range of ages. In the definition of effective dose, these factors apply to workers, to the whole population and to males and females.

[a] For the purposes of calculation, the 'remainder' is composed of the following additional tissues and organs: adrenal glands, brain, upper large intestine, small intestine, kidney, muscle, pancreas, spleen, thymus and uterus. The list includes organs that are likely to be irradiated selectively and some organs which are known to be susceptible to cancer induction. If other tissues and organs are subsequently identified as being at significant risk for induced cancer, they will either be given a specific weighting factor or included in the 'remainder'. In the exceptional case in which one of the 'remainder' tissues or organs receives an equivalent dose in excess of the highest dose received by any of the 12 organs for which a weighting factor is specified, a weighting factor of 0.025 should be applied to that tissue or organ and a weighting factor of 0.025 to the average dose for the rest of the 'remainder', as defined above.

concentration of any mixture of short-lived ^{220}Rn or ^{222}Rn decay products is the sum of the potential α energy of these atoms per unit volume of air (expressed in J/m^3). The potential α energy concentration has also been expressed in terms of working level (WL). One WL is defined as a concentration of potential α energy of 1.30×10^8 MeV/m^3. The exposure to ^{220}Rn or ^{222}Rn and their decay products is the time integral of the potential α energy concentration in air, expressed in J h/m^3 or in working-level months (WLM). Because the WLM was initially defined to specify occupational exposure, one month corresponds to 170 h. In SI units, the historical unit WLM can be written as 3.54×10^{-3} J h/m^3. In terms of effective dose, 1 WLM is usually taken to correspond to 5 mSv for workers (ICRP, 1993).

(*c*) *Dose and dose limits of radiation from internalized radionuclides*

When radionuclides have entered the body, cells and tissues will continue to be exposed to the emitted radiation until the radionuclide has been completely excreted or has fully decayed. Dose limits for occupational exposure are generally derived from the dose of the radionuclide integrated over 50 years after the intake. The committed effective dose for occupational exposure, E(50), is defined as the sum of the products of the committed organ or equivalent doses and the appropriate organ or tissue weighting factors, where '50' indicates the integration time in years after intake. In calculating the E(50), the dose coefficient, i.e. the committed effective dose per unit intake, expressed in Sv/Bq, is frequently used.

The recommended upper limit for annual intake of radionuclides is based on a committed annual effective dose of 20 mSv (ICRP, 1991). The annual limit on intake in becquerels can be calculated by dividing this value (0.02 Sv) by the dose coefficient. For inhalation and ingestion, the dose coefficients for occupational exposure to radionuclides are given by ICRP (1994).

1.3 *Routes of internal exposure to ionizing radiation*

The human body is, and always has been, exposed to background radiation. This irradiation may arise from outside the body, for example from cosmic rays from outer space and γ-rays from the decay of the natural radionuclides of the uranium and thorium series that are present in rocks and other components of the earth's crust. In addition, some individuals or groups may receive whole- or partial-body external radiation from occupational exposure, medical procedures such as X-ray examinations, radiation therapy or accidents in nuclear facilities resulting in the release into the environment of radionuclides that emit γ-rays (IARC, 2000). All human beings are also irradiated by the radiation emitted within organs and tissues by the decay of natural and anthropogenic radionuclides that have entered the body by inhalation or by ingestion of food and drinking-water. This irradiation arises naturally from the decay of the radioactive isotope of the essential element potassium, ^{40}K, and from uranium and thorium and their radioactive decay products, especially radon (IARC, 1988; UNSCEAR, 1988, 1993). In addition, there are contributions from fall-out from atmospheric nuclear weapons testing, from accidents at nuclear facilities or from nuclear medicine, i.e. diagnostic or therapeutic medical procedures with radionuclides.

Overviews of the exposures resulting from sources of radiation and the resulting health effects have been published by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1982, 1988, 1993, 1994, 2000). Recommendations on appropriate radiological protection standards are made by the ICRP (ICRP, 1991).

The passage of ionizing radiation through the human or animal body results in the deposition of energy within the irradiated tissue volume. The amount of radiation energy deposited will depend on the length of time over which the individual is

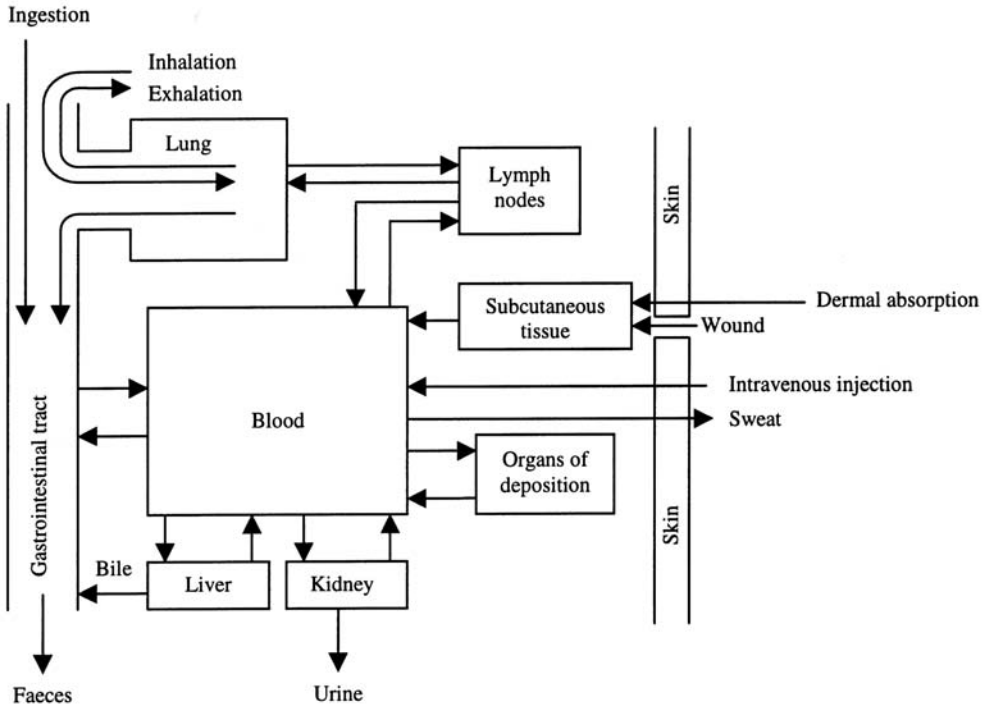
irradiated, the strength of the source and the physical nature of the radiation, e.g. X- or γ-rays, cosmic rays, α-, β- or other particles (see section 2). The immediate result of the energy deposition is the production of ion pairs and, subsequently, free radicals and other highly reactive species, predominantly through the breakdown of water molecules, which comprise about 65–70% of most tissues, but also directly in DNA and other molecules. These highly reactive species can damage sensitive biological macromolecules such as DNA, RNA and proteins. The damage to DNA may be severe enough to produce cell death or may result in various degrees of non-lethal damage. Non-lethal damage is particularly important since it may result in heritable changes in gene expression that, after one or more cell divisions, may manifest themselves as cancers or serious genetic disorders. In broad terms, cell death and other effects result largely from unrepairable DNA damage or DNA damage that is inadequately repaired.

α-Radiation is not normally regarded as an external radiation hazard (except perhaps to skin) because it is poorly penetrating, but once α-particle-emitting radionuclides are in the body they can become a health hazard. However, X- and γ- radiations and neutrons can generally penetrate sensitive organs of the body. As the higher-energy β-radiation can penetrate to about 10 mm into tissue, it can pose both an external hazard and an internal hazard when emissions occur within the body. Unlike exposure to internal radiation, that to external radiation can usually be controlled by reducing the duration of exposure, increasing the distance from the radiation source and/or using shielding. Radioactive materials may pose an insignificant external hazard, but once they come into contact with or penetrate the body they increase the risk.

The biological effects of deposited radionuclides within the body depend on the amount of radionuclide deposited, the type of radiation emitted, the physical half-life of the isotope, the organs and tissues in which the radionuclide is retained and the duration of retention. Once inside the body, the exposure rate of the radionuclide is maximized, and it will continue to irradiate the body until either the radioactivity has decayed (physical half-lives may vary from fractions of a second to millions of years) or until the substance has been excreted from the body. The rate of excretion, expressed as retention half-time in the body, may vary from a few days to tens of years, depending primarily on the physical and chemical characteristics and chemical form of the radionuclide. The chemical properties of the radionuclide (or the compound in which it may be incorporated) determine its behaviour within the body, including absorption, elimination route, elimination rate and also transfer to and retention at deposition sites and subsequent redistribution. Furthermore, the health effects of some elements with low specific activity may also be related to their chemical properties (e.g. heavy metals) rather than their radiation.

Four main routes result in internal exposure to radionuclides (Figure 1): inhalation, ingestion, dermal absorption and direct injection (or through a wound).

Figure 1. Absorption, distribution and elimination of radionuclides in the body



Modified from ICRP (1968)

(*a*) *Inhalation*

Radioactive gases, vapours or particulate materials enter the body when inhaled. The respiratory tract has a total surface area of about 75 m^2, beginning with the nasal and other air passages of 10–20 mm in diameter and ending in a large number of extremely fine tubes and ducts closed by tiny air pockets which are a fraction of a millimetre across. The vital capacity of the adult lung is about 4 L, and about 23 m^3 of air are inhaled per day (ICRP, 1975). The epithelial layer of the larger bronchi is about 40 μm thick, becoming thinner as the bronchi diminish in size. In the terminal bronchioles, the single-cell layer of the epithelium is only a few micrometres thick.

Gases can pass freely into the lungs and are rapidly absorbed into the bloodstream through the thin alveolar membranes and the highly vascularized alveoli. Generally, the uptake is governed by the dissolution rate, partition coefficient, solubility and residence time of the gas in the respiratory tract.

Liquid or solid radioactive compounds inhaled in the form of aerosols have a number of possible fates, depending on their physicochemical properties. The extent to which particulate matter is deposited is a function of particle size and shape, the density of the aerosol, the lung structure and respiratory characteristics. Only a

fraction of the inhaled material is deposited in the respiratory tree, and the remainder is exhaled. The size of inhaled particles is likely to cover a wide range. Particles are deposited in the respiratory tract by one of three mechanisms: diffusion, impaction and sedimentation, and the efficiency of these processes varies greatly with particle size. Large particles and ultra-fine particles are deposited in the nasal passages by impaction and diffusion and intermediate-sized particles in the bronchial tree by impaction and in the alveoli by sedimentation. Ultra-fine particles are also deposited in the alveoli by diffusion. Deposited material in the upper respiratory passages may be expelled into the gastrointestinal tract by ciliary action. Phagocytes in the air sacs and on the alveolar walls can remove particulate matter by either migrating up to where they can be removed by ciliary action or by entering the lymphatic system through the alveolar epithelium. Depending principally on the chemical nature and reactions of the radioactive compound, soluble radionuclides may be completely and rapidly absorbed. Otherwise, they are partially eliminated and partially absorbed and may persist in the lungs for many months or years. Models are used to estimate the deposition and retention of airborne contaminants in the respiratory tract (see section 4.1.23(*a*) of the monograph; ICRP, 1994; National Council on Radiation Protection and Measurements, 1997).

Gases that are inhaled include radon (Burkart, 1991) and tritium (^{3}H) (Hill & Johnson, 1993). Studies of volunteers who inhaled ^{3}H showed that only about 0.1% of that inhaled was dissolved in the body fluids and tissues (Hill & Johnson, 1993).

An example of an inhaled material with long pulmonary retention is the highly insoluble actinide oxide, $^{239}PuO_2$; studies in dogs indicate an exponential clearance of 98% of the inhaled material, with a half-time of approximately three years (ICRP, 1986). In contrast, after inhalation of the more soluble compound $^{239}Pu(NO_3)_4$, about 40% of the initial lung burden was lost within three months and about 80% within one year (Dagle *et al*., 1983).

It has been suggested that inhalation of a few highly radioactive particles (hot particles) might lead to highly non-uniform pulmonary irradiation and to a higher risk for tumours than that resulting from inhalation of the same amount of radioactivity at a lower specific activity (Dean & Langham, 1969). Anderson *et al*. (1979) reported a study in which Syrian hamsters received different numbers of radioactive microspheres by intratracheal instillation to induce localized or diffuse irradiation of the lungs. When only 1 or 5% of the lung was irradiated by α-particles, no tumours were observed in 85 animals; however, when the fraction of the lung irradiated was increased to 28%, the tumour incidence rose to 19 tumours in 160 animals. This suggests that intense irradiation of a small area of the lung with a hot particle does not increase the risk for tumour induction.

Table 4 summarizes the known or predicted absorption pattern after inhalation of 20 elements. The data indicate that, depending on the chemical form of the inhaled radioactive material, irradiation of the lung may be essentially complete within a few days or may continue for several years.

Table 4. Absorption of elements in the human lung after inhalation

Z[a]	Element	Chemical form	Absorption to blood[b]
1	Hydrogen	Gas, water, other compounds	Fast
6	Carbon	Dioxide, monoxide, methane, other compounds	Fast
15	Phosphorus	Most compounds except poorly soluble phosphates	Medium
16	Sulfur	SO_2, COS, H_2S, CS_2	Fast
31	Gallium	Most soluble compounds	Medium
38	Strontium	Most soluble compounds	Fast
43	Technetium	Pertechnetate	Fast
53	Iodine	Iodide, iodate	Fast
55	Caesium	Most soluble compounds	Fast
75	Rhenium	Perrhenate	Fast
83	Bismuth	Most compounds	Medium
84	Polonium	Most compounds	Medium
85	Astatine	Most compounds	Medium
86	Radon	Gas	Fast; small proportion[c]
88	Radium	Most compounds	Medium
90	Thorium	Soluble compounds Oxides	Medium Slow
92	Uranium	UF_6, UF_4, $UO_2(NO_3)_2$	Medium
93	Neptunium	Most compounds	Medium
94	Plutonium	Soluble compounds Oxides	Medium Slow
95	Americium	Most compounds	Medium
96	Curium	Most compounds	Medium

[a] Atomic number

[b] Defined by default categories in the ICRP model and expressed as approximate half-times for one or two components of clearance. The rates correspond to: fast, 10 min (100%); medium, 10 min (10%), 140 days (90%); slow, 10 min (0.1%), 7000 days (99.9%). Specific data on absorption are used when available for a particular chemical form of a radionuclide.

[c] Only a small proportion of radon is rapidly absorbed; the remainder is exhaled.

(*b*) *Ingestion*

Radionuclides may be ingested in food and drink, and are absorbed principally from the small intestine, facilitated by its immense surface area of about 200 m^2 (ICRP, 1975) provided by the epithelial villi. If the material is not absorbable, most traverses the gastrointestinal tract and is excreted in the faeces. For absorbable materials, a significant fraction is absorbed into the blood and lymphatic system. The actual degree of absorption may depend on the metabolism and nutrition of the individual as well as the chemical compound in which the radionuclide is ingested.

Harrison (1995) reviewed the anatomical, physiological and radiobiological aspects of radionuclide ingestion. Ingestion is an important route of entry into the human body since, in addition to those radionuclides present in drinking-water and the diet, a fraction of any inhaled material is swallowed. Some radionuclides such as ^{3}H, ^{40}K, ^{131}I and ^{137}Cs are almost completely absorbed from the human gastrointestinal tract into the systemic circulation, but the absorption of others is incomplete, from about 30% of ^{90}Sr to < 0.05% of highly insoluble oxides like $^{239}PuO_2$ (< 0.001%). The degree to which any given radionuclide compound is actually absorbed cannot be predicted precisely because absorption is influenced by both the chemical form of the ingested radionuclide and the chemical environment in the absorptive regions of the upper small intestine; the latter varies depending on the presence or absence of food residues and other complexing ligands.

(*c*) *Injection and entry through wounds or intact skin*

The direct entry of a radioactive nuclide into the body as a result of intravenous injection is normally a deliberate act, undertaken mainly for medical purposes. In such situations, the chemical form of the radionuclide will have been selected to achieve a desired pattern of deposition in the organs and tissues through normal or pathological biochemical processes. A radionuclide may, however, be injected accidentally into the body through a puncture wound. Under these circumstances, its fate will be determined by its physicochemical properties. In some instances, the injected material may pass relatively quickly from the entry site into the blood; but in others, the material reacts with tissue components to form a poorly soluble deposit, from which absorption into the blood may occur over a period that ranges from hours to many months. In other cases, insoluble material may remain *in situ* or become located in regional lymph nodes.

Generally, intact skin provides an effective barrier against the entry of radioactive materials into the body. An exception of practical importance is the absorption of $^{3}H_2O$ as a liquid or a vapour. Since the surface area of the skin is about 1.7 m^2 (ICRP, 1975), the extent of transport may be sufficient to pose a radiological hazard even if the rate of transport is low. Transport typically occurs by diffusion through and between epidermal cells. Similarly, many ^{3}H- and ^{14}C-labelled compounds may be absorbed through the skin, especially if it has been shaved.

Contamination of the intact skin by α- and β-particle- or very weakly γ-ray-emitting radionuclides that are not absorbed into the systemic circulation may be a special case. Irradiation of the body tissues is confined to a few micrometres below the skin surface, because of the poor penetrating power of these types of radiation, or even to the most superficial layers of the skin itself. Highly radioactive 'hot particles' that may arise during reactor operations or as a result of nuclear accidents may be fragments of fuel or highly radioactive metallic particles and produce energetic particles. If such particles remain on the skin for even a short time, they can cause intense irradiation of a small volume of tissue, resulting in the death of cells in interphase in various layers of the skin. The depth of the skin at which cells are killed depends on the energy of the emitted α- or β-particles and the total radiation dose. The damage may be severe enough to cause open ulcerative lesions and/or scabs within 1–3 weeks of irradiation. These changes occur faster than those normally associated with radiation-induced moist desquamation (Hopewell *et al.*, 1993).

1.4 *Transport and deposition*

The subsequent behaviour of radionuclides in the body depends on the element concerned and the chemical form of the exposure, which determine the solubility of the radionuclide and the extent to which it is dissolved and absorbed into blood. On reaching the blood, the distribution, redistribution and retention in body tissues depend on the chemical nature of the element. Radionuclides may be distributed throughout the body, be deposited selectively in a particular tissue or be deposited in significant quantities in a number of tissues.

Insoluble materials may move intact from wounds or the lungs through the lymphatic system. Movement along lymphatic vessels can lead to accumulation of radionuclides in regional lymph nodes and then to their discharge into the circulatory system. Particles may reach the bloodstream, from which they are removed rapidly by phagocytic cells of the reticuloendothelial system in the liver, spleen and bone marrow.

1.5 *Elimination*

Radionuclides may be eliminated from the body principally by exhalation and excretion in urine, faeces, sweat, saliva and potentially in milk. Exhalation is a major pathway for the undeposited fraction of inhaled aerosols, $^{3}H_2O$ vapour and gases such as those containing ^{14}C and ^{220}Rn and ^{222}Rn produced in the radioactive decay of internally deposited thorium and radium. In the course of urinary excretion, certain radionuclides deliver a dose to the kidney and bladder. Radionuclides in the faeces result either from ingested radionuclides that have not been absorbed during gastrointestinal transit or from radionuclides absorbed and subsequently excreted back into the gastrointestinal tract — most often via biliary excretion.

1.6 *Doses from internal irradiation*

The absorbed doses in various organs and tissues calculated for reference infants, children and adults for unit intakes of radionuclides are given in recent ICRP publications (ICRP, 1989, 1993, 1994, 1995a,b, 1996). Calculated coefficients are also provided for workers (ICRP, 1995c) and for patients given radiolabelled pharmaceuticals (ICRP, 1988, 1998). The ICRP database is available on CD-ROM (ICRP, 1999). The ICRP evaluations are based on reviews of the biokinetics of radionuclides in humans and animals. Internal doses are determined from measurements of nuclides in exhaled air, tissues, excreta or the whole body.

2. Modes of decay of radionuclides

Each atom has a small, very dense nucleus with a radius of about 10^{-6} nm, composed of positively charged protons and neutral neutrons, collectively known as nucleons. The nucleus is surrounded by electrons, equal in number to protons, making the atom electrically neutral and occupying a space with a radius of about 0.1 nm.

The atoms of different elements differ in the constitution of their nuclei and the number and arrangement of their electrons. Each atom of a particular chemical element has the same number of protons, which is defined as the atomic number (Z). Any nuclide is uniquely defined by the number of protons (Z) and the number of neutrons (N) in the nucleus. The atomic mass number ($A = Z + N$) gives the total number of nucleons. The nuclide is specified as ${}^{A}_{X}X$, where X represents the letter symbol for the particular chemical element (e.g. ${}^{12}_{6}\mathrm{C}$ for stable carbon-12). Table 5 shows the main characteristics of electrons and nucleons.

Most elements consist of a mixture of several atomic species with the same extranuclear structure but different nuclear masses, i.e. mass number A, owing to different numbers of neutrons. Atoms composed of nuclei with the same number of protons (Z) but different number of neutrons (N) are called isotopes. They have a different mass number (A) but are the same chemical element and generally have identical chemical properties. More than one isotope of an element may be found naturally within the environment; for example, the natural abundance of uranium is 99.27% ^{238}U, 0.72% ^{235}U and 0.01% ^{234}U, and that of potassium is 93.26% ^{39}K, 6.73% ^{41}K and 0.01% ^{40}K. Atoms composed of nuclei with the same total number of nucleons (A) but

Table 5. Main characteristics of electrons and nucleons

Name	Symbol	Charge	Mass (kg)	Relative mass
Electron	e	–1	9.109×10^{-31}	1
Proton	p	+1	1.6726×10^{-27}	1836
Neutron	n	0	1.6749×10^{-27}	1839

different numbers of protons (Z) are called isobars. They are different chemical elements. Isotopes and isobars may be stable or unstable and undergo change in their nuclear structure, and sometimes atomic structure, spontaneously, with the emission of energetic particles and/or photons. This process is called radioactive decay. Any nuclear species that is capable of undergoing spontaneous radioactive decay is called a radionuclide.

The atom consists of a positively charged nucleus surrounded by sufficient electrons in closed shells to make the atom electrically neutral. These electron shells are identified by sequential letters of the alphabet, the innermost shell being identified as the K shell. Each electron in the shell or sub-shell structure has a uniquely defined energy state determined by quantum numbers. The maximum number of electrons that can exist in a shell is $2n^2$, where n is the principal quantum number ($n = 1$ for the K shell, which is closest to the nucleus), as a result of the Pauli exclusion principle which states that no two electrons can have the same set of quantum numbers and exist in the same energy state. The atom is in the ground state, or most stable configuration, when all the electrons are in the lowest possible energy state. The binding energy of an electron in a specific shell of an atom is defined as the energy that must be given to the electron to remove it completely from the atom and make it a free electron.

Mass, m, is a form of energy, E, and they are related by the equation, $E = mc^2$, where c is the velocity of light in vacuum. Therefore, the atomic mass unit (u) which is defined as 1/12 the mass of the ^{12}C atom can also be defined in terms of energy:

$1\ u = 1.66054 \times 10^{-27}$ kg = 931.5 MeV (where 1 eV = 1.6022×10^{-19} J).

The energy that holds the nucleus together (i.e. the nuclear binding energy) is produced when a small proportion of the mass of each nucleon is given up. The binding energy of the nucleus can therefore be determined by calculating the difference between the total mass of the individual nucleons and the mass of the composite nucleus.

Six emissions can result from radioactive decay, as presented in Table 6.

The α-particle consists of two neutrons and two protons and therefore has a charge of +2. It is the nucleus of the helium atom, ^4_2He. The β^--particle is a negatively charged

Table 6. Modes of emission in relation to electrical charge and mass

Particle	Symbol	Charge	Mass (kg)
α	α	+2	6.645×10^{-27}
Electron (β^-)	e^- (β^-)	–1	9.109×10^{-31}
Positron (β^+)	e^+ (β^+)	+1	9.109×10^{-31}
Neutrino	ν	0	~ 0
Antineutrino	$\bar{\nu}$	0	~ 0
Electromagnetic radiation (photon)	γ or X	0	0

electron and the β^+-particle or positron (the antiparticle of the electron) is a positively charged electron. The neutrino and its antiparticle, the antineutrino, are particles with essentially no 'rest' mass and no charge. γ- and X-rays are high-frequency electromagnetic radiation that travel at the speed of light. These photons are essentially identical except for their origins: γ-rays result from de-excitation of the nucleus, while characteristic X-rays result from de-excitation of an atom (electronic shells). The term X-ray also refers to *bremsstrahlung*, which is the electromagnetic radiation produced by deceleration of charged particles (typically electrons) as they pass through matter.

A radioactive atom may decay by one of several processes: by emission of α-particles; by emission of β-particles, including β^- (electron) and β^+ (positron) emission; isomeric transitions such as γ emission (excited state and metastable state) with internal conversion being a competing process; and spontaneous fission (not considered in this monograph).

2.1 *Decay by emission of α-particles*

α-Particles are emitted mainly from heavy nuclei. In such disintegrations, a helium nucleus, consisting of two protons and two neutrons, is ejected. Thus, the decay product (*D*) has an atomic number that is two less, and a mass number four less than that of the parent (*P*), as characterized by the following equation:

$$ {}^{A}_{Z}P \rightarrow {}^{A-4}_{Z-2}D + {}^{4}_{2}\alpha, $$

e.g. $ {}^{226}_{88}\mathrm{Ra} \rightarrow {}^{222}_{86}\mathrm{Rn} + \alpha. $

The energy, *Q*, released as a result of the decay, arises from the net loss in mass:

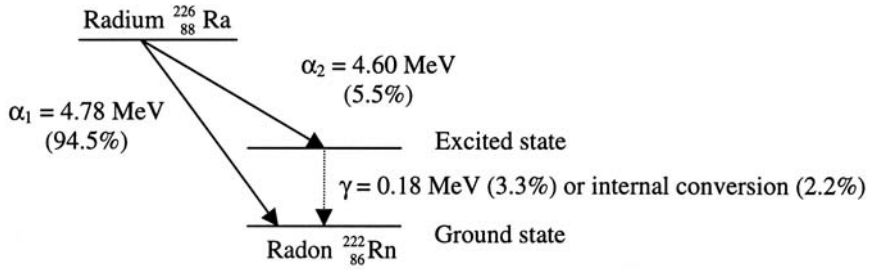
$$ Q = m_P - m_D - m_\alpha. $$

This energy is shared between the α-particle and the recoil nucleus. The α-particles emitted from a given type of decay are monoenergetic and carry most of the energy because their mass is smaller than that of the residual nucleus. Some α-particle emitters decay not only directly to the ground state but also to various excited states of the progeny nuclei, with different probabilities. If the parent decays to the excited state of the progeny, then a monoenergetic α-particle will be emitted with an energy less than *Q*. The nucleons in the excited progeny then reconfigure to the most stable configuration, the ground state, and release the additional energy by emitting one or more photons (γ-rays). Part of the energy of the excited state can also set electrons in motion by internal conversion in the K, L and M shells (discussed in section 2.2).

For instance, in 94.5% of its disintegrations, natural radium ($ {}^{226}_{88}\mathrm{Ra} $) decays directly to the ground state of its decay product, radon ($ {}^{222}_{86}\mathrm{Rn} $), by emitting a monoenergetic α-particle with an energy equal to *Q* of 4.78 MeV (Figure 2). In the remaining 5.5% of the disintegrations, radium decays to an excited state of radon, emitting a lower-energy α-particle of 4.60 MeV; the additional energy is released either by the emission

of a photon (γ-ray) of 0.18 MeV (3.3%) or an internal conversion electron (2.2%), as the nucleus moves to the ground state.

Figure 2. An example of α-particle decay is the decay of $^{226}_{88}$Ra to $^{222}_{86}$Rn



2.2 *Decay by emission of β-particles*

(*a*) *β⁻-Particles (electrons)*

A nuclide undergoing β-particle decay emits a negatively charged electron (known as a β-particle, β^-) from the nucleus, resulting in a decay product with an atomic number that is one higher than that of the parent but with the same atomic mass number. This is illustrated by the following equation:

$$^{A}_{Z}P \rightarrow {}^{A}_{Z+1}D + \beta^- + \bar{\nu}\,.$$

e.g. $^{131}_{53}\mathrm{I} \rightarrow {}^{131}_{54}\mathrm{Xe} + \beta^- + \bar{\nu}\,.$

This process results from the transformation of a neutron (n) into a proton (p) in the nucleus with the emission of an electron (β^-) and an antineutrino ($\bar{\nu}$), following the equation:

$$^{1}_{0}n \rightarrow {}^{1}_{1}p + \beta^- + \bar{\nu}\,.$$

The difference in energy between the initial atom and the final atom is Q, which is shared between the electron and antineutrino. The electron can be emitted with a range of energies from 0 to $E_{max} = Q$ because this is a three-body decay. Of interest is the mean energy, $\bar{E}$, deposited in tissue from a β-particle emitter. The ratio $\bar{E}/E_{max}$ is different for each β-particle-emitting radionuclide but is usually about 1/3.

Some β-particle emitters decay not only to the ground state but also to various excited states of the progeny nuclei, with different probabilities. If the parent decays to the excited state of the progeny, then β-particles will be emitted with a correspondingly reduced range of energies. The nucleons in the excited progeny decay subsequently to the ground state with the emission of one or more photons (γ-rays) or by ejecting atomic electrons by internal conversion.

(*b*) *β^+-Particles (positrons)*

A nuclide undergoing positron decay emits a positively charged electron, called a positron, from the nucleus, resulting in a decay product with an atomic number that is one less than that of the parent but with the same atomic mass number. This is illustrated by the following nuclear equation:

$${}^{A}_{Z}P \rightarrow {}^{A}_{Z-1}D + \beta^+ + \nu,$$

e.g. ${}^{15}_{8}\mathrm{O} \rightarrow {}^{15}_{7}\mathrm{N} + \beta^+ + \nu.$

This process results from the transformation of a proton (*p*) into a neutron (*n*) in the nucleus with the emission of a positron (β^+)and a neutrino (ν), following the equation:

$${}^{1}_{1}p \rightarrow {}^{1}_{0}n + \beta^+ + \nu.$$

The difference in energy between the initial atom and the final atom is *Q*, which is shared between the positron and neutrino. Since the combined mass of the neutron and positron is greater than that of the proton, this process is possible within the nucleus only if the nuclear masses of the parent and progeny differ (because of different binding energies) by two times the energy equivalent to the rest mass of the electron (2×0.511 MeV).

The positron can be emitted with a range of energies, from 0 to *Q*, because this is a three-body decay. The total kinetic energy shared between the positron and the neutrino (i.e. the maximum energy given to the positron) is the difference between the atomic masses of the parent and progeny nuclei reduced by 1.022 MeV.

The positron, after losing its kinetic energy, is subsequently annihilated by interaction with a negatively charged electron, which results in the conversion of the masses of the two particles into energy (1.022 MeV). Since this process usually occurs when the particles are at rest, the annihilation process produces two photons, equivalent to γ-rays, each with an energy of 0.511 MeV, travelling in opposite directions from the annihilation site.

(*c*) *Electron capture*

Electron capture decay is characterized by the absorption of an atomic inner-shell electron by the parent nucleus. This is illustrated by the following equation:

$${}^{A}_{Z}P + e^- \rightarrow {}^{A}_{Z-1}D + \nu\,,$$

e.g. ${}^{125}_{53}\mathrm{I} + \mathrm{e}^- \rightarrow {}^{125}_{52}\mathrm{Te} + \nu\,.$

The captured electron combines with a proton to form a neutron, and the excess energy is carried off by the emission of a neutrino, following the equation:

$${}^{1}_{1}p + e^- \rightarrow {}^{1}_{0}n + \nu.$$

This results in a decay product that has the same atomic mass number and an atomic number that is one less than that of the parent.

In electron capture most of the available energy is radiated from the system as neutrinos. After electron capture the nucleus may still be in an excited state, and the excess energy is subsequently emitted as γ-rays or an electron by internal conversion.

The captured electron is typically from the K shell, although capture from the L and M shells can also occur. This leaves the atom in an unstable state because of the vacancy created in the inner shell of the atom. This hole can be filled in many ways, outer-shell electrons dropping down to fill the inner-shell vacancies, resulting in the emission of X-ray or Auger electrons characteristic of the decay product (Figure 3; discussed in section 2.4). The energy of the characteristic X-rays emitted is determined by the difference between the corresponding atomic energy levels involved.

2.3 *Isomeric decay processes*

The nucleus is often left in an excited state after α- and β-particle emission. The excess energy is subsequently emitted as γ-rays or an electron by internal conversion. The nucleus before and after an isomeric decay is identical, apart from the energy state.

(*a*) *Production of γ-rays*

Usually the nucleus de-excites into a more stable configuration by γ-ray emission, the atomic number and atomic mass number remaining unchanged. This process may occur in one step with the emission of a single γ-ray or via one or more intermediate excited states resulting in the emission of two or more γ-rays. Typically more than one de-excitation pathway exists with various competing probabilities.

The life-times of nuclear excited states vary, but 0.1 ns can be regarded as typical for these nuclear electromagnetic decays. In some cases, the excited state may be almost stable, and the nucleus may remain in this state for seconds, minutes or even days. Nuclei in this state appear experimentally to act like separate isotopes and are called isomers. The transition to the ground state is called isomeric transition, and the excited state is referred to as a metastable state. An example of an isobaric transition to form a metastable state is the decay of $^{99}_{42}$Mo to $^{99m}_{43}$Tc. The isomeric transition then occurs as $^{99m}_{43}$Tc decays to $^{99}_{43}$Tc with a 6-h half-life.

(*b*) *Internal conversion*

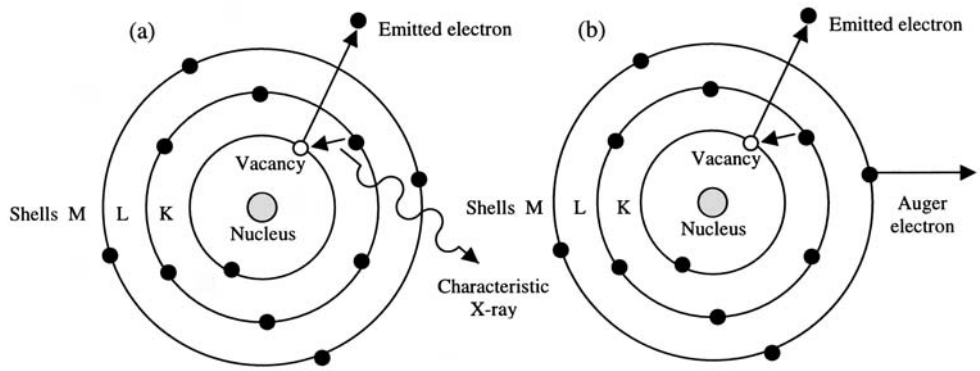
As an alternative to the emission of a γ-ray (energy, γ_1), an excited nucleus may lose its excess energy by internal conversion. In this process, the energy released in the transition of an excited nuclear state to a lower state is transferred to an inner-shell electron (typically K or L shell). This results in ejection of the electron from the atom with energy $E = \gamma_1 - E_B$, where E_B is the binding energy of the electron to its atom. As is the case with electron capture, the atom is left in an unstable state after this process because of the vacancy created in an inner shell of the atom.

Internal conversion competes with γ-ray emission, resulting in a decrease in measured γ-ray intensity. The ratio of the total number of electrons emitted to the total number of γ-rays emitted is called the internal conversion coefficient, which increases as Z^3 and decreases with γ_l. Therefore, γ-ray decay predominates in light nuclei, and internal conversion is prevalent for heavy nuclei especially in the decay of low-lying excited states.

2.4 *Auger electrons and characteristic X-rays*

If the energy transferred to an electron exceeds the binding energy, the electron is ejected from the atom with a kinetic energy equal to the difference between the absorbed energy and the binding energy. The ionization of the atom results in an ion pair (the electron and the positively charged ion). Electrons can be removed from the K, L or M shell by electron capture, internal conversion or by passage of ionizing radiation resulting in an electron hole. The atom is left in an unstable state. The energy released by this transition may be radiated in the form of characteristic X-rays of an energy equal to the difference in the binding energies of the two shells involved in the transition, or alternatively by the ejection of monoenergetic Auger electrons, with an energy equal to that of the characteristic X-ray minus the binding energy of the emitted electron. This process continues until the vacancy moves to the outermost shell and is subsequently filled by a free electron. These processes are illustrated in Figure 3.

Figure 3. Competing processes of (a) characteristic X-ray emission and (b) Auger electron production, after removal of an inner-shell electron



The relative probability of the emission of characteristic radiation to emission of an Auger electron is called the fluorescent yield. The fluorescent yield increases with increasing atomic number, *Z*.

The decay of Auger electron-emitting radionuclides is initiated when electron capture or internal conversion creates a vacancy in an inner atomic shell. The filling of this vacancy produces a cascade of inner-shell electron transitions with the emission

of numerous Auger electrons from the single atom. This can result in a high density of ionizing particles close to the point of decay and also leave the residual atom in a highly positively charged state by loss of electrons.

3. Exposure to internal sources of radiation

3.1 *Radionuclides considered in this monograph*

As described in section 2, the decay of a radioactive atom may occur through one of several processes which give rise to the emission of four major types of radiation: α, electron (β^-), positron (β^+) and γ-radiation (in this discussion we ignore neutrino and antineutrino radiation). Many types of radioactive decay produce more than one type of radiation: decay of a radionuclide to an excited state of its decay product can result in subsequent stabilization of the progeny nucleus and atom by emission of γ-radiation (or conversion electrons) and X-rays, respectively. One example is the β-particle decay of $^{131}_{53}$I to an excited state of $^{131}_{54}$Xe, which is stabilized by the release of a substantial amount of γ-radiation (see Figure 4; discussed in detail below). In other cases, the primary decay of a radionuclide may lead directly to the ground state of its progeny nuclide. The progeny nuclide may also be radioactive and subject to further decay. An example is the α-particle decay of radium (^{226}Ra) directly to radon (^{222}Rn), which subsequently enters an extensive series of disintegrations that terminates with the stable isotope ^{206}Pb. The biological effects observed after internal deposition of these types of radionuclides must be considered to result from the sum of the interactions with cells and tissues of the various types of radiation emitted during each step of the decay chain. For this reason, a previous IARC working group that evaluated the radioactive gas radon, classified 'radon and its decay products' as *carcinogenic to humans (Group 1)* (IARC, 1988).

Evaluation of the human cancer hazard of these radionuclides would not be adequate if it were based on a simple distinction between α- and β-particle-emitting radionuclides. Secondary emissions (e.g. γ- and X-rays) produced by the excited atom after release of an α- or β-particle may contribute considerably to the radiation dose, as may the characteristic X-rays produced after electron capture decay (see section 2.2). It should be noted that both X- and γ-radiation have been classified as human carcinogens (Group 1; IARC, 2000). With most internally deposited radionuclides that emit α-radiation, the dose of α-particles in the organs where the radionuclide accumulates is substantially greater than that from the accompanying β-particle and γ-ray emissions.

(*a*) *Categorization of radionuclides*

The radionuclides considered in this monograph are listed in Tables 7 and 8 in order of increasing atomic mass number. Table 7 shows the decay mode of the radionuclide, the energy of the emitted radiation, its half-life, its decay product (stable/unstable), the presence of other types of emitted radiation and — when relevant — the

Table 7. Radionuclides mentioned in this monograph that undergo decay by emission of α- and/or β-particles

Radio-nuclide	Decay	Energy[a] (keV)	Half-life	Decay product[b]		Emitter type[c]	Other emissions[d]	Δ/ΣΔ (%)[e]	Truncation[f]	Cate-gory[g]
^{3}H	β^-	18.6	12.33 y	^{3}He	(stable)	Pure β	None	β, 100	–	A-1
^{14}C	β^-	156.5	5730 y	^{14}N	(stable)	Pure β	None	β, 100	–	A-1
^{32}P	β^-	1710.7	14.26 d	^{32}S	(stable)	Pure β	None	β, 100	–	A-1
^{33}P	β^-	248.5	25.34 d	^{33}S	(stable)	Pure β	None	β, 100	–	A-1
^{35}S	β	167.1	87.32 d	^{35}Cl	(stable)	Pure β	None	β, 100	–	A-1
^{45}Ca	β^-	256.8	162.6 d	^{45}Sc	(stable)	Pure β	None	β, 100	–	A-1
^{89}Sr	β^-	1495.1	50.53 d	^{89}Y	(stable)	Pure β	γ-Rays (0.01%)	β, 100	–	A-1
^{90}Sr	β^-	546.0	28.79 y	^{90}Y	(unstable)	Pure β	None[h]	β, 100	Full chain	A-2
^{90}Y	β^-	2280.1	64.0 h	^{90}Zr	(stable)	Pure β	γ-Rays (0.01%)[h]	β, 100	–	A-1
^{91}Y	β^-	1544.8	58.5 d	^{91}Zr	(stable)	Pure β	γ-Rays (0.3%)	β, 100	–	A-1
^{106}Ru	β^-	39.4	373.59 d	^{106}Rh	(unstable)	Mixed β	γ-Rays	β, 88; γ, 12	Full chain	B-2
^{106}Rh	β^-	3541	29.8 s	^{106}Pd	(stable)	Mixed β	γ-Rays	β, 87; γ, 13	–	B-1
^{131}I	β^-	970.8	8.02 d	^{131}Xe	(stable)	Mixed β	γ-Rays	β, 34; γ, 66	–	B-1
^{137}Cs	β^-	1175.6	30.07 y	^{137}Ba	(stable)	Mixed β	γ-Rays	β, 31; γ, 69	–	B-1
^{140}Ba	β^-	1050	12.75 d	^{140}La	(unstable)	Mixed β	γ-Rays	β, 25; γ, 75	Full chain	B-2
^{141}Ce	β^-	580.7	32.50 d	^{141}Pr	(stable)	Mixed β	γ-Rays	β, 69; γ, 31	–	B-1
^{144}Ce	β^-	318.7	284.89 d	^{144}Pr	(unstable)	Mixed β	γ-Rays	β, 96; γ, 4	Full chain	B-2
^{147}Pm	β^-	224.1	2.623 y	^{147}Sm	('stable')	Pure β	γ-Rays (0.01%)	β, 100	^{147}Sm (10^{11} y)	A-1
^{188}Re	β^-	2120.4	17.00 h	^{188}Os	(stable)	Mixed β	γ-Rays	β, 93; γ, 7	–	B-1
^{210}Pb[i]	β^-	63.5	22.3 y	^{210}Bi	(unstable)	Mixed β	γ-Rays	α, 92; β, 8	Full chain	B-2
^{210}Bi[j]	β^-	1162	5.01 d	^{210}Po	(unstable)	Pure β	None	α, 93;β, 7	Full chain	A-2
^{210}Po	α	5407.5	138.38 d	^{206}Pb	(stable)	Pure α	γ-Rays (0.001%)	α, 100	–	A-1
^{212}Bi[k]	β^-	2254.0	60.55 m	^{212}Po	(unstable)	Mixed α/β^-	γ-Rays	α, 79; β, 7; γ, 14	Full chain	B-2
	α	6207.1		^{208}Tl	(unstable)		γ-Rays			
^{220}Rn	α	6404.7	55.6 s	^{216}Po	(unstable)	Mixed α	β/γ -Rays	α, 89; β, 4; γ, 7	Full chain	B-2
^{222}Rn	α	5590.3	3.82 d	^{218}Po	(unstable)	Mixed α	β/γ -Rays	α, 88; β, 4; γ, 8	^{210}Pb (22.3 y)	B-2

Table 7 (contd)

Radio-nuclide	Decay	Energy[a] (keV)	Half-life	Decay product[b]		Emitter type[c]	Other emissions[d]	Δ/ΣΔ (%)[e]	Truncation[f]	Cate-gory[g]
^{224}Ra	α	5788.9	3.66 d	^{220}Rn	(unstable)	Mixed α	β/γ-Rays	α, 92; β, 3; γ, 5	Full chain	B-2
^{226}Ra	α	4870.6	1600 y	^{222}Rn	(unstable)	Mixed α	β/γ-Rays	α, 90; β, 3; γ, 7	^{210}Pb (22.3 y)	B-2
^{228}Ra	β^-	45.9	5.75 y	^{228}Ac	(unstable)	Mixed β[l]	γ-Rays	β, 34; γ, 66	^{228}Th (1.91 y)	B2
						Mixed α[l]	β/γ-Rays	α, 89; β, 4; γ, 7	Full chain	
^{227}Th	α	6146.4	18.72 d	^{223}Ra	(unstable)	Mixed α	β/γ-Rays	α, 96; β, 3; γ, 1	Full chain	B2
^{228}Th	α	5520.1	1.91 y	^{224}Ra	(unstable)	Mixed α	β/γ-Rays	α, 93; β, 3; γ, 4	Full chain	B2
^{230}Th	α	4770.0	7.54×10^4 y	^{226}Ra	(‘stable’)	Pure α	None	α, 100	^{226}Ra (1600 y)	A1
^{232}Th	α	4082.8	1.41×10^{10} y	^{228}Ra	(unstable)	Mixed α[m]	β/γ-Rays	α, 90; β, 4; γ, 6	Full chain	B2
						Pure α[m]	None	α, 100	^{228}Ra (5.75 y)	
^{233}U	α	4908.6	1.58×10^5 y	^{229}Th	(‘stable’)	Pure α	None	α, 100	^{229}Th (7.3×10^3 y)	A1
^{234}U	α	4858.5	2.44×10^5 y	^{230}Th	(‘stable’)	Pure α	None	α, 100	^{230}Th (7.7×10^4 y)	A1
^{235}U	α	4678.7	7.04×10^8 y	^{231}Th	(unstable)	Mixed α	β/γ-Rays	α, 92; β, 4; γ, 4	^{231}Pa (3.3×10^4 y)	B2
^{238}U	α	4270.0	4.47×10^9 y	^{234}Th	(unstable)	Mixed α	β/γ-Rays	α, 82; β, 17; γ, 1	^{234}U (2.4×10^5 y)	B2
^{238}Pu	α	5593.2	87.7 y	^{234}U	(‘stable’)	Pure α	None	α, 100	^{234}U (2.4×10^5 y)	A1
^{239}Pu	α	5244.5	24110 y	^{235}U	(‘stable’)	Pure α	None	α, 100	^{235}U (7×10^8 y)	A1
^{240}Pu	α	5255.8	6537 y	^{236}U	(‘stable’)	Pure α	None	α, 100	^{236}U (2.34×10^7 y)	A1
^{237}Np	α	4959.1	2.14×10^6 y	^{233}Pa	(unstable)	Mixed α	γ-Rays	α, 90; β, 5; γ, 5	^{233}U (1.6×10^5 y)	B2
^{239}Np	β^-	721.8	2.36 d	^{239}Pu	(‘stable’)	Mixed β	γ-Rays	β, 60; γ, 40	^{239}Pu (2.4×10^4 y)	B1
^{241}Am	α	5637.8	432.2 y	^{237}Np	(‘stable’)	Mixed α	γ-Rays	α, 98; β, 1; γ, 1	^{237}Np (2.1×10^6 y)	B1
^{242}Cm	α	6215.6	162.8 d	^{238}Pu	(‘stable’)	Pure α	None	α, 100	^{238}Pu (88 y)	A1
^{243}Cm[n]	α	6168.8	29.1 y	^{239}Pu	(‘stable’)	Mixed α	β/γ-Rays	α, 96; β, 2; γ, 2	^{239}Pu (2.4×10^4 y)	B1
	EC/β^+	8.9		^{243}Am	(‘stable’)				^{243}Am (7370 y)	
^{244}Cm	α	5901.6	18.1 y	^{240}Pu	(‘stable’)	Pure α	None	α, 100	^{240}Pu (6537 y)	A1
^{249}Cf	α	6295.0	351 y	^{245}Cm	(‘stable’)	Mixed α	β/γ-Rays	α, 94; β, 1; γ, 5	^{245}Cm (8.5×10^3 y)	B1

Table 7 (contd)

Radio-nuclide	Decay	Energy[a] (keV)	Half-life	Decay product[b]	Emitter type[c]	Other emissions[d]	$\Delta/\Sigma\Delta$ (%)[e]	Truncation[f]	Cate-gory[g]
^{252}Cf[o]	α	6216.9	2.65 y	^{248}Cm (‘stable’)	Mixed α	β/γ -Rays	α, 65; β, 1; γ, 34	^{248}Cm (3.4×10^5 y)	B1
	SF					Fission neutrons			

d, days; m, months; y, years

[a] Difference (in keV) between the energies of the decaying radionuclide and its first decay product. For β^- decay, the maximum energy value is given (E_{max}); it should be noted that the average energy (E_{ave}) of β-radiation is often 30–40% of the E_{max} (^{3}H, 5.7 keV; ^{35}S , 48.6 keV).

[b] Decay products of the first decay step are listed. Stable: the decay product is non-radioactive; unstable: the decay product is radioactive; ‘stable’: the decay product is radioactive, but it has a long half-life, which justifies truncation of the decay chain at this point for calculation of energy contributions (see footnote e).

[c] α- and β-Particle-emitting radionuclides producing ≤ 1% energy contribution from ‘other emissions’ are considered pure emitters.

[d] ‘Other emissions’ refer to the first decay step only.

[e] Values were calculated from the nuclear data tables of Martin and Blichert-Toft (1970) or were provided by the National Radiological Protection Board; the data from these two sources show good agreement; the energy components of the conversion and Auger electrons have been included with β-particles, those of X-rays with γ-rays; for nuclides with unstable decay products, energy contributions were calculated for the entire decay chain or up to a long-lived decay product (see footnote b).

[f] Point in the decay chain beyond which the energy contributions are ignored; the radioactive half-life of the corresponding radionuclide is indicated.

[g] A-1/A-2: pure emitters with stable/unstable decay products, respectively (first decay step only); B-1/B-2: mixed emitters with stable/unstable decay products, respectively (first decay step only)

[h] The two-step disintegration $^{90}Sr \rightarrow {}^{90}Y \rightarrow {}^{90}Zr$ can be considered pure β^- decay.

[i] In short-term experiments, ^{210}Pb acts as a nearly pure β-particle emitter (β, 99%; γ, 1%); over the full decay chain, α-radiation from ^{210}Po predominates.

[j] In short-term experiments, ^{210}Bi acts as a pure β-particle emitter (β, 100%); over the full decay chain, α-radiation from ^{210}Po predominates.

[k] This radionuclide disintegrates by α-particle (36%) and β^- decay (64%); the energy contributions are calculated for the combined decay pathways.

[l] The radionuclide ^{228}Ra may be considered a mixed β-particle emitter in two-year carcinogenicity bioassays with rodents (with truncation of the decay chain at ^{228}Th; half-life, 1.91 years), whereas the effects of α-radiation predominate in long-term human exposure.

[m] The radionuclide ^{232}Th may be considered a pure α-particle emitter in two-year carcinogenicity bioassays with rodents.

[n] This radionuclide disintegrates by α-particle decay (99.7%) and electron capture (EC) + β^+ decay (0.3%); the energy contributions are calculated for the combined decay pathways.

[o] This radionuclide disintegrates by α-particle decay (97%) and spontaneous fission (SF; 3%); the dose from the fission neutrons is not included in the calculation of energy contributions.

Table 8. Radionuclides mentioned in this monograph that undergo electron capture (EC) and internal conversion (IC) decay

Radio-nuclide	Decay	Energy[a] (keV)	Half-life	Decay product[b]		Emitter type	Other emissions[c]	$\Delta/\Sigma\Delta$ (%)[d]	Truncation[e]	Category[f]
^{40}K[g]	β^-	1311.1	1.277×10^9 y	^{40}Ca	(stable)	Mixed β	γ-Rays	β, 76; γ, 24	–	B1
	EC	1504.9		^{40}Ar	(stable)					
^{55}Fe	EC	231.4	2.73 y	^{55}Mn	(stable)	Mixed Ae^-	X-Rays	Ae^-, 73; X, 27	–	B1
^{67}Ga	EC	1000.5	3.26 d	^{67}Zn	(stable)	Mixed Ae^-	γ-Rays	Ae^-, 21; γ, 79	–	B1
^{111}In	EC	865.5	2.80 d	^{111}Cd	(stable)	Mixed Ae^-	γ-Rays	Ae^-, 8; γ, 92	–	B1
^{125}I	EC	185.8	59.40 d	^{125}Te	(stable)	Mixed Ae^-	γ-Rays	Ae^-, 32; γ, 68	–	B1
^{211}At[h]	α	5982.4	7.214 h	^{207}Bi	(unstable)	Mixed α	γ-Rays	α, 94; γ, 6	Full chain	B2
	EC	786.1		^{211}Po	(unstable)					
^{99m}Tc	IC	142.7	6.01 h	^{99}Tc	('stable')	Mixed γ	ce^-	ce^-, 11; γ, 89	^{99}Tc (2.1×10^5 y)	B1

Abbreviations: d, days; y, years; Ae^-, Auger electrons; ce^-, conversion electrons

[a] Difference (in keV) between the energies of the decaying radionuclide and its first decay product

[b] Decay products of the first decay step are listed. Stable: the decay product is non-radioactive; unstable: the decay product is radioactive; 'stable': the decay product is radioactive, but it has a long half-life, which justifies truncation of the decay chain at this point for calculation of energy contributions (see footnote d).

[c] 'Other emissions' refer to the first decay step only.

[d] Values were calculated from the nuclear data tables of Martin and Blichert-Toft (1970) or were provided by the National Radiological Protection Board; the data from these two sources show good agreement; the energy components of the conversion and Auger electrons have been included with β-particles, those of X-rays with γ-rays; for nuclides with unstable decay products, energy contributions were calculated for the entire decay chain or up to a long-lived decay product (see footnote b).

[e] Point in the decay chain beyond which the energy contributions are ignored; the radioactive half-life of the corresponding radionuclide is indicated.

[f] B-1/B-2: mixed emitters with stable/unstable decay products, respectively (first decay step only)

[g] This radionuclide disintegrates by β^- (89%) and electron capture (EC) decay (11%); the energy contributions are calculated for the combined decay pathways.

[h] This radionuclide disintegrates by α-particle (42%) and electron capture (EC) decay (58%); the energy contributions are calculated for the combined decay pathways.

relative energy contribution of this 'contaminating' radiation, expressed as a percentage of the equilibrium rate constant (see below).

To distinguish radioactive decay processes of different complexity, radionuclides can be categorized into groups according to the 'purity' of the emitted radiation and the stability of their decay products, as follows:

Category A. 'Pure' emitters: decay occurs through emission of solely α- or β-particles.

This category includes those radionuclides that emit almost exclusively α- or β-particles (Tables 7 and 8). These radionuclides may also produce γ- and X-ray emissions, but their contribution to the dose is ≤ 1% (see below). Although some α-particle emitters have a low probability of spontaneous fission, this decay process and the irradiation of tissues by fission fragments is not reviewed in this monograph. Furthermore, although all β^-- and β^+-particle emissions are accompanied by the emission of a neutrino or antineutrino, these particles do not cause biological damage and have been ignored.

Category B. 'Mixed' emitters: α- or β-particle decay also involves emission of γ-radiation and/or X-radiation.

For each of the categories A and B, subcategories exist:

Subcategory 1. Nuclides with stable progeny, i.e. with a stable isotope as the decay product.

Subcategory 2. Nuclides with decay products that are also radioactive.

Data on radioisotopes of category A-1, i.e. pure α- or β-particle-emitting radionuclides with stable decay products, would theoretically provide the most straightforward basis for evaluating the carcinogenic hazard of α- or β-radiation *per se* from internally deposited sources. For a number of pure β-particle emitters (e.g. ^{3}H, ^{32}P) with stable progeny (^{3}He, ^{32}S, respectively), relevant data are available on which to evaluate the carcinogenic hazard of internal exposure. For most of the α-particle-emitting radionuclides — even for those of group A-1 — the situation is somewhat different, owing to secondary radiation (γ- and/or X-radiation) from the excited nucleus and atom (see above). Pure α-particle emitters in the strict sense are, therefore, rare. The effects of α-particle emitters should not be evaluated without considering the amount and possible impact of these 'contaminating' radiations. Radionuclides in categories A-2 and B-2 often result in a more complex situation because of the additional effects of the emissions in the decay chain after the primary decay. The decay sequence of a radionuclide in category A-2 may be considered only in rare instances to represent a pure emission (e.g. the two-step β-particle decay of ^{90}Sr via ^{90}Y to ^{90}Zr; see Table 7).

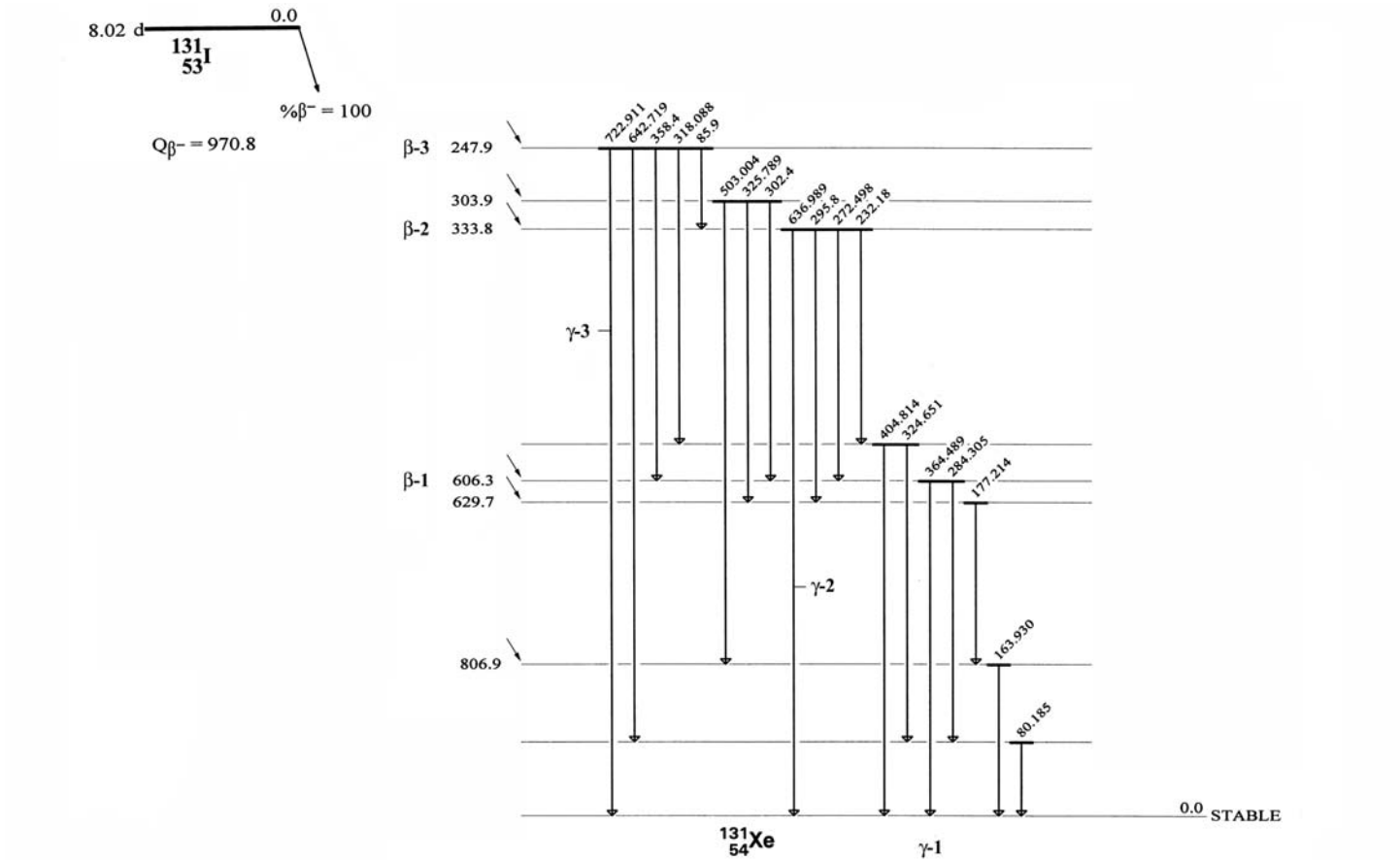
(*b*) *Types of radiation produced during decay of 'mixed' emitters*

The relative contributions of the various emissions produced during the radioactive decay of 'mixed' emitters is often considered at the state of 'ideal equilibrium', i.e. at the stage of the decay at which the activity of the decaying radionuclide is equal to the activity of the decay product. For example, the β-particle decay of ^{131}I gives rise to an excited state of the xenon isotope ^{131m}Xe, which is stabilized by emission of (mainly) γ-radiation, producing the stable nuclide ^{131}Xe (Figure 4). Assuming that the ^{131}I is initially pure, it can be calculated that the state of ideal energy equilibrium is reached after 14.1 days. The β-particle decay of ^{131}I occurs along three major emissions (β-1, β-2 and β-3), and, subsequently, the intermediate product ^{131m}Xe releases its energy by emission of a series of three major γ-rays (γ-1, γ-2 and γ-3). The relative contributions of the β- and γ-radiation emissions during the decay of ^{131}I can be assessed by calculating for each emission the energy emitted per disintegration (Δ, defined for an infinite medium), and then the relative energy contribution over all emissions ($\Delta/\Sigma\Delta$%). The calculated values for all emissions with intensity > 0.01% can be found in the nuclear data tables of Martin and Blichert-Toft (1970). Table 9 shows the results for the three major β- and γ-radiation emissions from ^{131}I mentioned above. During the decay of the 'mixed' β-particle emitter ^{131}I, the energy contribution from γ-radiation is approximately twice that from β-radiation. The relative contribution of energy imparted to the surrounding medium (or the absorbed dose) by γ-rays will, however, be much lower in finite volumes because of the escaping fraction of this penetrating radiation. Therefore, the values of $\Delta/\Sigma\Delta$ for the α- and β-particle emissions, which have low penetration, represent lower limits to the relative contribution to dose of these emissions in cells and tissues.

3.2 *Physical aspects of exposure: Linear energy transfer*

Interactions of ionizing radiations in mammalian cells induce a large number of different types of molecular damage, which subsequently lead to a diversity of cellular responses, including cell killing, chromosomal aberrations, mutations and carcinogenesis. Most effects of direct relevance to humans are due to damage to individual cells, much of which is caused by alterations to macromolecules such as DNA. The effects that radiation has on the medium through which it passes and therefore its efficiency in producing biological effects are related not only to the amount of energy transferred per unit mass, i.e. the absorbed dose, but also to the microdistribution of energy, determined by the type of radiation. For different types of ionizing radiations, the numbers of moving charged particles (per unit dose) and the structures of their radiation tracks are different at all tissue, cellular and subcellular levels. Ionizing radiation deposits energy in the form of molecular ionizations and excitations from interaction of the individual moving particles with the medium. The highly structured spatial pattern of interactions from a particle and its secondary particles is termed the *radiation track* of the particle. Energy depositions within the

Figure 4. Decay of ^{131}I, showing the major β-particle and γ-ray emissions



Total energy difference between ^{131}I and ^{131}Xe is ~ 970 keV. The majority of the β-particles (~ 90%, β-1) have a maximum energy (E_{max}) of ~ 606 keV; the remaining 364 keV are contributed by γ-ray emission (γ-1). About 7% of the β-particles (β-2) have an E_{max} of ~ 334 keV, which is complemented by 636 keV of γ-ray emission (γ-2), while about 2% of the β-particles (β-3) have an E_{max} of ~ 248 keV, leaving 722 keV for γ-ray emission (γ-3). In each case, the γ-ray emission may in fact be a combination of various lower-energy γ-ray decays, as indicated. The remaining β-particle emissions (with maximum energies of ~ 807, 630 and 304 keV) together constitute about 1% of all β (see also Table 9).

Table 9. Energy contributions of the major β^- and γ-radiation emissions during radioactive decay of ^{131}I

^{131}I decay[a]	Energy (keV)[b]	Intensity (%)	Δ (kg.Gy/Bq.s)[c]	$\Delta/\Sigma\Delta$ (%)[d]
β-1	606.3 (192.2)	90.2 of all β	2.77×10^{-14}	32.2
β-2	333.9 (96.8)	7.0 of all β	0.11×10^{-14}	1.35
β-3	247.9 (69.5)	1.9 of all β	0.02×10^{-14}	0.2
γ-1	364.5	82.4 of all γ	4.81×10^{-14}	55.9
γ-2	636.9	6.9 of all γ	0.71×10^{-14}	8.2
γ-3	722.9	1.6 of all γ	0.19×10^{-14}	2.2

From Martin & Blichert-Toft (1970)

[a] Of the β^- and γ-radiation emissions, only the three major ones are listed (see Figure 4).

[b] For the β-particle emissions, the maximum energy is given; the value in parentheses is the average energy.

[c] Δ, energy emitted per disintegration for an infinite and homogeneous medium in which a source is homogeneously dispersed

[d] Relative contribution of this emission, expressed as percentage of all emissions

track occur as isolated ionizations and also as clusters of ionizations. This interaction is qualitatively different from the reactions of most other mutagens or carcinogens with a medium. At the cellular level, there is considerable non-uniformity at natural background doses, and at the DNA level there is massive non-uniformity at all doses. Measurements in randomly selected microscopic volumes yield energy concentrations or concentrations of subsequent radiation products that deviate considerably from their average values. These variations depend in intricate ways on the size of the reference volume, the magnitude of the dose and the type of ionizing radiation (ICRU, 1983; Kellerer, 1985; Goodhead, 1987, 1992).

The quality of radiation is commonly described in terms of LET, which is a measure of the average energy deposited per unit path length along the tracks of charged particles of given type and energy. Sparsely ionizing radiation, such as electrons, X-rays and γ-rays, produces on average only a few interactions per micrometre of track and is referred to as 'low-LET', whereas charged particles such as slow α-particles, which produce dense ionizations along their tracks, are generally referred to as 'high-LET' radiation.

Ionizing radiations produce tracks of ionizations and excitations which vary greatly with the stochastic nature of each atomic interaction. The stochastic aspects can be simulated down to atomic levels (sub-nanometre) by theoretical track structure codes, which provide most of the submicroscopic descriptions currently available (Paretzke *et al*., 1995; Nikjoo *et al*., 1998). Stochastic properties can also be measured experimentally by a variety of techniques, but mostly only over dimensions greater than about 0.3 μm (ICRU, 1983).

Over the dimensions of a mammalian cell and its internal structures, the tracks of ionizing radiations are the primary determinants of the nature and consequence of the damage. Radiolysis of water molecules, which constitute much of the cell contents, leads to the production of reactive free radicals (e.g. •OH), which diffuse on average only a few nanometres because of the high reactivity of the cellular environment (Roots & Okada, 1975). Therefore, the pattern of their points of reaction largely preserves the spatial structure of the track. For most biological end-points, DNA is believed to be the critical target. Damage to DNA can result either from direct interaction of the radiation with the DNA or from reactions with nearby radicals (•OH in particular) or from combinations of these two. Ionizing radiations can produce many different possible clusters of ionizations within a track and therefore of spatially adjacent damage within a macromolecule. Analyses of track structures caused by different types of radiations show that clustered DNA damage more complex than a single double-strand break can occur at biologically relevant frequencies with all types of ionizing radiations (Goodhead, 1987; Brenner & Ward, 1992; Goodhead, 1994). Such clustered damage in DNA is produced mainly within a single track, with a probability that increases with increasing ionization density. Damage from a single track can also be seen over larger dimensions in a cell, including within the chromatin structure, among chromosomes and among adjacent cells if the particle range is sufficient.

At the level of DNA and its structure, most of the information comes from theoretical simulations (Pomplun *et al*., 1996; Nikjoo *et al*., 1997), which led to quantitative estimates of the spectra of DNA damage, including single-strand breaks, simple double-strand breaks and complex double-strand breaks (simple double-strand breaks with additional damage within a few base-pairs). Calculations and experimental measurements showed that the total yield of double-strand breaks per unit absorbed dose is fairly independent of LET for a variety of common radiations; however, the complexity of double-strand breaks and their association with additional damage along the track is greater with higher LET radiations. In general, a substantial proportion of the double-strand breaks produced by ionizing radiations are more complex. It has been estimated that with low-LET radiations such as γ-rays and X-rays, about a quarter of all double-strand breaks have at least one additional break within a few base-pairs. α-Particle radiation induces a higher proportion of complex double-strand breaks, estimated as > 70% for 2-MeV α-particles, and much greater complexity (Goodhead & Nikjoo, 1997). The degree of complexity of the damage induced by all ionizing radiations is even greater if base damage is taken into account.

For a given absorbed dose, the total number of ionizations per unit mass is approximately independent of the type of ionizing radiation, i.e. the average energy per ionization is approximately constant. Nevertheless, the spatial distribution of the ionizations (i.e. radiation track) affects the spectrum of microscopic damage within the cell, as described above; in addition, the average ionization density or LET determines the fluence of particles per unit dose. The consequence for low-level radiation is that individual cells may receive no track at all or only single tracks well isolated in time

and space. For example, for a typical uniform, environmental γ-ray dose of 1 mGy/year (equivalent-dose rate, 1 mSv/year), each cell nucleus in a tissue will experience on average approximately one electron track per year. For 1 mGy of α-radiation (equivalent dose, 20 mSv), such as from radon, only about 0.3% of the nuclei in the irradiated tissue is struck by a track; the remaining 99.7% is totally unirradiated. The energy deposited in such individual single-track events does not depend on dose, and, therefore, the effect on individual cells does not change with tissue dose. At these low doses, only the proportion of cells that is subject to a track will vary linearly with the tissue dose.

Tracks not only directly affect cell nuclei, but there is now evidence that cellular effects, including mutations and chromosomal aberrations, can result from radiation tracks through the cell cytoplasm (Wu *et al*., 1999), and some responses can be induced even in nearby cells — an effect commonly referred to as the 'bystander effect' (Little, 2000).

Nevertheless, for uniform low-level exposures, individual radiation tracks usually remain quite isolated in time and space, unless very long-range and/or long-lived biological processes are involved. Exceptions may be seen after exposure of particular tissues to highly localized low-LET energy, for which the average whole-body effective dose is described as low level but the numbers of tracks in the target cells may be quite substantial.

The dose of all radionuclides to individual target cells within the body depends on the biodistribution of radionuclides. Even for high-energy penetrating radiations such as γ-rays, the dose to distant organs is reduced by geometric factors. For charged particle emissions, the location is even more critical, depending on the range of particles. The ranges can extend to several millimetres for high-energy β-particle emitters such as ^{32}P but are mostly < 0.1 mm for α-particle emitters. In the case of Auger decay, most Auger electrons are confined to single cells or subcellular compartments, and the biological effects vary greatly depending on whether the Auger emitter is attached to DNA, free in the nucleus or in the cytoplasm. Large differences in energy deposition, even at the organ and tissue levels, can occur with different radionuclides or radiolabelled compounds because of heterogeneous distribution of radionuclides, the stochastic nature of the radionuclide decay processes and the emission of short-range radiation (i.e. α-particles, low-energy β-particles, Auger electrons and low-energy X-rays). Detailed knowledge of the cellular and subcellular localization in the relevant tissue of the particular radionuclide and any associated molecule may be relevant before a full assessment can be made of the implications of the internal emitter.

Additional mechanisms of DNA damage may result from the presence of the nuclide within the cell. These include molecular effects after transmutation of a radionuclide to a different progeny nuclide, recoil of the progeny nucleus and charge accumulation on the progeny atom after an Auger cascade. If the decaying atom is appropriately positioned, the recoil nucleus may have considerable energy and can

cause considerable cellular damage. The effects of the recoil nucleus are not considered in this monograph.

(*a*) *γ-Rays*

γ-Rays typically travel long distances (many centimetres) from the emitting radionuclide before interacting in the tissue to eject low-LET electrons with ranges of micrometres to millimetres. The LET of electrons from ^{60}Co γ-rays averaged over their track is about 0.2 keV/μm. Typically high-energy electrons, such as those set in motion by interactions of X-rays and γ-rays, produce a spectrum of low-energy secondary electrons as they slow down and their LET increases, with an increase in scatter. A major part of the energy of high-energy electrons is deposited as sparse ionizations and excitations well isolated from others, but about 30% or more is deposited as more concentrated clusters of ionizations from secondary low-energy electrons, with energies ranging from about 100 eV to 5 keV (Nikjoo & Goodhead, 1991) and approximate values of LET ranging from 30 to 4 keV/μm, respectively (based on mass stopping powers).

(*b*) *α-Particles*

All natural α-particle emitters produce high-LET particles with a range in tissues of approximately 35–90 μm. The low-energy α-particle emitter ^{226}Ra produces α-particles of 4.8 MeV which have an initial LET of about 100 keV/μm. The high-energy emitter, ^{214}Po, produces α-particles of 7.7 MeV, which have a LET of about 70 keV/μm at the point of emission, rising to a maximum of about 200 keV/μm at the Bragg peak (about 0.6 MeV) and then decreasing for the remaining very short track. Due to the high ionization density of the α-particle tracks, they can cause gross and, presumably, unrepairable local damage at the DNA level and associated structures, over and above that achievable by low-LET radiations.

(*c*) *β-Particles*

β-Particles (electrons or positrons) have short to moderate ranges. For example, low-energy electrons from ^{3}H have a maximal range of about 7 μm, while higher-energy electrons from ^{40}K have a maximal range of about 6 mm. Low-energy electrons from β-particle decay have a higher LET. For example, 1-keV electrons have an average LET of about 13 keV/μm, and the effective ionization density is further enhanced by the high scatter and tortuous path of the electron. If β-particle emitters are incorporated into DNA, there is the additional possibility of biological effects due to transmutations of the nuclides themselves.

(*d*) *Auger electrons*

Depending on the radionuclide, Auger emitters emit multiple electrons with a typical range of energies from a few electron volts up to a few tens of kiloelectron

volts. The majority of Auger electrons are of low energy and are often emitted in large numbers after the decay of a single radionuclide (Humm *et al*., 1994). For example, ^{125}I decays first via electron capture to a metastable state of tellurium (^{125m}Te), which usually (93% of the transitions) undergoes electron capture. The number of electrons emitted in a single decay of ^{125}I may vary from 1 to about 50, many with energies < 1 keV and ranges of < 50 nm (Charlton *et al*., 1978; Charlton & Booz, 1981; Pomplun *et al*., 1996). Therefore, the ionization density is greatly enhanced very locally (within a few nanometres) around the point of decay, because of the proximity of many electrons. For this reason, Auger emitters are sometimes regarded as having the properties of high-LET radiation. Four general situations can be considered, depending on the location of the Auger-emitting radionuclides:

- Excluded from the target cell, the Auger electrons should have little mutagenic potential.
- Randomly distributed, the effect of the Auger electrons should be generally similar to that of β-particles.
- Selectively concentrated within cell nuclei, they should lead to a substantial enhancement of the effect.
- Incorporated into the DNA, Auger electrons from a single decay are capable of delivering a very localized dose which is larger than that delivered by a traversing α-particle. Therefore, the damage produced to DNA can be similar to that produced by high-LET radiation but without the substantial associated damage to other parts of the genome and adjacent cells.

3.3 *Biological aspects of exposure*

(*a*) *Non-uniform distribution of radionuclides in organs and tissues*

The third component of background exposure to ionizing radiation after cosmic rays and terrestrial γ-rays is that from the inhalation and ingestion of long-lived natural radionuclides. In terms of dose, the primordial radionuclides are ^{40}K (half-life, 1.3×10^9 years), ^{232}Th (1.4×10^{10} years) and ^{238}U (4.5×10^{10} years), with ^{87}Rb (4.7×10^{10} years) and ^{235}U (7.0×10^8 years) being of secondary importance (IARC, 2000).

Apart from specific exposures to ^{40}K, the concentrations of this radionuclide in soft tissues do not depend on those in food, water or air and are relatively constant, because the concentration of potassium is under homeostatic control in the body. The body content of potassium is about 0.2%, and the isotope abundance of ^{40}K is about 0.012%. The internal radiation is delivered mainly as β-particles and amounts to an annual effective dose equivalent of 165 μSv for adults and 185 μSv for children (UNSCEAR, 1993).

The internal doses from the radionuclides ^{232}Th, ^{238}U and their decay products reflect their intake from diet and air. Age-weighted annual intakes have been calculated by UNSCEAR (1993). The total annual effective doses associated with the

intake of long-lived radionuclides in the uranium and thorium series are 52 μSv by ingestion and 10 μSv by inhalation. Approximately 65% of this dose is from ^{210}Pb and is delivered mainly as β-particles (UNSCEAR, 1993; IARC, 2000).

It should be noted that radon is the most significant source of human exposure to radiation from natural sources. The average annual effective dose resulting from inhalation of radon and its short-lived decay products is estimated to be 1200 μSv (UNSCEAR, 1993).

Depending on the radionuclide, its radiation characteristics and the chemical form in which it enters the body, the subsequent radiation energy deposited may range from short, more or less uniform irradiation of all tissues to a highly heterogeneous distribution of dose. For example, $^{3}H_2O$ irradiates all the tissues of the body more or less uniformly, but, because the radionuclide is eliminated from the body with a biological half-time of about 10 days, the vast majority of the radiation dose is delivered within a period of ~ 15 days; the situation with ^{137}Cs is similar (see section 4.1), except that the radiation dose is delivered over a period of up to about one year. In such circumstances, the pattern of radiation effects may be very similar to that observed after a similar dose of external irradiation. When ^{137}Cs was injected into beagles, the pattern of late effects was similar to that observed after an equal dose of external γ-irradiation (Nikula *et al*., 1994).

In contrast, for bone-seeking radionuclides such as ^{239}Pu or ^{226}Ra, the combination of the long physical half-life of the radionuclide and its tenacious retention in the human skeleton means that this tissue will be irradiated for the remainder of the subject's life, and the major late effect of radiation is the induction of bone tumours. Similarly, the deposition of ^{232}Th (from the X-ray contrast medium Thorotrast) in the liver may lead to liver tumours, and the accumulation of ^{131}I in the thyroid may lead to malignancies in that gland. The biodistribution of radionuclides in human adults is shown in Table 10.

If the amount of the radionuclide that enters the body is sufficiently large, the resulting irradiation may lead to the appearance of acute effects. For example, damage to the intestinal mucosa has been observed in animals given large oral doses of insoluble radionuclides (Harrison, 1995). Varying degrees of bone-marrow depression were observed in some individuals exposed to ^{137}Cs internally and externally in an accident in Goiânia, Brazil (IAEA, 1988), and a variety of haematological deterministic effects have been reported in dogs exposed to bone-seeking radionuclides (Dougherty *et al*., 1962). Unplanned human intakes of radionuclides large enough to cause acute effects should be rare, however, and the major concern lies in the smaller intake of radionuclides which may result in the induction of neoplasia.

An important finding is that the carcinogenicity of the α-particle-emitting actinide radionuclides often differs quite markedly from that of ^{226}Ra. Lloyd *et al*. (1994) calculated the relative risks for induction of skeletal tumours in humans (Table 11). It can be seen that the bone surface-seekers ^{224}Ra, ^{228}Th, ^{239}Pu and ^{241}Am are five or more times more effective in inducing bone tumours than the bone volume-seeker ^{226}Ra, and the toxicity is attributed to decay of a greater fraction of these radionuclides

Table 10. Biodistribution of elements in human adults

Element	Principal deposition sites (% entering blood)	Retention half-time
Hydrogen	^3H_2O; similar concentration in all tissues	~ 10 days
Carbon	Similar concentrations in all tissues; dependent on type of compound	Up to 40 days
Phosphorus	Skeleton (30%)	> 20 years
Sulfur	Similar concentrations in all tissues; dependent on type of compound	Weeks to years
Gallium	Skeleton (30%), liver (~ 10%)	1–50 days
Strontium	Skeleton (25%)	≥ 20 years
Technetium	Pertechnetate; thyroid (4%), stomach (10%), liver (3%)	Thyroid, 12 h; other tissues, 2–22 days
Iodine	Thyroid (30%; range, 5–55%)	80 days
Caesium	Similar concentrations in all tissues	50–200 days
Plutonium	Liver (30%), skeleton (30%)	~ 20 years, > 20 years
Astatine	Stomach (14%), liver (5%), kidneys (3%), thyroid (2%)	Up to 2 days
Radon	Similar concentrations in all tissues except fatty tissues, where it is higher	
Radium	Skeleton (25%)	≥ 20 years
Thorium	Skeleton (~ 50%)	≥ 20 years
Uranium	Skeleton (~ 10%)	≥ 20 years
Neptunium	Liver (10%), skeleton (45–50%)	2–3 years, > 20 years
Polonium	Liver (~ 30%), kidney (10%), red bone marrow (10%)	~ 50 days
Americium	Liver (50%), skeleton (30%)	2–3 years, > 20 years
Curium	Liver (50%), skeleton (30%)	2–3 years, > 20 years

Based on data reviewed by ICRP (1979, 1980, 1981, 1989, 1993, 1995a,b)

close to bone surfaces. Decay close to bone surfaces is considered to be more effective in producing bone tumours because the cells of these tumours are in the soft tissues within bone spaces. The dosimetry is complicated considerably, however, by the growth processes within bone which result in redistribution of surface-deposited radionuclides. Accordingly, the dosimetry of bone-seeking radionuclides in general has been the topic of considerable research (Polig, 1978; Spiers *et al.*, 1978, 1981; Thorne, 1985; Spiers, 1988; Priest, 1990; Priest & Tasker, 1990; Austin *et al.*, 1999).

Table 11. Estimated risk coefficients for the induction of bone tumours by ^{226}Ra and other bone-seeking radionuclides, based on the human risk coefficient for ^{226}Ra and the relative toxicity of the other nuclides in beagle dogs

Radionuclide	Risk (%/Gy average skeletal dose) ± standard deviation
^{90}Sr	
High dose	0.17 ± 0.09
Low dose	0.009 ± 0.005
Very low dose	0.002 ± 0.002
^{224}Ra	
Single exposure	0.43 ± 0.14
Chronic exposure	2.74 ± 0.86
^{226}Ra	0.171
^{228}Ra	0.34 ± 0.09
^{228}Th	1.45 ± 0.40
^{239}Pu	
Monomeric	2.74 ± 0.86
Polymeric	5.50 ± 2.00
^{241}Am	1.00 ± 0.13

From Lloyd *et al*. (1994)

(*b*) *Non-uniform deposition of radionuclides at the cellular and subcellular level*

Non-uniform deposition at the cellular or subcellular level must also be taken into consideration. Inhaled, insoluble radioactive particles may be taken up by phagocytosis into macrophages, in the airway wall or in the alveoli of the lungs. If the particle contains an α- or soft β-particle-emitting radionuclide, high local doses may be given to the lung tissue immediately surrounding the macrophage. Dean and Langham (1969) pointed out that the local dose to the surrounding cells from a single particle of 0.2-μm diameter containing 590 Bq of ^{239}Pu engulfed in a fixed macrophage could be more than five orders of magnitude greater than the dose to the lung calculated on the assumption that the radiation is uniformly distributed throughout the lung tissue (1.4×10^4 Gy compared with 32 mGy).

Radioactive atoms of radionuclides of the actinide and lanthanide series and other easily hydrolysable metallic radionuclides (e.g. ^{67}Ga) may tend to aggregate and concentrate within lysosomes (Taylor, 1972; Berry *et al*., 1983; Tsan & Scheffel, 1986; Galle *et al*., 1992; Duffield *et al*., 1994). This creates a non-uniform distribution of the radioactivity at the intracellular level, which could in principle lead to more intense radiation-induced changes in the immediate vicinity of the decaying atom.

Other investigations have shown that, at least in liver cells, the intracellular distribution of plutonium and neptunium may also be mass dependent. Comparative studies of the intracellular distribution of ^{238}Pu and ^{239}Pu in rat hepatocytes *in vitro* indicated that ^{239}Pu tended to localize in the cell nuclei, whereas the higher-specific activity nuclide ^{238}Pu localized predominantly in the lysosomes (Schuler & Taylor, 1987). A mass-dependent difference in intracellular localization has been observed for neptunium. In rats 24 h after intravenous injection of 1.2 mg/kg bw ^{237}Np or 17 pg/kg bw ^{239}Np, the association of ^{237}Np with the liver cell nuclei was double that found with ^{239}Np (Paquet *et al*., 1996). Although these studies clearly indicated mass differences in the intracellular localization of neptunium and plutonium, the practical radiotoxicological significance of these observations remains to be assessed. Nevertheless, any possible nuclear association of radionuclides may have radiotoxicological importance, especially as the nuclides emit Auger electrons (e.g. ^{67}Ga and ^{125}I). The radiobiological effects of the various ^{125}I-labelled DNA precursors have been described (Hofer, 1998). The nuclear association of the Auger-emitting radiopharmaceutical ^{67}Ga citrate has been shown to be very low, probably less than several percent of the total cellular radioactivity being deposited in the cell nucleus.

Certain ^{3}H- and ^{14}C-labelled compounds, such as [^{3}H]- or [^{14}C]thymidine, may be incorporated preferentially into the DNA of dividing cells. In the case of ^{3}H, this may result in doses to the cell nucleus as much as 50 times those resulting from uniform distribution of ^{3}H throughout the cell. However, the average energy of the ^{14}C β-particle is about nine times larger than that of ^{3}H; thus, tissues are irradiated more uniformly from ^{14}C than they are from ^{3}H incorporated into DNA. It has been shown that the absorbed dose in a ^{14}C-labelled cell nucleus does not differ significantly from the mean dose from uniformly distributed ^{14}C compounds. The β-particle dose is not the only consideration, however, and transmutation effects could be important if ^{14}C is placed in molecular positions where such effects may arise, although there is little probability of incorporation of ^{14}C into such positions from most ^{14}C-labelled compounds (ICRP, 1981).

(*c*) *Factors that may modify radionuclide metabolism and toxicity*

A number of factors may modify radiotoxicity by altering the biokinetics of the radionuclide or influencing the tissue response. For example, pregnancy reduces the retention of ^{137}Cs (Thornberg & Mattsson, 2000), and sex influences its retention (Melo *et al*., 1997). The behaviour of a radionuclide after inhalation may be affected by allergies and diseases such as chronic bronchitis and emphysema. These conditions may affect the pattern of particle deposition and retention within the lung and may even influence the absorption of radionuclides from the lung. Smoking, which may cause chronic obstructive lung disease, can also alter the clearance of radionuclides and increase the risk for lung cancer (ICRP, 1994). Similarly, acute or chronic renal disease may decrease the natural rate of elimination of radionuclides from the body, thus increasing the radiation dose to organs and tissues.

Ever since the recognition that radionuclides deposited in the human body could induce cancer and related diseases, there has been wide interest in methods to accelerate their elimination from the body. This can be achieved either by preventing or decreasing their uptake into the systemic circulation from the site of entry and/or by enhancing their natural rate of excretion; the latter approach is often called decorporation therapy. The assumption made is that such treatment reduces the risks for radiation-induced late effects (Taylor *et al*., 2000).

The management of radionuclide contamination has been reviewed, including discussion of such questions as the radiation doses at which treatment is appropriate and the indications and contraindications for treatment (Volf, 1978; Bhattacharrya *et al*., 1992; Hengé-Napoli *et al*., 2000). The medical aspects of decorporation treatment of workers and the general public have also been reviewed (Wood *et al*., 2000). Possible treatment includes lung washing (lavage) (Nolibé *et al*., 1975) and decorporation therapy with chelating agents such as salts of diethylenetriaminepentaacetic acid (Breitenstein & Palmer, 1989).

3.4 *Target tissues*

(*a*) *Liver*

In the period 1930–55, a large number of patients were injected intravenously with a colloidal suspension of thorium dioxide (Thorotrast) to allow visualization of the vascular system. Because of its colloidal characteristics, most Thorotrast is deposited within the reticuloendothelial system, principally in the liver, spleen, bone marrow and lymph nodes, for life. Approximately 60% of injected Thorotrast remains in the liver, where it induces deterministic effects (fibrosis, cirrhosis and peliosis) and causes cancer after a latency of more than 10 years (Ishikawa *et al.*, 1989; Andersson *et al.*, 1994; van Kaick *et al.*, 1995; Mori *et al.*, 1995). The relative risk of these patients for dying from liver cancer has been found to be 129 in Germany and 36 in Japan. In comparison with the general population, the risk for liver cancer was 121 in Denmark and 71 in Portugal (see section 2 of the monograph) (van Kaick *et al.*, 1999; Andersson, 1997; Mori *et al.*, 1999a,b; Martling *et al.*, 1999; dos Santos Silva *et al.*, 1999).

In the Danish study, three types of liver cancer were observed: hepatocellular carcinoma, cholangiocarcinoma and angiosarcoma, about two-thirds being carcinomas and one-third angiosarcomas. A specific feature of Thorotrast-induced liver cancers is the high proportion of cholangiocarcinomas and angiosarcomas (Andersson *et al.*, 1994).

(*b*) *Lung*

Radioactive gases and particles may enter the body by inhalation. The main exposure of concern for public health is inhalation of the short-lived decay products (^{218}Po and ^{214}Po) of the noble gas ^{222}Rn. A number of studies, including a joint analysis of 11 cohorts of underground miners, revealed carcinogenic effects of radon and its decay products (IARC, 1988; Lubin *et al*., 1994a). A combined analysis of the studies

of miners showed that the excess relative risk for lung cancer was linearly related to cumulative exposure to radon progeny, estimated as WLM. The overall estimate of excess relative risk per WLM was 0.49% (Lubin *et al.*, 1994). Whether residential exposure to radon is also carcinogenic is more controversial and is discussed in the monograph.

The commonest primary lung tumours in the male population of the USA are squamous-cell carcinoma (35%), small-cell carcinoma (17%), adenocarcinoma (25%) and large-cell carcinoma (9%) (Percy & Sobin, 1983). The distribution of the histological types of the lung cancers observed in the case–control studies of residential exposure to radon presented in section 2 of the monograph reflects these proportions. In uranium miners (especially in the 1950s), small-cell carcinomas represented the majority of cases until the late 1970s (Saccomanno *et al.*, 1996; Wiethege *et al.*, 1999).

(*c*) *Bone*

Exposure to external radiation or to bone-seeking radionuclides may result in damage to the skeletal system including growth disturbances, degenerative and reparative processes in the osseous tissue and the formation of bone tumours. An extensive review of the literature on the pathological effects of irradiation on the skeleton was published (Vaughan, 1973). The first cases of malignant bone tumours occurring after therapeutic X-irradiation were reported by Beck (1922), and detailed reports of post-irradiation neoplasia in bone after therapeutic external irradiation have been published (Unni, 1996). Bone sarcomas subsequent to internal radiation from ^{226}Ra and ^{228}Ra were first reported in radium-dial workers by Martland and Humphries (1929). About 64 cases of malignant bone tumours were observed in about 2600 patients (Rowland, 1994; Fry, 1998). A detailed study of the histopathology of ^{226}Ra- and ^{228}Ra-induced bone sarcomas in humans has been published (Schlenker *et al.*, 1989). Induction of bone sarcomas was also observed in patients with tuberculosis or ankylosing spondylitis treated with the short-lived α-particle-emitting ^{224}Ra. In a cohort of 899 patients (455 with tuberculosis, including 214 under the age of 21 years) treated with high doses of ^{224}Ra (mean bone surface dose, about 30 Gy), 56 malignant bone tumours occurred, with less than one expected (Nekolla *et al.*, 2000). In 1577 patients exposed to ^{224}Ra as therapy for ankylosing spondylitis (mean bone surface dose, about 5 Gy), four bone tumours were found, with 1.3 cases expected from statistics for the general population (Wick *et al*., 1999).

A revision of the histology of bone tumours in patients treated with ^{224}Ra revealed a high proportion of bone sarcomas of the fibrous connective tissue type. A comparison with bone sarcomas arising after incorporation of ^{226}Ra, ^{228}Ra and external irradiation and with tumours arising at sites of pre-existing bone lesions (Paget disease) showed the same spectrum of tumours. These results suggest that the cells at risk are not fully committed to bone formation (probably multipotent mesenchymal precursors) and that a close histogenetic relationship may exist between disorders of

the microenvironment caused by deterministic radiation damage (osteodysplasia) and the induction of these fibrous connective tissue-type bone sarcomas (Gössner, 1999).

(*d*) *Thyroid gland*

The only radionuclides that are actively absorbed in the thyroid gland are the radioiodines. The healthy thyroid gland absorbs 20–30% of ingested ^{131}I, but a patient with hyperthyroidism could absorb as much as 60%, and almost none might be absorbed after administration of stable iodine. ^{131}I is essentially a β-particle emitter, contributing 85% of the absorbed tissue dose, while the contribution of γ-radiation is 15%. This fact is used in medical practice, where radioiodines have been administered for the last 50 years in the treatment of hyperthyroidism and thyroid cancer. Radioiodine not only locally irradiates the thyroid gland but also becomes associated with thyroid hormones, thus influencing other organs of the body.

Thyroid cancers can be differentiated (papillary, follicular and medullary) or undifferentiated (anaplastic carcinoma). The thyroid cancer known to be caused by ionizing radiation is papillary carcinoma, as shown among the atomic bomb survivors (Wood *et al.*, 1969) and recently in the Chernobyl area. In a study of 577 Ukrainian patients less than 19 years of age in whom thyroid cancer was diagnosed, 290 cases were evaluated histopathologically and > 90% were found to be papillary carcinomas (Tronko *et al.*, 1999). Similar frequencies were seen in a study in the USA of 4296 patients previously irradiated for benign disorders: thyroid cancers were found in 41 children (mean age at diagnosis, 16 years), of which 95% were papillary carcinomas (Visvanathan *et al.*, 1994). Thyroid nodules have also been related to exposure to radioiodine (Hall *et al.*, 1996).

(*e*) *Haematopoietic tissues*

Various types of leukaemia, with the exception of chronic lymphocytic leukaemia and adult T-cell leukaemia, are known to be caused by external irradiation, as shown among the atomic bomb survivors (Preston *et al.*, 1994).

The studies of patients treated with Thorotrast showed that 10–25% of the injected dose is deposited in the bone marrow; the effects are deterministic (aplastic anaemia) and carcinogenic (myelodysplastic syndrome and leukaemia). In a combined analysis of patients in Germany and Denmark, the following subtypes of leukaemia were seen: acute myeloid leukaemia (52%), myelodysplastic syndrome (39%), chronic myeloid leukaemia (7%) and acute lymphoblastic leukaemia (2%). The corresponding figures for the atomic bomb survivors are 39%, 8%, 20% and 33%, respectively. A much higher frequency of myelodysplastic syndrome and a lower frequency of acute and chronic leukaemia were found among the Thorotrast-treated patients than among the atomic bomb survivors (Visfeldt & Andersson, 1995).

4. References

Anderson, E.C., Holland, L.M., Prine, J.R. & Smith, D.M. (1979) Lung tumorigenesis in the Syrian hamster from particulate sources of ^{147}Pm β radiation. *Radiat. Res.*, **79**, 349–367

Andersson, M. (1997) Long-term effects of internally deposited α-particle emitting radionuclides. *Dan. med. Bull.*, **44**, 169–190

Andersson, M., Vyberg, M., Visfeldt, J., Carstensen, B. & Storm, H.H. (1994) Primary liver tumors among Danish patients exposed to Thorotrast. *Radiat. Res.*, **137**, 262–273

Austin, A.L., Ellender, M., Haines, J.W., Harrison, J.D. & Lord, B.I. (1999) Temporal change in microdosimetry to bone marrow and stromal progenitor cells from alpha-particle-emitting radionuclides incorporated in bone. *Radiat. Res.*, **152**, S38–S42

Beck, A. (1922) [On the question of X-ray induced sarcoma; a contribution to the pathogenesis of sarcoma]. *Munch. Medizin. Wochenschr.*, **17**, 623–625 (in German)

Berry, J.P., Escaig, F., Poupon, M.F. & Galle, P. (1983) Localization of gallium in tumor cells. Electron microscopy, electron probe microanalysis and analytical ion microscopy. *Int. J. nucl. Med. Biol.*, **10**, 199–204

Bhattacharrya, M.H., Breitenstein, B.D., Métivier, H., Muggenburg, B.A., Stradling, G.N. & Volf, V. (1992) Guidebook for the treatment of accidental internal radionuclide contamination of workers. *Radiat. Prot. Dosim.*, **41**, 1–49

Boice, J.D., Jr, Land, C.E. & Preston, D.L. (1996) Ionizing radiation. In: Schottenfeld, D. & Fraumeni, J.F., Jr, eds, *Cancer Epidemiology and Prevention*, New York, Oxford University Press, pp. 319–354

Breitenstein, B.D. & Palmer, H.E. (1989) Lifetime follow-up of the 1976 americium accident victim. *Radiat. Prot. Dosim.*, **26**, 317–322

Brenner, D.J. & Ward, J.F. (1992) Constraints on energy deposition and target size of multiply-damaged sites associated with DNA double-strand breaks. *Int. J. Radiat. Biol.*, **61**, 737–748

Burkart, W. (1991) Lung cancer and alpha radiation. *Soz. Präventivmed.*, **36**, 255–265

Burkart, W. (1996) Radioepidemiology of the aftermath of the nuclear program of the former Soviet Union: Unique lessons to be learnt. *Radiat. Environ. Biophys.*, **35**, 65–73

Charlton, D.E. & Booz, J. (1981) A Monte Carlo treatment of the decay of ^{125}I. *Radiat. Res.*, **87**, 10–23

Charlton, D.E., Booz, J., Fidorra, J., Smith, T. & Feinendegen, L.E. (1978) Microdosimetry of radioactive nuclei incorporated into the DNA of mammalian cells. In: Booz, J. & Ebert, H.G., eds, *Sixth Symposium on Microdosimetry*, Newark, NJ, Harwood Academic, pp. 91–110

Dagle, G.E., Cannon, W.C., Stevens, D.L. & McShane, J.F. (1983) Comparative disposition of inhaled ^{238}Pu amd ^{239}Pu nitrates in beagles. *Health Phys.*, **44**, 275–277

Dean, P.N. & Langham, W.H. (1969) Tumorigenicity of small highly radioactive particles. *Health Phys.*, **16**, 79–84

Dougherty, T.F., Stover, B.J., Dougherty, J.H., Jee, W.S.S., Mays, C.W., Rehfeld, C.E., Christensen, W.R. & Goldthorpe, H.C. (1962) Studies of the biological effects of Ra^{226}, Pu^{239}, Ra^{228}($MsTh_1$), Th^{228}(RdTh), and Sr^{90} in adult beagles. *Radiat. Res.*, **17**, 625–681

Duffield, J.R., Taylor, D.M. & Williams, D.R. (1994) The biochemistry of the f-elements. In: Gschneider, K.A., Jr, Eyring, L., Choppin, G.R. & Lander, G.H., eds, *Handbook of the Physics and Chemistry of the Rare Earths*, Vol. 18, *Lanthanides/Actinides*, Amsterdam, Elsevier Science, pp. 591–621

Fry, S.A. (1998) Studies of US radium dial workers: An epidemiological classic. *Radiat. Res.*, **150** (Suppl.), S21–S29

Galle, P., Boulahdour, H. & Métivier, H. (1992) [Selective localization of neptunium-237 in nuclei of mammalian cells.] *C. R. Acad. Sci. III*, **314**, 1–5 (in French)

Goodhead, D.T. (1987) Relationship of microdosimetric techniques to applications in biological systems. In: Kase, K.R., Bjärngard, B.E. & Attix, F.H., eds, *The Dosimetry of Ionizing Radiation*, Vol. II, Orlando, FL, Academic Press, pp. 1–89

Goodhead, D.T. (1992) Track structure considerations in low dose and low dose rate effects of ionizing radition. *Adv. Radiat. Biol.*, **16**, 7–44

Goodhead, D.T. (1994) Initial events in the cellular effects of ionizing radiations: Clustered damage in DNA. *Int. J. Radiat. Biol.*, **65**, 7–17

Goodhead, D.T. & Nikjoo, H. (1997) Clustered damage in DNA: Estimates from track structure simulations. *Radiat. Res.*, **148**, 485–486

Gössner, W. (1999) Pathology of radium-induced bone tumors: New aspects of histopathology and histogenesis. *Radiat. Res.*, **152**, S12–S15

Hall, P., Fürst, C.J., Mattson, A., Holm, L.-E., Boice, J.D., Jr & Inskip, P.D. (1996) Thyroid nodularity after diagnostic administration of iodine 131. *Radiat. Res.*, **146**, 673–682

Harrison, J.D. (1995) Ingested radionuclides. In: Potten, C.S. & Hendry, J.H., eds, *Radiation and Gut*, Amsterdam, Elsevier Science, pp. 253–289

Hengé-Napoli, M.H., Stradling, N.G. & Taylor, D.M. (2000) Decorporation of radionuclides from the human body. *Radiat. Prot. Dosim.*, **87**, 1–57

Hill, R.L. & Johnson, J.R. (1993) Metabolism and dosimetry of tritium. *Health Phys.*, **65**, 628–647

Hofer, K.G. (1998) Dosimetry and biological effects of incorporated Auger emitters. *Radiat. Prot. Dosim.*, **79**, 405–410

Hopewell, J.W., Sieber, V.K., Heryet, J.C., Wells, J. & Charles, M.W. (1993) Dose- and source-size-related changes in the late response of pig skin to irradiation with single doses of beta radiation from sources of differing energy. *Radiat. Res.*, **133**, 303–311

Humm, J.L., Howell, R.W. & Rao, D.V. (1994) Dosimetry of Auger-electron emitting radionuclides: Report No. 3 of AAPM Nuclear Medicine Task Group No. 6. *Med. Phys.*, **21**, 1901–1915

IAEA (International Atomic Energy Agency) (1988) *The Radiological Accident in Goiânia (STI/PUB/815)*, Vienna

IARC (1988) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 43, *Man-made Mineral Fibres and Radon*, Lyon, IARC*Press*, pp. 173–259

IARC (2000) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 75, *Ionizing Radiation, Part 1: X- and Gamma(γ)-Radiation, and Neutrons*, Lyon, IARC*Press*

ICRP (International Commission on Radiological Protection) (1968) *Evaluation of Radiation Doses to Body Tissues from Internal Contamination due to Occupational Exposure* (ICRP Publication 10), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1975) *Report of the Task Group on Reference Man* (ICRP Publication 23), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1979) *Limits for Intakes of Radionuclides by Workers*, Part 1 (ICRP Publication 30; Annals of the ICRP, Vol. 2, No. 3/4), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1980) *Limits for Intakes of Radionuclides by Workers*, Part 2 (ICRP Publication 30; Annals of the ICRP, Vol. 4, No. 3/4), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1981) Limits for intakes of radionuclides by workers (ICRP Publication 30, Part 3; Annals of the ICRP, Vol. 6), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1986) The metabolism of plutonium and related elements (ICRP Publication 48; Annals of the ICRP, Vol. 16, No. 2/3), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1988) Radiation dose to patients from radiopharmaceuticals (ICRP Publication 53; Annals of the ICRP, Vol. 18), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1989) Age-dependent doses to members of the public from intake of radionuclides: Part 1 (ICRP Publication 56; Annals of the ICRP, Vol. 20), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1991) 1990 Recommendations of the International Commission on Radiological Protection (ICRP Publication 60; Annals of the ICRP, Vol. 21), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1993) Age-dependent doses to members of the public from intake of radionuclides: Part 2. Ingestion dose coefficients (ICRP Publication 67; Annals of the ICRP, Vol. 23), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1994) Human respiratory tract model for radiological protection (ICRP Publication 66; Annals of the ICRP, Vol. 24), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1995a) Age-dependent doses to members of the public from intake of radionuclides: Part 3. Ingestion dose coefficients (ICRP Publication 69; Annals of the ICRP, Vol. 25), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1995b) Age-dependent doses to members of the public from intake of radionuclides: Part 4. Inhalation dose coefficients (ICRP Publication 71; Annals of the ICRP, Vol. 25), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1995c) Dose coefficients for intakes of radionuclides by workers (ICRP Publication 68; Annals of the ICRP, Vol. 24), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1996) Age-dependent doses to members of the public from intake of radionuclides: Part 5. Compilation of ingestion and inhalation dose coefficients (ICRP Publication 72; Annals of the ICRP, Vol. 26), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1998) Radiation dose to patients from radiopharmaceuticals. Addendum to ICRP 53 (ICRP Publication 80; Annals of the ICRP, Vol. 28), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1999) *The ICRP Database of Dose Coefficients: Workers and Members of the Public (Version 1.0)*, Amsterdam, Pergamon [CD-ROM]

ICRU (International Commission on Radiation Units and Measurements) (1983) *Microdosimery* (ICRU Report 36), Bethesda, MD, 68–71

Ishikawa, Y., Kato, Y. & Hatakeyama, S. (1989) Late effects of alpha-particles on Thorotrast patients in Japan. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology, pp. 129–131

van Kaick, G., Wesch, H., Lührs, H., Liebermann, D. & Kaul, A. (1995) Epidemiologic results and dosimetric calculations — An update of the German Thorotrast study. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 171–175

van Kaick, G., Dalheimer, A., Hornik, S., Kaul, A., Liebermann, D., Lührs, H., Spiethoff, A., Wegener, K. & Wesch, H. (1999) The German Thorotrast Study: Recent results and assessment of risks. *Radiat. Res.*, **152**, S64–S71

Kellerer, A.M. (1985) Fundamentals of microdosimetry. In: Kase, K.R., Bjarngard, B.E. & Attix, F.H., eds, *Dosimetry of Ionizing* Radiation, Vol. 1, Orlando, FL, Academic Press, pp. 77–162

Little, J.B. (2000) Radiation carcinogenesis. *Carcinogenesis*, **21**, 397–404

Lloyd, R.D., Miller, S.C., Taylor, G.N., Bruenger, F.W., Jee, W.S.S. & Angus, W. (1994) Relative effectiveness of ^{239}Pu and some other internal emitters for bone cancer induction in beagles. *Health Phys.*, **67**, 346–353

Lubin, J.H., Boice, J.D., Jr, Edling, C., Hornung, R.W., Howe, G., Kunz, E., Kusiak, R.A., Morrison, H.I., Radford, E.P., Samet, J.M., Tirmarche, M., Woodward, A., Yao, X.S. & Pierce, D.A. (1994) *Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Studies* (NIH Publication No. 94-3644), Bethesda, MD, National Cancer Institute

Martin, M.J. & Blichert-Toft, P.H. (1970) Radioactive atoms; Auger electron, alpha, beta, gamma and X-ray data. *Nucl. Data Tables*, **A8**, 1–198

Martland, H.S. & Humphries, R.E. (1929) Osteogenic sarcoma in dial painters using luminous paint. *Arch. Pathol.*, **7**, 406–417

Martling, U., Mattsson, A., Travis, L.B., Holm, L.-E. & Hall, P. (1999) Mortality after long-term exposure to radioactive Thorotrast: A forty-year follow-up survey in Sweden. *Radiat. Res.*, **151**, 293–299

Melo, D.R., Lipsztein, J.L., Oliveira, C.A., Lundgren, D.L., Muggenburg, B.A. & Guilmette, R.A. (1997) A biokinetic model for ^{137}Cs. *Health Phys.*, **73**, 320–332

Mori, T., Kato, Y., Matsudaira, H., Akita, Y., Fukutomi, K., Hatakeyama, S., Tanooka, H., Marayama, T. & Kumatori, T. (1995) Recent results in the first series of the Japanese follow-up study of Thorotrast patients and their relationships with statistical analyses of autopsy series. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 181–191

Mori, T., Fukutomi, K., Kato, Y., Hatakeyama, S., Machinami, R., Tanooka, H., Ishikawa, Y. & Kumatori, T. (1999a) 1998 results of the first series of follow-up studies on Japanese Thorotrast patients and their relationships to an autopsy series. *Radiat. Res.*, **152**, S72–S80

Mori, T., Kido, C., Fukutomi, K., Kato, Y., Hatakeyama, S., Machinami, R. Ishikawa, Y., Kumatori, T., Sasaki, F., Hirota, Y., Kiyosawa, K., Hayashi, S., Tanooka, H. & Sobue, T. (1999b) Summary of entire Japanese Thorotrast follow-up study: Updated 1998. *Radiat. Res.*, **152**, S84–S87

National Council on Radiation Protection and Measurements (1997) *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (NCRP Report No. 125), Bethesda, MD

Nekolla, E.A., Kreisheimer, M., Kellerer, A.M., Kuse-Isingschulte, M., Gössner, W. & Spiess, H. (2000) Induction of malignant bone tumors in radium-224 patients: Risk estimates based on the improved dosimetry. *Radiat. Res.*, **153**, 93–103

Nikjoo, K. & Goodhead, D.T. (1991) Track structure analysis illustrating the prominent role of low-energy electrons in radiobiological effects of low-LET radiations. *Phys. Med. Biol.*, **36**, 229–238

Nikjoo, H., O'Neill, P., Goodhead, D.T. & Terrissol, M. (1997) Computational modelling of low-energy electron-induced DNA damage by early physical and chemical events. *Int. J. Radiat. Biol.*, **71**, 467–473

Nikjoo, H., Uehara, S., Wilson, W.E., Hoshi, M. & Goodhead, D.T. (1998) Track structure in radiation biology: Theory and applications. *Int. J. Radiat. Biol.*, **73**, 355–364

Nikula, K.J., Muggenburg, B.A., Griffith, W.C., Hahn, F.F. & Boecker, B.B. (1994) Late biological effects of ^{137}CsCl injected into beagle dogs. In: Belinsky, S.A., Hoover, M.D. & Bradley, P.L., eds, *Annual Report of the Inhalation Toxicology Research Institute* (ITRI-144), Albuquerque, NM, Inhalation Toxicology Research Institute, pp. 84–87

Nolibé, D., Métivier, H., Masse, R. & Lafuma, J. (1975) Therapeutic effect of pulmonary lavage in vivo after inhalation of insoluble radioactive particles. *Inhaled Part.*, **4**, 597–613

Paquet, F., Ramounet, B., Métivier, H. & Taylor, D.M. (1996) The effect of the mass and initial chemical form of neptunium on its molecular association in blood and liver. *Radiat. Res.*, **146**, 306–312

Paretzke, H.G., Goodhead, D.T., Kaplan, I.G. & Terrissol, M. (1995) Atomic and molecular data for radiotherapy and radiation research. In: *International Atomic Energy Agency Report* (IAEA-TECDOC-799), Vienna, International Atomic Energy Agency, pp. 633–721

Percy, C. & Sobin, L. (1983) Surveillance, epidemiology, and end results lung cancer data applied to the World Health Organization's classifications of lung tumors. *J. natl Cancer Inst.*, **70**, 663–666

Polig, E. (1978) The localized dosimetry of internally deposited alpha-emitters. *Curr. Top. Radiat. Res.*, **13**, 189–327

Pomplun, E., Terrissol, M. & Demonchy, M. (1996) Modelling of initial events and chemical behaviour of species induced in DNA units by Auger electrons from ^{125}I, ^{123}I and carbon. *Acta oncol.*, **35**, 857–862

Preston, D.L., Kusumi, S., Tomonaga, M., Izumi, S., Ron, E., Kuramoto, A., Kamada, N., Dohy, H., Matsuo, T., Nonaka, H., Thompson, D.E., Soda, M. & Mabuchi, K. (1994) Cancer incidence in atomic bomb survivors, Part III. Leukemia, lymphoma, and multiple myeloma 1950–1987. *Radiat. Res.*, **137**, S68–S97

Priest, N.D. (1990) The distribution and behaviour of heavy metals in the skeleton and bone: Studies with bone-seeking radionuclides. In: Priest, N.D. & van de Vyver, F., eds, *Trace Metals and Fluoride in Bones and Teeth*, Boca Raton, FL, CRC Press, pp. 83–139

Priest, N.D. & Tasker, A. (1990) The toxicity of plutonium in the skeleton. *Atom*, **October**, 16–19

Roots, R. & Okada, S. (1975) Estimation of life times and diffusion distances of radicals involved in X-ray-induced DNA strand breaks or killing of mammalian cells. *Radiat. Res.*, **64**, 306–320

Rowland, R.E. (1994) *Radium in Humans. A Review of US Studies*, Argonne, IL, Argonne National Laboratory

Saccomanno, G., Auerbach, O., Kuschner, M., Harley, N.H., Michels, R.Y., Anderson, M.W. & Bechtel. J.J. (1996) A comparison between the localization of lung tumors in uranium miners and in nonminers from 1947 to 1991. *Cancer*, **77**, 1278–1283

dos Santos Silva, I., Jones, M., Malveiro, F. & Swerdlow, A. (1999) Mortality in the Portugese Thorotrast Study. *Radiat. Res*., **152**, S88–S92

Schlenker, R.A., Keane, A.T. & Unni, K.K. (1989) Comparison of radium-induced and natural bone sarcomas by histological type, subject age and site of occurrence. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology, pp. 55–63

Schuler, F. & Taylor, D.M. (1987) The subcellular distribution of ^{238}Pu and ^{239}Pu in primary cultures of rat hepatocytes. *Radiat. Res*., **110**, 362–371

Spiers, F.W. (1988) Particle dosimetry in bone and the toxicity of bone-seeking radionuclides. *Phys. med. Biol*., **33**, 395–411

Spiers, F.W., Whitwell, J.R. & Beddoe, A.H. (1978) Calculated dose factors for the radio-sensitive tissues in bone irradiated by surface-deposited radionuclides. *Phys. med. Biol.*, **23**, 481–494

Spiers, F.W., Beddoe, A.H. & Whitwell, J.R. (1981) Mean skeletal dose factors for beta-particle emitters in human bone. Part II: Surface-seeking radionuclides. *Br. J. Radiol*., **54**, 500–504

Taylor, D.M. (1972) Interactions between transuranium elements and the components of cells and tissues. *Health Phys*., **22**, 575–581

Taylor, D.M., Stradling, G.N. & Hengé-Napoli, M.-H. (2000) The scientific background to decorporation. *Radiat. Prot. Dosim*., **87**, 11–17

Thornberg, C. & Mattsson, S. (2000) Increased ^{137}Cs metabolism during pregnancy. *Health Phys*., **78**, 502–506

Thorne, M.C. (1985) Microdisimetry of bone: Implications in radiological protection. In: Priest, N.D., ed., *Metals in Bone*, Lancaster, MTP Press, pp. 249–268

Tronko, M., Bogdanova, T., Komisarenko, I., Rybakov, S., Kovalenko, A., Epshtein, O., Oliynyk, V., Tereshchenko, V., Likhtarev, I.A., Kairo, I. & Chepurnoy M. (1999) The post-Chernobyl incidence of childhood thyroid cancer in Ukraine. In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer (EUR 18552 EN)*, Singapore, World Scientific, pp. 61–70

Tsan, M.-F. & Scheffel, U. (1986) Mechanism of gallium-67 accumulation in tumors. *J. nucl. Med*., **27**, 1215–1219

Unni, K.K. (1996) *Dahlin's Bone Tumors. General Aspects and Data on 11,087 Cases*, 5th Ed., Philadelphia, PA, Lippincott–Raven

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1982) *Ionizing Radiation: Sources and Biological Effects* (United Nations Sales Publication E.82.IX.8), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1988) *Sources, Effects and Risks of Ionizing Radiation* (United Nations Sales Publication E.88.IX.7), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1993) *Sources and Effects and Risks of Ionizing Radiation* (United Nations Sales Publication E.94.IX.2), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1994) *Sources and Effects of Ionizing Radiation* (United Nations Sales Publication E.94.IX.11), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2000) *Sources and Effects of Ionizing Radiation*, Vols I and II (United Nations Sales Publications E.00.IX.3 and E.00.IX.4), New York, United Nations

Vaughan, J.M. (1973) *The Effects of Irradiation on the Skeleton*, Oxford, Clarendon Press

Visfeldt, J. & Andersson, M. (1995) Pathoanatomical studies of leukemia and other related haematological disorders among 1003 Danish patients exposed to Thorotrast. In: van Kaick, G., Karaoglu, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium*, Singapore, World Scientific, pp. 53–67

Visvanathan, K., Gierlowski, T.C. & Schneider, A.B. (1994) Childhood thyroid cancer. Characteristics and long-term outcome in children irradiated for benign conditions of the head and neck. *Arch. Pediatr. Adolesc. Med.*, **148**, 260–265

Volf, V. (1978) *Treatment of Incorporated Transuranium Elements* (Technical Report Series No. 184), Vienna, International Atomic Energy Agency

Wick, R.R., Nekolla, E.A., Gössner, W. & Kellerer, A.M. (1999) Late effects in ankylosing spondylitis patients treated with ^{224}Ra. *Radiat. Res.*, **152**, S8–S11

Wiethege, T., Wesch, H., Wegener, K., Müller, K.-M., Mehlborn, J., Spiethoff, A., Schömig, D., Hollstein, M., Bartsch, H. and the German Uranium Miner Study, Research Group Pathology (1999) German uranium miner study — Pathological and molecular genetic findings. *Radiat. Res.*, **152**, 552–555

Wood, J.W., Tamagaki, H., Neriishi, S., Sato, T., Sheldon, W.F., Archer, P.G., Hamilton, H.B. & Johnson, K.G. (1969) Thyroid carcinoma in atomic bomb survivors, Hiroshima and Nagasaki. *Am. J. Epidemiol.*, **89**, 4–14

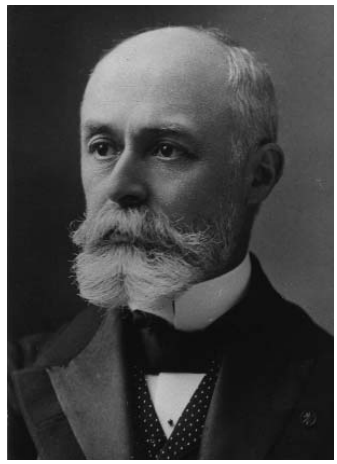
Wood, R., Sharp, C., Gourmelon, P., Le Guen, B., Stradling, G.N., Taylor, D.M. & Hengé-Napoli, M.H. (2000) Decorporation treatment — medical overview. *Radiat. Prot. Dosim.*, **87**, 51–57

Wu, L.-J., Randers-Pehrson, G., Xu, A., Waldren, C.A., Geard, C.R., Yu, Z. & Hei, T.K. (1999) Targeted cytoplasmic irradiation with alpha particles induces mutations in mammalian cells. *Proc. natl Acad. Sci. USA*, **96**, 4959–4964

SOME INTERNALLY DEPOSITED RADIONUCLIDES

Three scientists shared the Nobel prize in Physics in 1903, in recognition of their work on radioactivity and radionuclides:

Antoine Henri Becquerel (1852–1908)

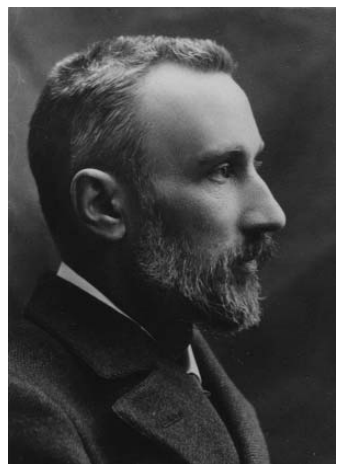


Ecole Polytechnique, Paris, France

'In recognition of the extraordinary services he has rendered by his discovery of spontaneous radioactivity'

Marie Curie (1867–1934)

Pierre Curie (1859–1906)



Ecole Municipale de Physique et de Chimie Industrielles, Paris, France

'In recognition of the extraordinary services they have rendered by their joint researches on the radiation phenomena discovered by Professor Henri Becquerel'

1. Exposure Data

1.1 Environmental exposure

1.1.1 *Detonation of nuclear weapons*

(*a*) *Sources*

The most important source of radioactive fall-out from nuclear explosions is the large number of nuclear weapons tests carried out in various parts of the world since 1945. A total of 543 identified atmospheric tests have been conducted worldwide. The largest number of atmospheric tests was carried out in the 1950s and in 1961–62 by the former Soviet Union (USSR) and the United States of America (USA). These countries and the United Kingdom ended their atmospheric testing after signing a limited test ban treaty (banning atmospheric tests) in 1963, but France and China conducted additional tests — although fewer — until 1974 and 1980, respectively. A larger number of underground nuclear tests (over 1850) have been carried out, but these resulted in less human exposure than the atmospheric tests. The majority of the underground tests were conducted after 1963 (Bouville *et al.*, 2000; UNSCEAR, 2000).

Fall-out can occur from other nuclear explosions. About 100 underground nuclear explosions have been carried out for peaceful purposes, such as excavation, mining and cratering, in the USA and the former USSR. The estimated collective doses from these peaceful nuclear explosions are very low. A similarly low collective dose is estimated to have resulted from the burn-up and re-entry of satellite power sources, which are commonly fuelled with ^{238}Pu (UNSCEAR, 1993). Another source is the wartime use of atomic bombs over Hiroshima and Nagasaki, which primarily resulted in acute exposure to γ-rays and neutrons emitted directly from the bombs. The health consequences of acute radiation have been the subject of extensive and continuing epidemiological investigations (see e.g. IARC, 2000). The fall-out radiation in Hiroshima and Nagasaki has been less well characterized than direct exposure but is considered to have been small.

In atmospheric tests, particles containing radionuclides are released during the explosion and are carried into the stratosphere, giving rise to worldwide fall-out. Human exposure to external irradiation occurs when the radionuclides are deposited on the earth's surface, and internal exposures occur when the radionuclides are incorporated into the body through ingested foods. Although a well-contained underground nuclear explosion delivers extremely low doses, on some occasions venting or diffusion of gases or liquids has resulted in leakage of radioactive materials after underground tests, leading to regional dissemination of radioactive debris (UNSCEAR, 1993).

(*b*) *Global exposures*

Exposures to radiation from nuclear weapons tests have been a major concern of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), which assesses and updates data on exposure on a global basis. The basic quantity used by UNSCEAR to express the radiation doses imposed on the world's population is the 'collective dose commitment'. This is the integral over infinite time of the collective dose rates delivered to the world's population, i.e. including doses to be delivered in future time until complete decay or removal of the radionuclides from the environment. Calculated in this way, collective doses have little meaning with respect to the dose received by the first generations after radionuclide release, as the collective dose is dominated by doses received from a few long-lived isotopes, e.g. ^{14}C and ^{237}Np, which deliver only a very small dose to individuals. It follows that it might be more appropriate to truncate the calculation of collective dose when the dose rate becomes insignificant. Currently, fall-out accounts for only 0.2% of the average background dose in the United Kingdom (National Radiological Protection Board, 2000). Sources of internal irradiation are inhalation of air contaminated with radionuclides and ingestion of contaminated foodstuffs. Internal exposures, especially through ingestion, are the major component of the total effective doses committed by the tests on a global basis. UNSCEAR estimated that the total effective dose commitment from atmospheric nuclear testing to the world's population is 30×10^6 person–Sv, of which about 93% (28×10^6 person–Sv) is from internal exposure due to ingestion or inhalation of radionuclides (Table 1) (UNSCEAR, 1993). By far the most important component is ingested ^{14}C, which accounts for almost 26×10^6 person–Sv because of its very long half-life (5730 years) and environmental mobility. This radionuclide will deliver very small dose rates to the world population during thousands of years at the same rate as it does now; it is the accumulation of these very small dose rates over a long period to a large population (including the future population) that explains the large contribution of ^{14}C. ^{137}Cs, which is the most important component (about 1.2×10^6 person–Sv) of external doses from the nuclear tests, is the second most important component of the internal doses (about 0.7×10^6 person–Sv) committed by the nuclear tests. This is followed by ^{90}Sr, which contributes a little over 0.4×10^6 person–Sv (IARC, 2000). These estimates do not include the exposure from local fall-out, discussed below, of people who live near the test sites and thus may receive relatively high doses.

(*c*) *Local and regional exposures*

Nuclear tests are conducted at isolated sites when the meteorological conditions are favourable, but unexpected events, such as the shift in winds during the Bravo test at Bikini Atoll in the Marshall Islands (see below), can result in heavy radiation exposure from local fall-out. Local and regional exposure doses have been estimated for several major nuclear test sites, including that in Nevada (USA), in the Pacific

Table 1. Collective effective dose commitment from atmospheric nuclear tests to internal exposure of the world's population

Radionuclide	Half-life	Collective effective dose commitment (1000 person–Sv)		
		Ingestion	Inhalation	Total internal exposure
^{14}C	5730 years	25 800	2.6	25 800
^{137}Cs	30.1 years	677	1.1	678
^{90}Sr	28.8 years	406	29	435
^{3}H	12.3 years	176	13	189
^{131}I	8.02 days	154	6.3	160
^{144}Ce	285 days		122	122
^{106}Ru	374 days		82	82
^{239}Pu	24 100 years	1.8	56	58
^{241}Am	432 years	8.7	44	53
^{240}Pu	6537 years	1.3	38	39
^{55}Fe	2.73 years	26	0.06	26
^{241}Pu	14.4 years	0.01	17	17
^{89}Sr	50.5 days	4.5	6.0	11
^{91}Y	58.5 days		8.9	8.9
^{95}Zr	64.0 days		6.1	6
^{95}Nb	35.0 days		2.6	2.6
^{103}Ru	39.3 days		1.8	1.8
^{140}Ba	12.8 days	0.81	0.66	1.5
^{141}Ce	32.5 days		1.4	1.4
^{54}Mn	312 days		0.4	0.4
^{125}Sb	2.76 years		0.2	0.2
Total (rounded)		27 300	440	27 700

From UNSCEAR (1993)

(Marshall Islands), Semipalatinsk and Novaya Zemlya in the former USSR, Lop Nor in China, Mururoa and Fangataufa (French test sites) and Australian test sites (used by the United Kingdom).

The doses to most organs and tissues from ingestion and inhalation after local fall-out are substantially lower than those from external exposure, with the important exception of doses to the thyroid, for which internal exposure to radioactive iodines predominates. The dose that the thyroid receives from internal exposure is often greater than that from external exposure or the doses that any other organ receives from internal exposure (Whicker *et al*., 1996; UNSCEAR, 2000).

(i) *Nevada test site, USA*

Between 1951 and 1962, at least 105 atmospheric tests were conducted at the Nevada test site, and 14 other tests at depths where containment was not expected. These resulted in the atmospheric release of ^{131}I, ^{137}Cs and other radionuclides. Extensive dose reconstruction has been undertaken for the population living in the vicinity of the test site during the period of atmospheric testing. In particular, the Off-site Radiation Exposure Review Project of the Department of Energy in the USA collected information on fall-out in off-site areas and provides dosimetric data by region, community, locale, age and occupation. The doses from external irradiation have been calculated by Monte Carlo techniques for each event for the residents of each town in the vicinity of the site and for each county in the affected region. The doses from internal exposure have been estimated by pathway models for combinations of location and event for various radionuclides, age groups and organs. The data from these projects, supplemented by additional work, were used in epidemiological studies on thyroid cancer and leukaemia in Utah (Stevens *et al.*, 1990; Kerber *et al.*, 1993; Simon *et al.*, 1995; Till *et al.*, 1995). In the study on thyroid cancer, special efforts were made to estimate individual doses to the thyroid from data on diet and lifestyle obtained from a survey.

Anspaugh *et al.* (1990) estimated the doses to the thyroid for an infant living in St George, Utah, when the event HARRY occurred on 19 May 1953, which resulted in fall-out over St George. This was one of the most heavily contaminated areas, and the test accounted for most of the doses to the thyroid in that area. Table 2 shows that previous estimates are comparable to that of Anspaugh *et al.* (1990).

The National Cancer Institute (1997) conducted a study to estimate the doses received by the thyroid for people living across the contiguous USA as a result of fall-out of ^{131}I from the Nevada test site. Table 3 presents the per-capita thyroid doses (summed over all Nevada test site events) estimated in the study. The results indicate that deposition of ^{131}I occurred at one time or another in every county of the contiguous USA between 1951 and 1958. The estimated collective thyroid dose was about 4×10^6 person–Gy, with a per-capita dose of about 20 mGy.

(ii) *Pacific test site, Marshall Islands*

The USA conducted at least 105 tests in the Pacific region between 1946 and 1962. In terms of radiation exposures, the tests conducted at Bikini atoll in the Marshall Islands were the most important. Of special importance is the Bravo thermonuclear test conducted in March 1954. Following this test, an unpredicted shift in winds resulted in exposure to radioactive fall-out of some 250 inhabitants of the Marshall Islands, 28 American servicemen on atolls to the east and 23 Japanese fishermen on their fishing vessel (Conard *et al.*, 1980; Bouville *et al.*, 2000).

The health effects on the Marshallese who resided on three atolls, Rongelap, Ailinginae and Utirik, at the time of detonation have been studied. These atolls were 100–300 miles from the detonation site. Exposure was largely from fall-out deposited

Table 2. Doses to the thyroid for an infant living in St George, Utah, USA, at the time of the event HARRY on 19 May 1953

Thyroid dose (Gy) (central estimate and/or range of uncertainty)	Reference
0.68	Mays (1963)
1–7	Reiss (1963)
0.84	Pendleton *et al.* (1963)
1.2–4.4	Knapp (1963)
0.78 (0.2–1.6)	Tamplin & Fisher (1967)
0.68	Perez & Robinson (1967)
0.66 (0.2–1.9)	Ng *et al.* (1990)
0.5 (0.2–1.4)	Anspaugh *et al.* (1990)

From Anspaugh *et al*. (1990)

Table 3. Estimated collective doses to the thyroid for the population in the USA due to fall-out from the Nevada atmospheric nuclear bomb tests

Series	Dates	Collective thyroid dose (person-Gy)
Ranger	January–February 1951	1.6×10^3
Buster-Jangle	October–November 1951	7.4×10^4
Tumbler-Snapper	April–June 1952	1.1×10^6
Upshot-Knothole	March–June 1953	8.9×10^5
Teapot	February–May 1955	4.1×10^5
Plumbbob	May–October 1957	1.2×10^6
Hardtack II	September–October 1958	1.6
All		3.7×10^6

From National Cancer Institute (1997)

on the skin and internal deposition of radionuclides from ingestion of contaminated food and water and involved a mixture of radionuclides (^{131}I, ^{132}I, ^{133}I, ^{134}I and ^{135}I), tellurium isotopes and γ-rays (Lessard *et al.*, 1985; UNSCEAR, 2000). The most extensive evaluation of doses to the thyroid was carried out by Lessard *et al*. (1985), on the basis of measurements of ^{131}I in a pooled urine sample collected on the 17th day after detonation of the Bravo bomb. The estimated doses, largely due to internal exposure (roughly 80–90%), were highly dependent on age (Table 4), infants receiving the highest doses. Although short-lived radioiodines (^{131}I, ^{133}I, ^{135}I) were not

Table 4. Estimated doses to the thyroid from internal and external exposure after the Bravo test in the Marshall Islands

Atoll	Age	Estimated dose (Gy)		
		Internal	External	Total
Rongelap	Adult	10	1.9	12
	9 years	20	1.9	22
	1 year	50	1.9	52
	Newborn	2.5	1.9	4.4
	In utero	6.8	1.9	8.7
Ailinginae	Adult	2.8	1.1	4.0
	9 years	5.4	1.1	6.6
	1 year	13.0	1.1	14.0
	In utero	4.9	1.1	6.1
Utirik	Adult	1.5	0.11	1.6
	9 years	3.0	0.11	3.1
	1 year	6.7	0.11	6.8
	Newborn	0.48	0.11	0.59
	In utero, 3rd trimester	0.98	0.11	1.1
	In utero, 2nd trimester	2.6	0.11	2.7

From Lessard *et al*. (1985)

measured, half of the dose was considered to be due to the intake of ^{133}I, while ^{131}I contributed 10–15% of the doses at Rongelap and Ailinginae and about 20% at Utirik (Lessard *et al*., 1985).

(iii) *Semipalatinsk test site, Kazakhstan*

At the Semipalatinsk test site in the Republic of Kazakhstan, in the former USSR, 116 uncontained nuclear and thermonuclear explosions were set off, starting in 1949. Most of the regional radioactive contamination, outside the bounds of the test site itself, was due to tests conducted between 1949 and 1956, contributing more than 95% of the expected collective doses of the non-occupationally exposed population living close to the test site (UNSCEAR, 1993; Dubasov *et al.*, 1994; UNSCEAR, 2000).

Several groups of investigators are reconstructing the doses from external and internal exposures of the population living in the vicinity of the test site. About 10 000 people living in the settlements bordering the site are reported to have been exposed to some extent (UNSCEAR, 1993, 2000). The total collective dose attributable to the tests during 1949–62 is estimated to be 2600 person–Sv from external irradiation and 2000 person-Sv from internal exposure due to ingestion of radionuclides. For internal exposure, the collective doses are estimated to be about 10 000 person–Sv to the thyroid and about 2000 person–Sv to bone marrow (UNSCEAR, 1993; Bouville *et al.*, 2000).

(iv) *Novaya Zemlya, Russian Federation*

More than 90 atmospheric nuclear tests were conducted on the Novaya Zemlya islands, Russian Federation, and these account for about half of the total energy yield of all nuclear tests carried out worldwide. Nevertheless, the local doses to off-site residents are considered to be relatively low, as most of the atmospheric explosions were conducted at high altitudes, most of the vented underground tests resulted in on-site contamination only, and the test site is large and isolated. Little information is available on local and regional doses, and then only on on-site contamination and doses received by reindeer herders and people who consume reindeer meat (UNSCEAR, 2000).

(v) *Lop Nor, China*

China conducted 22 atmospheric tests between 1964 and 1980 at the Lop Nor test site. The estimated effective doses from external exposure of populations 400–800 km downwind from the test site ranged from 0.006 to 0.11 mSv, with a mean of 0.044 mSv (UNSCEAR, 2000). The doses to the thyroid from internal exposure to ^{131}I for adults ranged from 0.059 to 2.5 mGy. The average dose to the thyroid received by the Chinese population from these tests is estimated to be about 0.14 mGy (Bouville *et al.*, 2000).

(vi) *Mururoa and Fangataufa, French Polynesia*

France conducted 46 atmospheric tests on the uninhabited atolls of Mururoa and Fangataufa, French Polynesia, between 1966 and 1974. About 5000 people lived within a 1000-km radius of the planned ground zero in Mururoa. After 1975, all tests were conducted underground. Doses have been reconstructed for the 110 000 inhabitants of Tahiti, located 1000 km from Mururoa and Fangataufa, and for the 140 inhabitants of the Tureia atoll. The doses to the thyroid from internal exposure to ^{131}I of infants in Tahiti during the atmospheric testing were estimated to be 0.12–6.8 mGy, the highest occurring in 1974 (UNSCEAR, 1977; Bouville *et al.*, 2000; UNSCEAR, 2000).

(vii) *Emu, Maralinga and Montebello, Australia*

The United Kingdom conducted 12 atmospheric tests in Australia between 1952 and 1957. The doses from internal exposure have been assessed on the basis of the estimated ingestion of fall-out radionuclides in food and drinking-water and inhalation of fall-out radionuclides in air. For the entire Australian population, the average effective dose from these tests was estimated to be 0.07 mSv and the collective effective dose equivalent to be 700 person–Sv (UNSCEAR, 2000).

1.1.2 *Accidents at nuclear installations*

(*a*) *Chernobyl*

During an engineering test of one of the four reactors at the Chernobyl nuclear power plant in the Ukraine on 26 April 1986, the safety systems had been switched off, and unstable operation of the reactor allowed an uncontrollable power surge to occur, leading to successive steam explosions and resulting in destruction of the reactor. Within days or weeks of this accident, 28 power-plant employees and firemen had died due to exposure to radiation. During 1986, about 220 000 people were evacuated from areas surrounding the reactor, and about 250 000 people were relocated subsequently. About 600 000 persons worked, and some still do, in cleaning-up the accident; they are known as 'recovery operation workers' or 'liquidators' (UNSCEAR, 2000).

The radionuclides were released mainly over a period of 10 days after the accident, contaminating vast areas of the Ukraine, Belarus, and the Russian Federation, and trace deposition of released radionuclides was measurable in all countries of the northern hemisphere (UNSCEAR, 1994, 2000). The contamination beyond the 30-km exclusion zone was determined primarily by wind direction. Globally, ^{131}I and ^{137}Cs are the most important radionuclides to be considered, except in the immediate area where deposition reflected the composition of the fuel, since they were responsible for most of the exposure to radiation of the general population. The total releases of ^{131}I and ^{137}Cs in 1996 are estimated to have been 1760 and 85 PBq (1760 and 85×10^{15} Bq; 50% and 30% of the core inventory), respectively (UNSCEAR, 2000).

Three categories of individuals who are likely to have been exposed after the Chernobyl accident to doses of ionizing radiation that could have a measurable effect were the workers involved in the accident (during the emergency or clean-up phase), the inhabitants of evacuated areas and the inhabitants of contaminated areas who were not evacuated. Additionally, individuals residing in the former USSR beyond the heavily contaminated areas and those living in the rest of Europe may have been exposed as a consequence of the accident; however, the dosimetry in these areas is even more complex and unreliable than in those close to Chernobyl.

(i) *Emergency workers*

The emergency workers are those who dealt with the consequences of the accident during the first few days, including staff of the plant, firemen, medical staff and guards. The main exposure was due to relatively uniform external whole-body γ-irradiation and β-irradiation of extensive body surfaces. Acute radiation syndrome was diagnosed in 134 workers (UNSCEAR, 2000), of whom 33 were selected for bone-marrow transplantation. Of these, 13 who were estimated to have received whole-body doses of 5.6–13.4 Gy received bone-marrow transplants (Baranov *et al.*, 1989).

(ii) *Recovery operation workers*

Of particular interest are the 226 000 recovery operation workers who were employed in the 30-km exclusion zone in 1986–87, as it is during this period that the

highest doses were received (UNSCEAR, 2000). The assessments were based largely on group dosimetry or time–activity diaries. The average recorded external doses decreased over time, from about 170 mSv in 1986 to 130 mSv in 1987, 30 mSv in 1988 and 15 mSv in 1989 (Tsyb *et al.*, 1992; Sevan'kaev *et al.*, 1995).

The recovery operation workers received doses not only from external γ- and β-irradiation but also from internal irradiation. Between 30 April and 7 May 1986, direct measurements were made on the thyroids of more than 600 recovery operation workers. The preliminary estimates showed an average dose of 210 mGy. The average effective dose received between June and September 1986 by about 300 recovery operation workers was estimated to have been about 30 mSv. The internal doses from intakes in later years are expected to be much lower: routine monitoring of the ^{137}Cs body burdens indicated average annual doses from ^{137}Cs of 0.1–0.2 mSv in 1987 and 1988 (UNSCEAR, 2000).

(iii) *Evacuees*

Approximately 116 000 individuals were evacuated in 1986 from contaminated areas around the Chernobyl reactor. The effective doses from external exposure for the persons evacuated from the Ukrainian part of the 30-km zone were estimated from measurements performed in this zone and responses to questionnaires from about 35 000 evacuees. The average effective dose from external irradiation for this cohort was estimated to be 17 mSv, with individual values varying from 0.1 to 380 mSv (UNSCEAR, 2000).

In calculations of the effective doses from external irradiation of evacuees from Belarus, it was assumed that 60–80% of the effective dose was contributed by the short-lived radionuclides ^{131}I, ^{132}Te plus ^{132}I, and ^{140}Ba plus ^{140}La, and the contribution from the long-lived radionuclide ^{137}Cs was estimated to be only 3–5%. Overall, it is estimated that about 30% of the people were exposed to effective doses < 10 mSv, about 86% were exposed to doses < 50 mSv, and only about 4% were exposed to doses > 100 mSv, with the average dose estimated to be 31 mSv. The highest average effective dose, about 300 mSv, was estimated to have been received by the populations of two villages located in the 30-km zone (UNSCEAR, 2000).

The average individual and collective doses to the thyroid of evacuees from villages and from the towns of Pripyat and Chernobyl, located in the 30-km zone, are shown in Table 5. The doses from ^{131}I in Pripyat, which were for the most part due to inhalation, were highest for children aged < 1–3 years (mean, about 1.4 Gy), and the average dose for the whole population of this town was 0.2 Gy. The main determinant of the individual dose was found to be the distance of the residence from the reactor (UNSCEAR, 2000).

(iv) *Unevacuated inhabitants of the former USSR*

In the European part of the former USSR, 3% of the land was contaminated after the Chernobyl accident, with ^{137}Cs deposition densities > 37 kBq/m^2. Many people

Table 5. Estimates of doses to the thyroid from intake of ^{131}I by Ukrainian evacuees of towns and villages within a 30-km zone of the Chernobyl reactor

Age at time of accident (years)	Pripyat town			Chernobyl town[a]			Evacuated villages[a]			Total collective dose (person–Gy)
	No. of persons	Arithmetic mean dose (Gy)	Collective dose (person–Gy)	No. of persons	Arithmetic mean dose (Gy)	Collective dose (person–Gy)	No. of persons	Arithmetic mean dose (Gy)	Collective dose (person–Gy)	
< 1	340	2.18	741	219	1.5	329	369	3.9	1 439	2 509
1–3	2 030	1.28	2 698	653	1	653	1 115	3.6	4 014	7 265
4–7	2 710	0.54	1 463	894	0.48	429	1 428	1.7	2 428	4 320
8–11	2 710	0.23	623	841	0.15	126	1 360	0.62	843	1 592
12–15	2 710	0.12	325	846	0.11	93	1 448	0.46	666	1 084
16–18	2 120	0.066	140	650	0.09	59	941	0.39	367	566
> 18	36 740	0.066	2 425	9 488	0.16	1 518	21 794	0.40	8 718	12 661
Total	49 360		8 315	13 591		3 206	28 455		18 475	29 996

From UNSCEAR (2000)

[a] Age distribution of population assumed to be the same as in Pripyat

continued to live in the contaminated territories surrounding the Chernobyl reactor; areas in which the ^{137}Cs deposition density was > 555 kBq/m^2 were considered to be areas of strict control. Initially, 786 settlements inhabited by 273 000 people were considered to be strict control zones. Within these areas, radiation monitoring and preventive measures were taken with the aim of maintaining the annual effective dose within 5 mSv; in 1995, about 150 000 people were living in the areas of strict control (UNSCEAR, 2000). The average effective individual dose received by the inhabitants of these zones was 37 mSv during the first year after the accident (UNSCEAR, 1993). The distribution of the population (a little more than 5 million people) residing in contaminated areas in 1995 according to ^{137}Cs deposition density interval (≥ 37 kBq/m^2) is shown in Table 6. The percentage of the population living in areas with the highest contamination was about 5% in Belarus and the Russian Federation and < 1% in the Ukraine (UNSCEAR, 2000).

Table 6. Distribution in 1995 of inhabitants of areas contaminated by the Chernobyl accident

^{137}Cs deposition density (kBq/m^2)	Population[a]			
	Belarus	Russian Federation	Ukraine	Total
37–185	1 543 514	1 634 175	1 188 600	4 366 289
185–555	239 505	233 626	106 700	579 831
555–1480	97 595	95 474	300	193 369
Total	1 880 614	1 963 275	1 295 600	5 139 489

From UNSCEAR (2000)

[a] For social and economic reasons, some of the populations living in areas contaminated with < 37 kBq/m^2 are also included.

The doses due to internal exposure came essentially from the intake of ^{131}I and other short-lived radioiodines during the first days or weeks after the accident and, subsequently, from intake of ^{134}Cs and ^{137}Cs. Other long-lived radionuclides, notably ^{90}Sr, ^{239}Pu and ^{240}Pu, have so far contributed relatively little to the internal doses, but they will play a more important role in the future. After the Chernobyl accident, about 350 000 measurements of ^{131}I in the thyroid and about 1 million measurements of ^{134}Cs and ^{137}Cs in the whole body were conducted in the three republics by means of γ-radiation detectors placed outside the body (UNSCEAR, 2000).

The main contaminated areas in the Russian Federation are located 150–250 km to the northeast of Chernobyl, and most of the short-lived iodine isotopes had already decayed when the radioactive plume reached this area. Rainfall in the area decreased the concentrations in air and reduced the intake by inhalation. Therefore, the dose to

the thyroid was due primarily to ^{131}I intake with milk and leafy vegetables, and the pattern of doses was similar throughout the region. About 45 000 direct measurements of radioactivity in the thyroid made in May–July 1986 showed a maximum on 16 and 17 May of up to 300 kBq. The doses to the thyroid were estimated in this manner for people in six age groups: < 1, 1–2, 3–5, 7–11, 12–17 and > 18 years. The variations between age groups differed for towns and villages, reflecting not only the age-related metabolism of iodine but also differences in social and nutritional habits. Estimates of doses to the thyroid in contaminated areas of the Russian Federation are presented in Table 7 (UNSCEAR, 2000).

Table 7. Estimated doses to the thyroid of inhabitants of districts of the Russian Federation contaminated by the Chernobyl accident

District/region	Population	Mean thyroid dose (Gy)	Collective thyroid dose (person–Gy)
Bryansk			
Controlled areas[a]	112 000	0.20	22 000
8 contaminated districts	360 000	0.092	33 000
Whole region	1 500 000	0.037	55 000
Tula			
12 contaminated districts	770 000	0.035	27 000
Whole region	1 900 000	0.026	50 000
Orel	870 000	0.017	15 000
Kaluga	1 000 000	0.015	15 000
Total	5 270 000	0.026	135 000

From UNSCEAR (2000)
[a] ^{137}Cs deposition density, > 555 kBq/m^2

(v) *Inhabitants of countries outside the former USSR*

Information on doses received by populations other than those of Belarus, the Russian Federation and the Ukraine is incomplete. The populations of Croatia, Greece, Hungary, Poland and Turkey have been considered in epidemiological studies of thyroid cancer. The average thyroid doses received by these populations were estimated to range from 1.5 to 15 mGy (UNSCEAR, 2000). The collective effective dose from the Chernobyl accident was 600 000 person–Sv (UNSCEAR, 1988), of which 40% is expected to have been received in the former USSR, 57% in the rest of Europe and 3% in other countries of the northern hemisphere (UNSCEAR, 1993).

(*b*) *Southern Ural Mountains*

(i) *History*

The Chelyabinsk region of the southern Ural Mountains was one of the main military production centres of the former USSR and included the Mayak nuclear materials production complex in the closed city of Ozersk. Accidents, nuclear waste disposal and day-to-day operation of the Mayak reactor and radiochemical plant contaminated the nearby Techa River. The period of most releases of radioactive material was 1949–56, with a peak in 1950–51 (UNSCEAR, 2000).

During the first years of the releases, 39 settlements were located along the banks of the Techa River, and the total population was about 28 000. Technical flaws and lack of expertise in radioactive waste management led to contamination of vast areas, and the population was not informed about the releases. The protective measures that were implemented (evacuations, restrictions on the use of flood lands and river water in agricultural production and for domestic purposes) proved to be ineffective, since they were implemented too late. Approximately 7500 people were evacuated from villages near the River between 1953 and 1960 (Akleyev & Lyubchansky, 1994; Degteva *et al.*, 1994).

In 1957, a nuclear waste storage facility in the Chelyabinsk region, near the town of Kyshtym, exploded (the Kyshtym accident) due to a chemical reaction, producing contamination referred to as the East Urals Radiation Trace (EURT). About 273 000 people lived in the contaminated area (Akleyev & Lyubchansky, 1994; UNSCEAR, 2000).

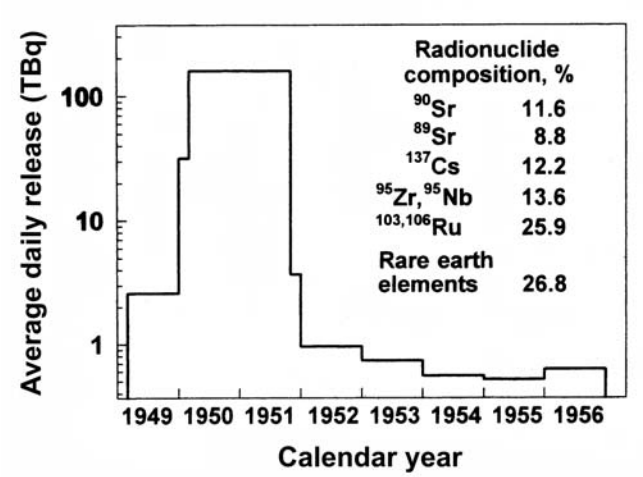
Ten years later, in 1967, after an exceptionally dry summer, the water of the Karachay Lake, an open depot of liquid radioactive waste, evaporated, and a storm transported radionuclides from the dry shores. Eleven thousand individuals were resettled as a result of the Kyshtym accident, of whom 1500 had previously been resettled from the Techa River (Akleyev & Lyubchansky, 1994; UNSCEAR, 2000).

(ii) *Dosimetry*

During 1949–56, 7.6×10^7 m^3 of liquid wastes with a total radioactivity of 100 PBq were released into the Techa–Isset–Tobol river system. The composition of the releases in relation to year of discharge is shown in Figure 1. Large populations were exposed over long periods to external γ-radiation, due largely to ^{137}Cs but also to other γ-emitting radionuclides such as ^{95}Zr, ^{95}Nb and ^{106}Ru present in the water and on the banks of the Techa River. The internal radiation dose was from ingestion of ^{90}Sr and ^{137}Cs over long periods. The doses were estimated as averages for different age groups, assuming that all persons of a specific age living in a specific village in a specific year had accumulated a similar dose (Akleyev & Lyubchansky, 1994; Degteva *et al.*, 1994; UNSCEAR, 2000).

The Techa River dosimetry system was developed in order to estimate the doses received by the persons in the extended Techa River cohort, which consists of approximately 30 000 people, including 5000 who migrated to the area after the period of highest releases. The Techa River offspring cohort consists of 14 000 persons born

Figure 1. Average amount of radioactivity released per day into the Techa River between 1949 and 1956, in relation to year of discharge and radionuclide composition



From Vorobiova *et al.* (1999)
1 TBq = 10^{12} Bq

after 1949 to at least one parent in the extended cohort (Degteva *et al.*, 1996; Kossenko *et al.*, 1997; Degteva *et al.*, 2000a).

The doses from external exposure have been calculated from measurements of external γ-radiation from the River. The internal doses, mainly from ^{90}Sr, have been calculated from the approximately 14 000 whole-body measurements performed since 1970 (Kozheurov & Degteva, 1994; Kossenko *et al.*, 1997; Vorobiova *et al.*, 1999; Degteva *et al.*, 2000a,b).

Recent analyses of the available dosimetry resulted in recalculations of the doses. The major change is increased gastrointestinal doses, due to a larger fraction of short-lived radionuclides and a somewhat smaller contribution from external exposure after revision of data on life-style factors. An important aspect has been reconstruction of what was actually discharged from the Mayak facility. The internal doses are now calculated on the basis of age- and location-specific mean annual intakes of all released radionuclides and individual residence histories. The median dose to the red bone marrow of persons in the extended cohort was 0.21 Gy, and about 50% of the subjects received doses of 0.10–0.50 Gy. The corresponding figures for the distal part of the colon were 0.10 Gy and 0.03–0.20 Gy, respectively. No other tissue except the upper gastrointestinal tract received doses > 0.05 Gy (Degteva *et al.*, 2000a,b).

The external exposure has been found to have been substantially lower because previous calculations were based on the assumption that all residents in a village received the same dose as those living closest to the riverbank (Degteva *et al.*, 1994).

Thus, distance from the River was not taken into consideration. Furthermore, the older calculations overestimated the time spent on the riverbank. External doses are not given in the most recent publication (Degteva *et al.*, 2000a).

(*c*) *Other accidents*

(i) *Windscale*

In October 1957 in Windscale, England, the fuel elements in a graphite-moderated nuclear reactor used to produce plutonium for military purposes caught fire. The fire was detected three days later and, when efforts to extinguish it with carbon dioxide failed, the core was flooded with water. A total of 1.5×10^{15} Bq of radioactive material were released into the environment (Stewart & Crooks, 1958; UNSCEAR, 1993; IARC, 2000), including the radionuclides ^{133}Xe (14×10^{15} Bq), ^{131}I (1.4×10^{15} Bq), ^{137}Cs (0.04×10^{15} Bq) and ^{210}Po (0.009×10^{15} Bq). The total collective effective dose was 2000 person–Sv, including 900 person-Sv from inhalation and 800 person-Sv from ingestion of milk and other foods. Children in the vicinity of the nuclear plant received doses to the thyroid of up to 100 mGy (Burch, 1959; UNSCEAR, 1993; IARC, 2000).

(ii) *Three Mile Island*

The releases of radiation from the accident at the Three Mile Island reactor in Pennsylvania, USA, in March 1979 were caused by failure to close a pressure relief valve, which led to melting of the uncooled fuel. The large release of radioactive material was dispersed to only a minor extent outside the containment building; however, ^{133}Xe (370×10^{15} Bq) and ^{131}I (550×10^{9} Bq) were released into the environment, leading to a total collective dose of 40 person–Sv and an average individual dose from external γ-radiation of 15 μSv. No individual was considered to have received doses to the thyroid of > 850 μSv (UNSCEAR, 1993; IARC, 2000).

The episodes of accidental or non-routine release of radionuclides are summarized in Table 8.

1.1.3 *Routine releases from nuclear installations*

(*a*) *Environmental exposure*

The fraction of electric energy generated by nuclear reactors has grown steadily since their introduction in 1956. By the end of 1997, 437 operating nuclear power reactors and 283 research reactors were in use in 31 countries throughout the world. A total of 285 reactors have now been closed down, 12 are currently under construction, and seven have been planned. The electricity produced by nuclear energy comprised 17% of the electricity generated in the world in 1997 (IAEA, 1997; UNSCEAR, 2000).

The nuclear fuel cycle includes mining and milling of uranium ore, conversion into fuel material, production of fuel elements, energy production and storage and reprocessing. The doses to individuals from routine releases from nuclear installations

Table 8. Characteristics of accidental or non-routine releases of radionuclides

Site	Approximate quantity released	Date	Collective effective dose	Individual effective dose
Chernobyl, Russian Federation	^{131}I, 1760 PBq; ^{137}Cs, 85 PBq	1986	600 000 person–Sv	31 mSv for evacuees
Techa River, southern Urals, Russian Federation	~ 100 PBq	1949–56	Not estimated	Average bone-marrow dose for those living along the River, 21 mSv
Kyshtym, southern Urals, Russian Federation	74 PBq	1957	Not estimated	Not estimated
Karachay Lake, southern Urals, Russian Federation	22 TBq	1967	Not estimated	Not estimated
Windscale, United Kingdom	^{131}I, 1.4 PBq	1957	2000 person–Sv	Dose to the thyroid: average, 5–125 μSv; maximum, 5 mSv
Three Mile Island, USA	^{131}I, 550 GBq; ^{133}Xe, 370 PBq	1979	40 person–Sv	External γ: average, 15 μSv; maximum 850 μSv

From UNSCEAR (1993); Akleyev & Lyubchansky (1994); Burkart (1996); Degteva *et al.* (2000a); UNSCEAR (2000)
P, peta = 10^{15}; T, tera = 10^{12}; G, giga = 10^{9}

vary considerably according to the installation and with time, but the most important determinant of dose is the distance from the release (UNSCEAR, 2000).

Airborne and liquid radioactive releases from nuclear reactors during routine operations have been reported with substantial completeness. Models for calculating the actual doses from the releases for each radionuclide and combination of radionuclides are complex. Factors to be taken into consideration include the geographical location of the reactor, population density and distribution, food production, consumption habits, environmental pathways, dilution of radionuclides, composition of radionuclides and type of reactor. The concentrations of radionuclides are generally not measurable, except close to the nuclear plant, and then only for a limited number of radionuclides. The calculation of individual and collective doses is therefore dependent on modelling of atmospheric and aquatic transport and environmental transfer before application of dosimetric models (UNSCEAR, 2000).

In a recent report (UNSCEAR, 2000), the total collective dose for the period 1990–94 was estimated to be 490 person–Sv, which represents a 25% increase over the preceding five-year period and corresponds to the approximate 25% increase in energy production during that time. The collective effective dose for a given reactor is described in person–sieverts per unit of electric energy generated. For the period 1990–94, that value was calculated to be 0.43 person–Sv/GW–year; noble gases and tritium (^{3}H) (airborne and liquid) contributed approximately 25% and 19%, respectively, while ^{131}I contributed 0.0002 person–Sv/GW–year (Table 9). The calculations were made under the assumption that the population density was 20/km^2 within 2000 km and 400/km^2 within 50 km of the release. The annual effective doses of most individuals throughout the world were calculated on the basis of the data above and, depending on the type of reactor, resulted in estimates of 0.4–10 μSv.

The change in releases over time and the collective effective doses of different nuclides are shown in Figure 2. The total collective dose has been stable since 1970–74, whereas the quantity of electrical energy generated increased between 1970 and 1994. The collective effective dose from ^{131}I has diminished dramatically after a peak in 1975–79 (UNSCEAR, 2000).

(*b*) *Occupational exposure* (see also section 1.2)

Occupational exposure in nuclear installations varies significantly, depending on the type, size and age of the reactor. Other factors that affect the radiation dose are changes in operating routines, piping, shielding and reactor water chemistry. In contrast to environmental exposure, in which internal exposure is the main component of dose, occupational exposure consists almost entirely of external exposure to γ-radiation and occurs mostly during scheduled maintenance and/or refuelling.

Occupational exposure at reactor sites, regardless of the type, has decreased steadily in the past few years throughout the world. Difficulties in comparing doses between countries arise due to differences in reporting, e.g. in some cases, only workers

Table 9. Normalized collective effective doses from radionuclides released from nuclear reactors, 1990–94

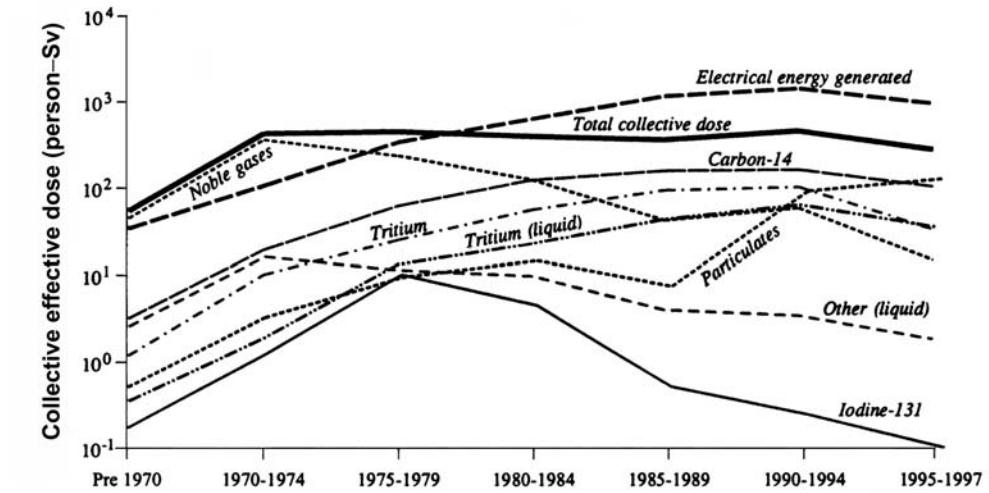
Reactor type	Electrical energy generated (%)	Collective effective dose per unit electrical energy generated (person–Sv/GW–year)						
		Airborne effluents					Liquid effluents	
		Noble gases	^{3}H	^{14}C[a]	^{131}I	Particulates	^{3}H	Other
PWR	65.04	0.003	0.005	0.059	0.0001	0.0004	0.014	0.006
BWR	21.95	0.15	0.002	0.14	0.0002	0.36	0.0006	0.014
GCR	3.65	1.44	0.010	0.38	0.0004	0.0006	0.14	0.17
HWR	5.04	0.23	1.4	0.43	0.0001	0.0001	0.32	0.043
LWGR	4.09	0.19	0.05	0.35	0.002	0.028	0.007	0.002
FBR	0.24	0.042	0.10	0.032	0.00009	0.024	0.0012	0.016
Weighted average		0.11	0.075	0.12	0.0002	0.080	0.031	0.016
Total					0.43			

From UNSCEAR (2000)

[a] Local and regional components only

BWR, boiling water reactor; FBR, fast breeder reactor; GCR, gas-cooled and graphite-moderated reactor; HWR, heavy water-cooled and -moderated reactor; LWGR, light water-cooled and graphite-moderated reactor; PWR, light water-moderated and -cooled pressurized reactor

Figure 2. Local and regional collective effective doses from average annual releases of radionuclides from reactors



From UNSCEAR (2000)

The increasing trend in electrical energy generated is indicated on the scale on the left, in units of GW-year.

with measurable doses are included, which affects the average dose of the workforce. The annual average collective effective dose for 1990–94 was calculated to be 900 person–Sv, which was lower than the dose of 1100 person–Sv calculated for the preceding period. In 1990–94, the annual effective dose among monitored workers, averaged over all reactors, was 1.4 mSv, and that for measurably exposed workers was 2.7 mSv (UNSCEAR, 2000).

1.1.4 *Dosimetry of radon-222*

Studies of underground miners indicate that the rate of mortality from lung cancer is related directly to the concentration of radon and its decay products in the air of uranium and other hard-rock mines. Exposure was reduced in many mines after recognition that breathing radon gas and its decay products is an occupational risk. Other important sources of exposure to radon have since been recognized; in particular, it has been shown that radon can accumulate in appreciable concentrations in homes, offices and other buildings where air exchange with outdoor air is restricted. Exposures from residential or indoor radon have been studied extensively around the world (Committee on the Biological Effects of Ionizing Radiations (BEIR IV), 1988; IARC, 1988; ICRP, 1993a; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999; Lubin *et al.*, 1995a, 1997; UNSCEAR, 2000).

The dosimetry of radon, i.e. the dose to the bronchial epithelium, is complex and depends on factors such as the concentrations of radon and radon decay products in inspired air, aerosol factors such as the size distribution of inhaled particles and the attachment of radioactive particles to the aerosol and the distribution of radionuclides. The physiological factors include lung morphology, depth of target cells, amount of air moving through the lung per time unit, particle deposition fraction, mucus thickness and transport rate through mucus. These considerations are dealt with comprehensively in several publications (Committee on the Biological Effects of Ionizing Radiations (BEIR IV), 1988; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999), and only a brief overview is given here.

The risk for lung cancer of miners exposed to radon is expressed in units of working-level months (WLM), whereas lung cancer risks in homes are evaluated in terms of Bq/m^3 or time-weighted average Bq/m^3. Living in an atmosphere of 1 pCi/L (37 Bq/m^3) for one year is comparable to 0.14 WLM, and 1 WLM results in a dose to the lung epithelium of about 6 mGy. Thus, a typical indoor concentration of radon of about 40 Bq/m^3 would result in a yearly dose to the lung of about 0.84 mGy (Committee on the Biological Effects of Ionizing Radiations (BEIR IV), 1988; UNSCEAR, 2000). Assuming a radiation weighting factor of 20 for α-particles would result in an equivalent dose to the lung of about 17 mSv/year. As described below, the dosimetry and conversions are complex and not entirely straightforward, and there remains some debate about the best dosimetry models and assumptions to be made.

Nevertheless, it is clear that the presence of radon at sufficiently high levels in residential areas poses an important risk for lung cancer.

(*a*) *Decay of radon and its progeny*

^{226}Ra is the immediate parent of ^{222}Rn, and radium is the fifth progeny of ^{238}U, which has a half-life of 4.5 thousand million years, which is similar to the age of the earth. A typical concentration of uranium in ordinary soil is 20 Bq/kg. ^{226}Ra has a half-life of 1600 years. The decay scheme of ^{222}Rn starts with ^{226}Ra and ends with stable ^{206}Pb. The first four progenies of radon (^{222}Rn), ^{218}Po, ^{214}Pb, ^{214}Bi and ^{214}Po, have half-lives that are shorter (all < 30 min) than the 22-year half-life of the fifth progeny, ^{210}Pb. Nearly 90% of the decay energy of the short-lived progenies occurs by α-particle emission, even though two of these decay by β-particle emission with associated γ-rays. Thus, under most circumstances, only the short-lived α-particle-emitting progenies are of consequence in the respiratory dosimetry of the radon chain. It should be mentioned that radon is an inert gas and ^{222}Rn has a half-life of 3.8 days, which is much longer than the time of ventilation (a few seconds). Because inhaled radon is largely exhaled again, it contributes negligibly to the dose to the lung, and it is only the short-lived progeny that are of concern. A typical concentration of radon in air over average soil is 4 Bq/m^3 (Committee on the Biological Effects of Ionizing Radiations (BEIR IV), 1988).

(*b*) *Quantities and units*

Holaday *et al*. (1957) introduced the working level (WL) as a convenient measure of the concentration of radon progeny in the air of uranium mines, which can be used as a measure of exposure. WL was defined as the combination of the short-lived progeny of radon (^{218}Po, ^{214}Pb, ^{214}Bi and ^{214}Po) in 1 L of air, under ambient temperature and pressure, that results in the ultimate emission of 1.3×10^5 MeV α-particle energy. This is approximately the total amount of energy released over a long period by the short-lived decay products in equilibrium with 100 pCi (3.7 Bq) of ^{222}Rn.

Only the short-lived progeny of radon are included in the definition of WL because they contribute most of the dose to the lung. The dose from β-particles is small, and the α-particles from radon itself are unlikely to be emitted within the body because almost all inhaled radon is exhaled. Most of the ^{210}Pb (22-year half-life) and subsequent progeny are probably eliminated from the body before they decay, although low levels of ^{210}Pb can be measured in heavily exposed miners many years later (Committee on the Biological Effects of Ionizing Radiations (BEIR IV), 1988; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999).

The SI unit for the potential α-energy concentration of radon decay products in air is J/m^3, where 1 J/m^3 = 6.24×10^{15} eV/L of air. 1 WL = 1.3×10^5 MeV/L = 2.08×10^{-5} J/m^3. The WLM was developed to account for both the duration and the level of exposure. It is defined as the product of the WL times the duration of exposure, i.e. during one month of 170 working hours. The unit WLM is equal to 170 WLh, i.e. exposure of 1 WL for 170 h (Committee on the Biological Effects of Ionizing Radiations

(BEIR IV), 1988). Activity is defined as the number of radioactive transformations of a radionuclide over unit time and is expressed in becquerels.

The concentration of radon decay products in indoor air is often expressed in terms of the 'equilibrium equivalent concentration' of radon. It corresponds to the activity concentration of radon for which the short-lived decay products in equilibrium with the parent have the same potential α-particle energy as radon itself. In practical terms, ventilation and deposition of radon decay products on surfaces are such that radioactive equilibrium is rarely reached. In order to account for this, an equilibrium factor (F) is used. The equilibrium factor is defined as the ratio of the potential α-particle energy concentration of the decay products to the corresponding concentration if they were in radioactive equilibrium with radon.

The equilibrium equivalent concentration of radon decay products in indoor air is expressed in units of Bq/m^3 as $F \times$ the activity concentration of radon (IARC, 1988).

(*c*) *Dose*

The relationship between exposure to radon progeny, whether measured as WLM or estimated as Bq/m^3, and the dose of α-energy delivered to cells in the respiratory tract, considered as targets for carcinogenesis, is extremely complex and depends on both biological and non-biological factors. Since the dose of α-energy delivered to the target cells in the lungs cannot be measured directly, models are used to simulate the sequence of events, from inhalation of radon progeny to cellular injury. These complex models generally include biological factors, such as airway geometry, mucociliary clearance, particle deposition, ventilation pattern and location of the target cells in the lung. Physical factors of importance are the amount of air inhaled, the aerosol size distribution and the proportion of progeny not attached to particles. Factors for converting exposure to an absorbed radiation dose can be calculated by using dosimetric models of the respiratory tract, but the range of published conversion factors is wide (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999).

The ratio of the dose of α-energy per unit exposure for a particular population group (men, women, children, infants), as given by the radon concentration, to the dose per unit radon concentration for miners is given by the K factor, which is defined as:

K = [dose (home)/exposure (home)]/[dose (mine)/exposure (mine)].

The K factor includes diverse environmental and physiological factors, and use of the double ratio simplifies the risk assessment for indoor radon. The dose-rate per unit radon concentration for miners is 7.0 nGy/h per Bq/m^3 . The National Research Council (1991), in its analysis of lung dosimetry, found a K factor of 0.75 for males and females and somewhat higher values for children and infants. The Committee on Health Effects of Exposure to Radon (BEIR VI) (1999) of the National Research Council determined that the median K factor in new computations was closer to 1, implying that the correction factor necessary for extrapolating data for mines to data for homes was not large (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999).

The latest report of UNSCEAR (2000) on natural activity summarized much of what is now accepted about exposure and dose to the lung for miners and from indoor radon concentrations: the studies of mines and homes give the same dose factor.

1.2 Occupational exposure

1.2.1 *Monitoring*

Differences in the results of monitoring of exposure of workers to radiation reflect changes over time in monitoring practices and techniques and simultaneous use of different methods to monitor the same exposure (UNSCEAR, 1993). Environmental or area monitoring, with air sampling or radiation monitoring devices at the entrance and exit of work areas, may provide information about the presence of radiation sources in the environment (UNSCEAR, 2000). Work surfaces may be routinely swabbed in order to obtain information about environmental contamination. When such contamination is detected, workers may be evaluated for internal exposure with mouth or nose swipes, estimates of contamination of clothing and/or skin and quantitative exposure assessments. When an incident has led to internal deposition of radioactive material, e.g. from a puncture wound while handling radioisotopes or accidental inhalation of volatile radioactive material, the exposure will usually be assessed by repeated individual monitoring

It is now quite common for workers with potential internal exposure to radiation to undergo routine (e.g. annual) monitoring, in order to ensure that the working conditions meet regulatory requirements (ICRP, 1991, 1994a; UNSCEAR, 2000). Task-related monitoring is sometimes undertaken to support decisions and actions to improve working conditions and to optimize protection. In general, individual monitoring involves more workers than are strictly necessary to meet regulatory requirements, and only a fraction of those monitored receive measurable doses (UNSCEAR, 2000).

(*a*) *Internal exposure*

Three main methods are used to assess individual internal exposure to radionuclides: personal air sampling, i.e. in the breathing zone of individual workers; in-vitro monitoring by analysis of biological materials; and in-vivo measurement of internal contamination by γ-spectroscopy. Personal air sampling may provide a measure of exposure in terms of the time-integrated air concentration of radionuclides in the breathing zone of individual workers. This is the only available method for routine monitoring of radon (UNSCEAR, 2000).

In-vitro monitoring involves measurement of radioactivity in concentrated or desiccated body fluids such as blood, urine or faeces. This type of monitoring has been used for many decades in the nuclear industry. For α- and β-particle emitters such as readily measurable, highly soluble radionuclides like ^{3}H, in-vitro monitoring is often the most sensitive method.

In-vivo monitoring of radionuclides that emit highly penetrating X- or γ-radiation, by counting of the whole body, thorax, skeleton and thyroid of a worker with a γ-ray spectrometer in a heavily shielded room, also gives the energy spectrum of the radionuclides. This technique was first used in the early 1960s. The two types of whole-body counters that have been used routinely are liquid scintillation counters, primarily in earlier periods, and solid crystal systems. When an internally deposited radionuclide does not emit X- or γ-radiation during radioactive decay, in-vivo monitoring may rely on detection of γ-rays emitted by associated radionuclides, such as γ-ray-emitting ^{241}Am, which is often deposited with plutonium. In-vivo monitoring of internal deposition of β-particle emitters, such as ^{32}P, may be based on the detection of the *bremsstrahlung* produced by the β-particles (McCunney *et al.*, 1999). In many situations, a combination of methods is used.

(*b*) *Accuracy and reliability of measurements*

The dose from intake of radioactive materials usually cannot be measured with the same degree of accuracy as that from external radiation. In particular, personal air sampling may not be adequate to estimate the annual intakes of individual workers exposed at the levels usually encountered in occupational settings. In a study of long-term low-level exposure of workers in nuclear fuel reprocessing, dose assessments obtained by static air sampling, personal air sampling and analysis of biological samples *in vitro* were compared. Personal air sampling provided a dose estimate that was about an order of magnitude higher that that deduced from static air sampling. For the group as a whole, there was reasonable agreement between the cumulative doses derived from biological sampling (23 mSv) and personal air sampling (30 mSv) over a seven-year period; however, at the individual level there was no correlation between the two sets of data (Britcher & Strong, 1994).

A number of factors may introduce uncertainty and/or bias into estimates of radiation dose from internally deposited radionuclides. One is uncertainty about the time of intake, which must be known in order to determine the organ burden from an in-vitro or in-vivo monitoring result. The most accurate assessment of organ or body burden can be made when an incident is known to have occurred and measurements were made *in vitro* and *in vivo* over time. In this case, a biological half-time can be obtained from the actual data. However, monitoring is usually conducted routinely (often annually), and organ burdens are difficult to deduce. When the time of intake is unknown, assumptions must be made about the pattern of activity between the time of first employment and the first measurement, about the organ burden between the time of the last measurement and the termination of employment and about the organ burden between measurements. If there is continuous intake of a radionuclide, it is reasonable to assume an average organ burden during the period between measurements, but this would not be appropriate if acute intake had occurred, and the method of integration must account for such intakes. In addition, accumulated activity and corresponding dose must be apportioned by year.

Internal dose can be calculated after γ-ray spectrometry *in vivo* from measurements of radioactive decompositions. When dose estimates derived from whole-body counting methods are used, the estimates of internal radiation dose may be erroneous, because of inhomogeneous distribution of radionuclides in the body and inappropriate assumptions about the ratios of radioisotopes ingested (e.g. the ratio of americium to plutonium). In addition, the detection limits of whole-body counters have changed over time and vary by radioisotope. In order to estimate internal organ doses from analyses of urine or any other biological sample, the amount of an isotope in a reference volume of the sample must be correlated with the amount in the body or in a specific organ. To achieve this, the activity of a nuclide eliminated per unit time must be determined, the activity in organs of interest must be inferred from the eliminated activity per unit time and the organ activity must be integrated over time to determine the cumulated organ burden and the total dose. Uncertainty in these estimates results from differences in excretion rates between individuals and within an individual over time and difficulties in characterizing the biological distribution of radionuclides in the body. Methods for calculating internal doses from in-vitro monitoring data follow from recommendations issued by the ICRP (1979, 1980, 1981, 1986). Estimates of internal exposure derived from air monitoring data are based on the integration over time of measured air concentrations of radioactive materials. Models are then used to estimate internal deposition from inhalation or ingestion of the radionuclide. While each of these internal dosimetry methods provides useful information for evaluating, and controlling, internal exposure to radiation, uncertainties in the estimates of the ensuing effective doses may be substantial and may be an important limitation when these data are to be used in epidemiological analyses. The accuracy of occupational exposure estimates has been assessed in several comparisons of estimates of body burden from analysis of urine samples and tissue taken at autopsy. Discrepancies were found: for example, urine-based assessments overestimated the plutonium body burden by approximately fivefold (Lagerquist *et al*., 1969; Heid, 1983).

1.2.2 *Exposed populations*

Workers employed in a number of industries have potential internal exposure to natural or man-made sources of ionizing radiation. Significant exposure can occur in mining of radioactive ores (uranium, mineral sands), and exposure to radon can occur in these and other mines, in caves open to tourists and in some above-ground workplaces. The luminizing industry provided an appalling example of the occupational hazards of radium. At present, however, occupational situations in which there is significant internal exposure to radionuclides are rare, and exposures have generally been decreasing. Activities in which exposure to internal radiation from man-made radionuclides may still be significant are the production of nuclear weapons, some situations in nuclear medicine for both diagnostic and therapeutic purposes and the nuclear fuel cycle.

Many of the data on occupational exposure cited below were taken from UNSCEAR (2000). Such data have been recorded systematically in various countries by national authorities and have been collected through an UNSCEAR questionnaire that is distributed throughout the world. In some cases, the data are supplemented by other — usually published — information; for example, the databank of the Organization for Economic Co-operation and Development (OECD)/Nuclear Energy Agency was used as an additional source of information on the nuclear power industry (OECD, 1996, 1998).

The generation of nuclear energy involves mining and milling of uranium, uranium enrichment, reactor fuel fabrication, reactor operation, nuclear fuel reprocessing, waste handling and disposal and research and development. For each main stage of this fuel cycle, except for treatment and disposal of solid radioactive waste, extensive data on occupational exposure and dose distributions are available. In the future, the decommissioning of nuclear reactors will become an important stage (UNSCEAR, 2000).

(*a*) *Uranium mining and milling*

Uranium mining and milling involve underground or open-pit removal of uranium ore, crushing and grinding of raw ore, followed by chemical leaching, separation of uranium from the leachate and precipitation as ‘yellowcake’. In the period 1990–92, worldwide uranium production by underground mining decreased from 55% to 45%, production by open-pit mining increased from 38% to 44%, while production by *in situ* leaching increased from 6% to 9%. Internal exposure during mining and milling of uranium ores may occur through inhalation of radon gas and radionuclides in ore dust. More internal exposure occurs in underground mines than in open mines, where inhalation of radioactive dust is probably the main source of internal exposure (UNSCEAR, 2000).

Urine was collected between 1950 and 1953 from 249 uranium mill workers in the USA and analysed for the presence of uranium. The concentrations were 0–3.0 μg/L for 80 workers, 3.1–9.0 μg/L for 116 workers, 9.1–30 μg/L for 46 workers and 30–160 μg/L for seven workers (Archer *et al.*, 1973).

The uranium mine at Rössing in Namibia consists of an open-pit area and a uranium milling plant. The average background radiation dose (excluding radon progeny) of all the miners was reported to be 1.8 mSv/year. Fourteen of these miners and six controls were chosen for assessment of uranium exposure by analysis of 24-h urine samples. The urinary concentration of ^{238}U (9.57 ± 7.9 mBq/L) was sixfold greater than the control level (1.5 ± 1.1 mBq/L; $p < 0.001$) (Zaire *et al.*, 1996).

Worldwide exposure during uranium mining and milling is summarized in Tables 10 and 11 (UNSCEAR, 2000).

Table 10. Occupational exposure in uranium mining worldwide

Period[a]	Annual amount of uranium ore extracted (thousand tonnes)	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	52	240	1300	5.5
1980–84	64	310	1600	5.1
1985–89	59	260	1100	4.4
1990–94	39	69	310	4.5

From UNSCEAR (2000)

[a] Data are annual averages over the periods indicated. For 1990–94, the worldwide estimates are extrapolated from the total amount of uranium mined worldwide relative to the sum of the total for which an estimate was made.

Table 11. Occupational exposure in uranium milling worldwide

Period[a]	Annual amount of uranium ore refined (thousand tonnes)	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	53	12	124	10.1
1980–84	64	23	117	5.1
1985–89	58	18	116	6.3
1990–94	39	6	20	3.3

From UNSCEAR (2000)

[a] Data are annual averages over the periods indicated. The worldwide estimate is based on the assumption that the amount of uranium ore refined is equal to the amount mined.

(*b*) *Uranium enrichment and conversion*

During uranium conversion, U_3O_8 from the milling process is reduced to UO_2 by reduction with hydrogen, and the UO_2 is then converted to UF_4 by addition of hydrofluoric acid, and subsequently to UF_6 with fluorine. The UF_6 is then enriched in ^{235}U (to about 3%; natural uranium contains about 0.7% ^{235}U) by gaseous centrifugation. After enrichment, UF_6 is reconverted into UO_2 for fuel fabrication. During these processes, occupational exposure is mainly to external radiation, but workers may be exposed to internal irradiation during maintenance work or in the event of leaks.

The Y12 plant in Oak Ridge, TN (USA), was built in 1943 for enrichment of uranium for nuclear weapons. In 1947, its activities shifted to fabrication of weapons parts and nuclear research. Exposure to airborne uranium dust was the major concern at this plant, in particular during the reduction of UF_4 to metal, casting of the metal

and extraction of the UF_4. Estimates of dose equivalents of uranium delivered to the lungs of 3490 workers were obtained from urine analysis and in-vivo counting of internally deposited uranium. For cumulative doses of internal α-irradiation, values of more than 0.3 Sv were found for about 5% of these workers, 0.1–0.3 Sv for about 25%, 0.01–0.1 Sv for about 50% and < 0.01 Sv for about 20%. These levels are at least an order of magnitude lower than those estimated for uranium miners (Checkoway *et al.*, 1988).

A group of 991 workers employed between 1943 and 1949 at the ceramics plant of Linde Air Products (Buffalo, NY, USA) were monitored for internal exposure to uranium. The plant was mainly involved in uranium processing and conversion to UF_4, and experimental work was done on conversion of UF_6 to UO_3. The potential doses to the lung were estimated from the concentration of uranium in the urine of these workers: 212 workers had an annual lung dose < 10 mSv, 402 workers had doses of 10–100 mSv, and 377 workers had doses > 100 mSv (Dupree *et al.*, 1987).

During four five-year periods between 1975 and 1994, 11 000, 4300, 5000 and 12 600 workers were monitored and found to have total annual collective effective doses of 5.3, 0.78, 0.43 and 1.28 person–Sv, respectively. These doses would correspond to average annual effective doses per worker of 0.46, 0.18, 0.08 and 0.10 mSv in these periods, respectively. It should be noted that uranium is enriched and converted in only seven countries and that the worldwide data should be considered rough estimates, as not all these countries provided data for each of the periods (UNSCEAR, 2000).

(*c*) *Reactor fuel manufacture*

Depending on the reactor type, four types of uranium fuel are used: un-enriched uranium metal fuel (used in gas-cooled Magnox reactors), low-enriched UO_2 fuel (used in advanced gas-cooled, graphite-moderated reactors and in light water-moderated and cooled reactors), un-enriched UO_2 fuel (heavy water-cooled and -moderated reactors) and mixed UO_2–PuO_2 fuel (used in light-water and fast-breeder reactors). The main source of exposure during fuel manufacture is uranium, because most decay products are removed during enrichment and conversion. Exposure is from external γ-irradiation and intake of airborne radionuclides. Exposure during reactor fuel manufacture is summarized in Table 12. Despite an approximately threefold increase in the volume of fuel produced, the collective dose has been relatively constant over time. It follows that the collective dose per amount of fuel or per unit energy produced has decreased considerably over the past 20 years (UNSCEAR, 2000).

(*d*) *Reactor operations*

Nuclear reactors for the generation of electrical energy are characterized by their coolant system and moderator: light water-moderated and -cooled pressurized or boiling-water reactors, heavy water-moderated and -cooled reactors, gas-cooled, graphite-moderated reactors and light water-cooled, graphite-moderated reactors. The

Table 12. Occupational exposure in nuclear fuel manufacture worldwide

Period[a]	Annual production of fuel (thousand tonnes of uranium)	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	3.6	20	36	1.8
1980–84	6.1	21	21	1.0
1985–89	9.7	28	22	0.8
1990–94	11.3	21	22	1.0

From UNSCEAR (2000)

[a] Data are annual averages over the periods indicated.

moderator material is used to slow down the fast neutrons generated during the fission of uranium. At the end of 1997, there were 437 nuclear power stations operating worldwide, with a capacity of about 352 GWe (net gigawatts electric), supplying approximately 17% of the total electric energy generated in the world and accounting for about 6% of the world's energy consumption. Over 300 of the nuclear power stations (three-quarters of the total number) are light-water reactors (UNSCEAR, 2000).

Occupational exposures during normal reactor operation can vary considerably, depending on the size, type and age of the reactor, reactor water chemistry and operating procedures. External exposure to γ-radiation is the most significant component of occupational exposure around nuclear reactors. Workers at heavy-water reactors may have internal exposure to radionuclides, particularly ^{3}H, as deuterated water is used as both the coolant and the moderator. In these reactors, neutron activation of deuterium produces a significant amount of ^{3}H (UNSCEAR, 2000).

Workers at the Dounreay Establishment (Atomic Energy Authority) in the United Kingdom, a prototype fast reactor in operation since 1973, were monitored for internal exposure to radionuclides by a combination of personal and static air sampling, excretion monitoring and in-vivo counting. In addition to electricity production, the reactor provides facilities for testing materials and developing advanced fuels. Plants for fuel reprocessing and manufacture of fuel elements are also located on this site. During 1987, the workforce (n = 1778) received a total dose of 3.93 person–Sv, of which 3.21 person–Sv were from external radiation and 0.72 person–Sv (committed effective dose equivalent) from internal radionuclides. In 1988 (workforce, 1702 persons), these values were 4.11 (total), 3.21 (external) and 0.90 person–Sv (internal exposure). The highest internal doses were received by workers in waste management, engineering support and analytical services. During these two years, the exposure of none of the workers exceeded the self-imposed target of 15 mSv (committed effective dose equivalent) (Smith *et al.*, 1991).

Internal exposure to radionuclides was measured for workers at nuclear power stations in France, as part of a routine medical control programme. Between 1980 and 1985, the number of urine analyses increased from about 2200 to 7300 per year, and < 0.5% of the samples were active. The major isotopes detected were ^{58}Co, ^{60}Co, ^{131}I and ^{137}Cs, with detection limits in routine analyses of 0.6, 0.5, 0.7 and 0.8 Bq, respectively (Kwadow & Chevalier, 1988).

Data on occupational exposures at reactors worldwide are given in Table 13. The annual effective dose of monitored workers, averaged over all reactors, decreased from 4.1 to 1.4 mSv over the periods 1975–79 and 1990–94, while the energy production increased by more than fourfold. Accordingly, the dose per unit of energy produced has decreased considerably over the past two decades (UNSCEAR, 2000).

Table 13. Occupational exposure in normal reactor operations worldwide

Period[a]	Total no. of reactors	Average amount of energy generated (GW–year)	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	190	5	150	600	4.1
1980–84	280	100	290	1000	3.5
1985–89	400	190	430	1100	2.5
1990–94	421	230	530	900	1.4

From UNSCEAR (2000)

[a] Data are annual averages over the periods indicated.

(*e*) *Fuel reprocessing*

Irradiated spent fuel from nuclear power stations on a commercial scale is reprocessed only in France and the United Kingdom, while smaller facilities are in operation in India, Japan and the Netherlands. The Russian Federation has been reprocessing fuel for reactors developed in that country. The process involves dissolution of the spent fuel elements in acid, followed by chemical separation of uranium and plutonium from the fission products and other compounds in the fuel. At the time of reprocessing, the fuel still contains high levels of radioactive materials, and heavy shielding and remote operations are required for adequate protection of workers. Both in France and the United Kingdom, the average annual effective dose of monitored workers decreased steadily over the four five-year periods between 1975 and 1994, from 4.03 to 0.36 mSv and from 8.31 to 2.03 mSv, respectively. The Japanese data showed an increase during the period 1975–89 from 0.44 to 0.98 mSv, and a decrease to an average of 0.32 mSv over the following five years. Data from the Russian Federation over the period 1990–94 showed an average annual effective dose of 2.82 mSv (UNSCEAR, 2000).

(*f*) *Waste management*

Only a very small portion of the radioactive waste from the nuclear fuel cycle has been moved to final repositories, but the doses associated with waste management are of increasing importance. In 1993, the cumulative total amount of spent fuel arising from all types of reactors was estimated to be about 145 000 tonnes of heavy metal, whereas the storage capacity at reactors is about 59 000 tonnes of heavy metal. The exposure associated specifically with waste management is not readily known, and the doses associated with waste management have been subsumed into data for reactor operation, reprocessing and research (UNSCEAR, 2000).

(*g*) *Research in the nuclear fuel cycle*

Worldwide occupational exposure arising in nuclear research is summarized in Table 14. The annual number of workers remained relatively constant, and the annual collective dose decreased from 170 to 90 person–Sv in the two decades between 1975 and 1994. Accordingly, the average annual effective dose per worker decreased from 1.4 to 0.8 mSv. Among the workers monitored, the proportion exposed to > 15 mSv decreased from 4% to 1% during the same period (UNSCEAR, 2000).

Table 14. Occupational exposure in research in the nuclear fuel cycle worldwide

Period[a]	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	120	170	1.4
1980–84	130	150	1.1
1985–89	130	100	0.8
1990–94	120	90	0.8

From UNSCEAR (2000)
[a] Data are annual averages over the periods indicated.

Worldwide annual exposure during the commercial nuclear fuel cycle is summarized in Table 15. The number of workers monitored increased to 880 000 up to 1989 and then decreased to 800 000, largely because of a substantial reduction in the number of workers in the mining sector. This also explains the decrease in collective effective dose during the period 1985–94. At present, about 530 000 workers (65%) are involved in reactor operation. Table 15 also shows the downward trend in the collective effective dose per unit nuclear energy generated, with an approximately twofold reduction over the periods studied. The trends in numbers of monitored workers and doses of workers in the various sectors of the nuclear fuel cycle are illustrated in Figure 3 (UNSCEAR, 2000).

Table 15. Average annual occupational exposure in the commercial fuel cycle worldwide

Period[a]	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Total annual collective effective dose per unit nuclear energy generated (person–Sv per GW–year)	Average annual effective dose (mSv)
1975–79	560	2300	20	4.1
1980–84	800	3000	18	3.7
1985–89	880	2500	12	2.9
1990–94	800	1400	9.8	1.8

From UNSCEAR (2000)
[a] Data are annual averages over the periods indicated.

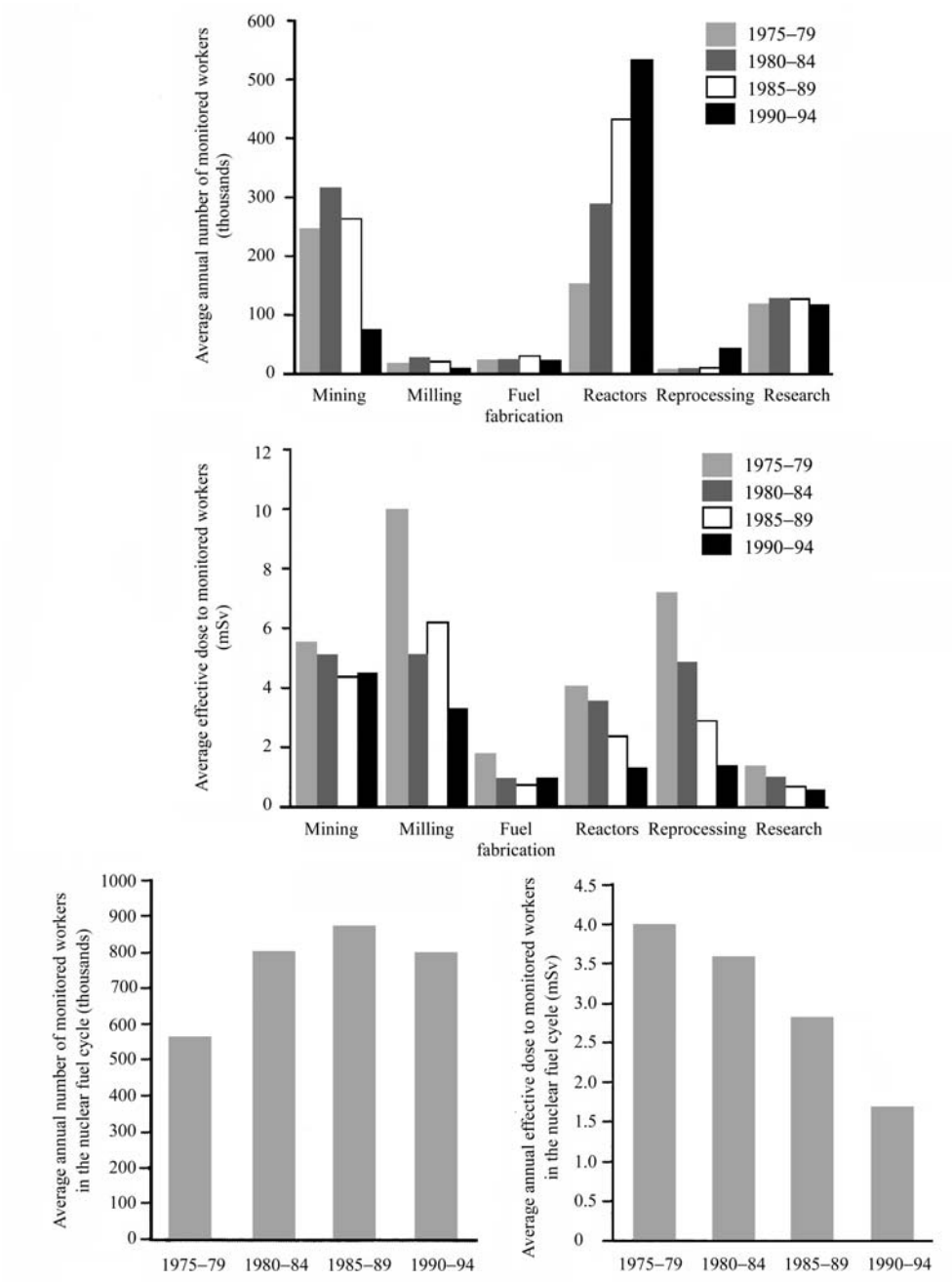
(*h*) *Mineral processing*

There is a substantial worldwide industry in which minerals and ores containing relatively high concentrations of uranium and thorium are mined, milled and processed, either to recover the metals themselves or to obtain the minerals that occur with them. Examples of such ores and minerals are bastneasite (thorium, 5 kBq/kg), monazite (uranium, 6–20 kBq/kg; thorium, 4–7% by weight), phosphate (uranium, 0.1–4 kBq/kg), pyrochlore and columbite (uranium, 50 kBq/kg; thorium, 50 kBq/kg). Exposure to dusts during dry operations in un-enclosed facilities is the major source of internal deposition of the radionuclides. It has been estimated that handling of materials containing activity concentrations of 1–10 kBq/kg could lead to annual effective doses to workers of approximately 1–2 mSv from external and internal exposure (UNSCEAR, 2000).

Mineral sands containing concentrations of thorium up to 8% are mined and processed in Australia, India, Malaysia and South Africa. Minerals recovered in mines in Western Australia are listed in Table 16, the main production activities being directed at ilmenite and zircon; however, monazite (containing 5–7% thorium) is an important component of inhalatory exposure, because it concentrates preferentially in airborne dust. Exposure has been reduced significantly in the Western Australian mineral sands industry: the mean annual dose declined from about 25 mSv (of which 10% was due to internal exposure) to around 6 mSv (15% internal exposure) in the period 1990–94 (UNSCEAR, 2000).

Measurement of ^{220}Rn in the exhaled breath of workers in thorium refineries is often used as an indication of internal contamination with ^{232}Th. These workers inhale the radionuclides ^{232}Th, ^{228}Ra, ^{228}Th, ^{224}Ra and their associated decay products. A certain fraction of ^{220}Rn produced by internally deposited thorium and radium is exhaled in breath. Workers at a thorium-processing plant in Trombay, India, were monitored for internally deposited ^{232}Th by analysis of exhaled air. The results are expressed in Q_{Ra} units, i.e. the equivalent activity (in Bq) of ^{224}Ra measured as ^{220}Rn at the mouth, with

Figure 3. Trends in numbers of monitored workers and doses to workers in the nuclear fuel cycle



From UNSCEAR (2000)

Table 16. Minerals recovered in the mineral sands industry in Western Australia

Mineral	Chemical formula	Per cent of production	Concentration (% by weight)	
			Thorium	Uranium
Ilmenite	$FeOTiO_2$	76	0.005–0.05	0.001–0.003
Monazite	$[Ce, La, Nd, Th]PO_4$	< 1	5–7	0.1–0.5
Rutile	TiO_2	< 5	0.005–0.01	0.001–0.003
Zircon	$ZrSiO_4$	19	0.01–0.025	0.015–0.03
Xenotine	YPO_4	< 1	1.5	0.4

From UNSCEAR (2000)

a lower detection limit of 0.56 Bq. For three categories of workers (100 operators, 55 maintenance workers and 21 supervisors), the Q_{Ra} values were < 0.56 Bq for 33%, 45.5% and 57.2% and 1.11–1.85 Bq for 27%, 18% and 14% of the workers, respectively. Q_{Ra} values of > 1.85 Bq were measured for 19% of the operators, for 1% of the maintenance workers and for none of the supervisors (Mayya *et al.*, 1986).

The Baiyan Obo rare-earth and iron mine is sited in Inner Mongolia in China and is one of the largest rare-earth mines in the world. It has been in operation since 1958. Its ore contains not only iron, rare-earth elements and silica but also 0.04% thorium. In a 14-year follow-up study, the lung burden of thorium was estimated for 638 miners who had inhaled dust, on the basis of measurements of exhaled ^{220}Rn, measured as ^{224}Ra equivalent activity. The average lung burden was estimated to be 1.60 Bq during 1983–84, and the highest value was 11.11 Bq. Of these workers, 585 (91.7%) had lung burdens < 2.22 Bq, while the average lung burden in 143 controls was calculated to be 0.30 Bq (Chen *et al.*, 2000). The airborne concentrations of ^{232}Th were in the range of 0.015–1.41 Bq/m^3, with an average of 0.3 Bq/m^3 (Chen *et al.*, 1993).

(i) *Nuclear weapons production*

The main potential sources of occupational exposure to radionuclides during the development and production of nuclear weapons are ^3H and the two fissile materials plutonium and uranium. Exposure may occur through intake of these materials into the body by inhalation or ingestion (or absorption through the skin in the case of ^3H), and through external irradiation from γ-rays and, to a lesser extent, neutrons. Application of safety measures and containment of the radioactive materials has reduced internal exposure to below external exposure (UNSCEAR, 2000).

Significant internal depositions of plutonium occurred in workers on the Manhattan Project at Los Alamos (USA) in 1944 and 1945. Twenty-six workers were selected in 1951 for long-term follow-up. They were exposed mainly by inhalation, owing to poor working conditions, use of open-faced chemical hoods and inadequate respiratory protection. Tissue contaminated through minor cuts or puncture wounds was excised from seven subjects on the day of the injury. The radioactivity in one of the tissue

samples amounted to 55 Bq, and the other samples contained < 1 Bq. Fifty years after the period of exposure, one subject still had residual activity (310 Bq) around the wound site, but the radioactivity in the excised tissue had not been measured in this case. Internal plutonium deposition was estimated on the basis of measurements of plutonium in urine. The effective doses, calculated as the sum of the annual effective doses through 1994 or the year of death, ranged from 0.1 to 7.2 Sv (mean, 2.08 Sv; median, 1.25 Sv). Direct in-vivo measurements of ^{239}Pu and ^{241}Am in the lungs showed activity over the background level in only one subject, who had 7 Bq of ^{241}Am on his chest count (Voelz *et al.*, 1997).

Kathren *et al.* (1987) reported an interlaboratory study to compare estimates of internally deposited plutonium from urine analysis and from measurements in autopsy tissue of 17 individuals in the Transuranium and Uranium Registry in the USA, after exposure to plutonium. Intake occurred mainly through acute inhalation, skin contamination or through contaminated wounds. Samples of the liver and skeleton, the major reservoir organs for plutonium, were collected at autopsy and analysed radiochemically for ^{239}Pu content. The estimated total body burden of the 17 subjects ranged from 0.01 to 0.77 kBq. Estimates of systemic deposition of plutonium on the basis of analysis of urine were compared with earlier observations (Langham, 1957) in 18 human subjects who were injected experimentally with plutonium citrate. In 16 cases, these estimates were consistently higher (1.5–22-fold) than those from the analysis of tissues collected at autopsy, particularly at lower levels of plutonium. The results suggest that the method used to convert urinary concentrations to body burden results in overestimates of the latter.

Internal exposure to incorporated ^{239}Pu was estimated for 500 workers at the Mayak nuclear enterprise in the southern Urals by analysis of the amount of ^{239}Pu in urine. The absorbed dose to the lung from internal α-radiation was estimated on the basis of the ICRP lung clearance models. The mean ^{239}Pu body burden was 0.01 kBq for 130 workers, 0.34 kBq for 68 workers, 1.2 kBq for 125 workers, 4.2 kBq for 95 workers, 16.5 kBq for 63 workers and 54.2 kBq for 19 workers. The mean absorbed lung dose was 0 Gy for 100 workers, 0.04 Gy for 166 workers, 0.35 Gy for 149 workers, 1.38 Gy for 31 workers, 3.30 Gy for 36 workers and 9.70 Gy for 18 workers. The mean exposure to external γ-radiation, determined from personal film badges, was 0.3 Gy for 230 workers, 1.4 Gy for 117 workers, 2.7 Gy for 144 workers and 5.4 Gy for nine workers (Tokarskaya *et al.*, 1997a).

An updated report on the characteristics of the Mayak workforce (n = 14 416) provided details on the plutonium body burden of 4186 workers (3136 men, 1050 women) on the basis of urinary excretion data. The results are shown in Table 17. In the group with the heaviest exposure (> 3.70 kBq), the average plutonium body burden was 12.91 kBq for men and 29.66 kBq for women. For all workers with a measurable body burden (0.74–3.70 kBq), the overall average values were 2.19 kBq for men and 4.02 kBq for women (Koshurnikova *et al.*, 1999).

Table 17. Distribution of plutonium body burden among workers at the Mayak nuclear plant, Russian Federation

Pu body burden (kBq)	Men	Women
Not detected	413 (13%)	174 (17%)
< 0.74	1492 (48%)	494 (47%)
0.74–1.47	516 (16%)	179 (17%)
1.48–2.95	342 (11%)	94 (9%)
2.96–3.69	64 (2%)	10 (1%)
> 3.70	309 (10%)	99 (9%)

From Koshurnikova *et al*. (1999)

Plutonium intake by workers at the Sellafield plant of British Nuclear Fuels (United Kingdom) was also assessed by monitoring urine samples. Exposure at Sellafield was to so-called 'plutonium α' isotopes (^{239}Pu and some ^{238}Pu and ^{240}Pu) and to ^{241}Pu, which decays by β-particle emission to the α-particle emitter ^{241}Am. Before 1960, the plant mainly produced plutonium for military purposes, and exposure to ^{241}Pu began only after that time, during commercial reprocessing of spent nuclear fuel. The uptake was estimated for about 4600 workers employed at Sellafield for some time between 1950 and 1990. The average annual intake of 'plutonium α' isotopes increased in the first years to 100 Bq per year and then decreased to near background levels in 1965. Intake of ^{241}Pu increased to an average annual value of 250 Bq in 1970, which decreased to 100 Bq in 1990 (Omar *et al.*, 1999).

Operations involving ^{210}Po were conducted at the Mound Facility in the USA from 1944 to 1972. The facility was established to support the Manhattan Project and focused on the separation and chemical preparation of polonium. Urine bioassays to monitor personnel for internal exposure to ^{210}Po were conducted throughout operation of the plant. The data from the urinary analyses were used to compute the estimated doses to the kidney and spleen, that to the kidney being assumed to represent the overall soft-tissue dose. Four dose groups were distinguished: < 10 mSv, 10–100 mSv, 100–1000 mSv and > 1000 mSv. Workers in these four groups had accumulated 40 700, 8000, 6760 and 4300 person–years, respectively, at the Mound facility. The mean effective dose from external radiation (26.5 mSv) was approximately the same for all groups, except for those exposed to > 1000-mSv, who had a mean effective dose of 36.1 mSv from external exposure (Wiggs *et al.*, 1991).

A worker at the Hanford nuclear waste treatment facility in the USA who was injured in 1976 during chemical explosion of an ion-exchange column used for the recovery of ^{241}Am, was monitored until his death in 1987. He was exposed to the radionuclide through inhalation and via wounds on his face and neck. The victim received calcium trisodium diethylene triamine pentaacetate (DTPA) and zinc DTPA as long-term decorporation therapy, with several daily doses during the first month.

A total of 583 g of DTPA was administered between 1976 and 1980, with no apparent toxic effects. Detailed external measurements of internally deposited ^{241}Am were started on the third day after exposure. Lung, liver, bone and the skin of the face and neck were found to have received the highest dose rates. Three days after the accident, the organ burdens were reported to be 26 MBq for skin, 960 kBq for lungs, 480 kBq for bone and 1400 kBq for liver. After 10 years, the values had decreased to 110 kBq for skin, 350 kBq for bone and 19 kBq for liver, with only residual activity (about 2 kBq) in the lungs. The total amount of radionuclide excreted from the body was 41 MBq, about half of which was excreted in the first three days. DTPA therapy appeared to be effective in preventing ^{241}Am deposition in bone and liver; significant re-deposition in the liver occurred upon termination of the DTPA treatment. The only radiation effects were depressed lymphocyte, platelet and neutrophil counts in the peripheral blood and cytogenetic effects in the lymphocytes (Breitenstein & Palmer, 1989).

Data on the exposure of workers in defence activities in the USA related to nuclear weapons are given in Table 18. Combined data for workers in the United Kingdom and the USA in all defence activities (nuclear weapons manufacture and associated activities, operating nuclear vessels and their support facilities) are given in Table 19 (UNSCEAR, 2000).

Table 18. Occupational exposure of workers in defence activities related to nuclear weapons (USA)

Year	Monitored workers (thousands)	Measurably exposed workers (thousands)	Average dose to measurably exposed workers (person–Sv)	Collective effective dose equivalent (person–Sv)		
				External[a]	Internal	Total
1990	108	36.0	0.85	22.3	8.2	30.5
1991	120	31.3	0.82	17.6	8.1	25.7
1992	124	29.4	0.78	15.0	7.9	22.9
1993	127	24.0	0.68	15.3	0.95[b]	16.3
1994	117	25.4	0.65	16.0	0.43	16.4
1995	127	23.6	0.78	18.1	0.31	18.4

From UNSCEAR (2000)
[a] γ-Radiation and neutrons
[b] Considerably less than that in previous years because of changes in calculating internal exposure

(*j*) *Nuclear medicine* (see also section 1.3)

The aim of nuclear medicine is to investigate physiological processes, in most cases by measuring organ function. The use of radionuclide generators, especially those of ^{99m}Tc, involves handling of large amounts of radioactivity. The radionuclides used in organ imaging (e.g. ^{99m}Tc) and in treatment (e.g. ^{131}I) emit penetrating γ-radiation, and

Table 19. Occupational exposure of workers in all defence activities (United Kingdom and USA)

Period[a]	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	104	137	1.3
1980–84	116	82	0.71
1985–89	127	84	0.66
1990–94	139	33	0.24

From UNSCEAR (2000)
[a] Data are annual averages over the periods indicated.

the main exposure of personnel occurs during imaging, i.e. while injecting the patient and positioning the patient and the camera. The internal exposures of personnel are usually much lower than these external exposures. Data on the exposure during nuclear medicine procedures worldwide are given in Table 20. While the number of monitored workers increased during the four five-year intervals studied, the average annual effective dose remained fairly constant at about 1.0 mSv during 1975–90 and decreased to approximately 0.8 mSv during the period 1990–94. Regional variations have been observed, most notably in Latin America and the Indian subcontinent, with a value of about 2.3 mSv (UNSCEAR, 2000).

The increasing number of new radiopharmaceuticals and the increased dose per patient may enhance the radiation burden of radiopharmacy personnel. At present, a medium-sized radiopharmacy may order seven to eight 3-Ci [11.1×10^4 MBq] ^{99}Mo/-^{99m}Tc generators per week and may perform 10–15 elutions per day. The maximum radiation exposure of radiopharmacy personnel occurs during generator elutions, compounding (kit preparation) and unit-dose dispensing. Additional exposure can occur

Table 20. Occupational exposure in nuclear medicine worldwide

Period[a]	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	61	62	1.01
1980–84	81	85	1.04
1985–89	90	85	0.95
1990–94	115	90	0.79

From UNSCEAR (2000)
[a] Data are annual averages over the periods indicated.

during receipt of radioactive packages, transport of prepared doses and storage and disposal of radioactive waste. Doses to the fingers and hands of 140–210 mSv/year have been reported. Such doses can be reduced by a number of techniques, including use of forceps during transfer of radioactive vials and syringes and use of a syringe shield during unit-dose dispensing. Most of the exposures mentioned here are from external radiation. During the preparation of unsealed doses or capsules of radioactive iodine, however, there is potential for a high internal dose from inhalation of volatile solutions (Heller, 1996).

Personnel working with ^{125}I at a Swedish hospital were monitored regularly over 20 years for the ^{125}I content of their thyroids. Four categories were studied: chemists performing ^{125}I-labelling of proteins and hormones, using up to 74 MBq per single labelling; laboratory staff performing mainly radioimmunoassays (approximately 1 kBq ^{125}I per sample); nuclear medicine staff giving intravenous injections of ^{125}I-labelled radiopharmaceuticals (up to 4 MBq per injection) to patients; and administrative staff working in the same departments as the above categories but not handling ^{125}I. Personnel from another department, not working with ^{125}I, were used as a control group. During the period 1977–90, the chemists had a mean ^{125}I activity of 1.5 kBq in their thyroids, giving a yearly absorbed dose of 10 mGy to this organ. A value of 7.4 kBq (53 mGy/year) was recorded on one occasion in one person. The mean activity for laboratory staff was 140 Bq, with an individual value of 4 kBq recorded in this group. For the nuclear medicine staff, an average thyroid activity of 30 Bq ^{125}I was recorded. Control personnel in the same department had received up to 25 Bq, indicating diffuse, low-level contamination with ^{125}I in the work area. Control subjects from elsewhere in the hospital showed no measurable ^{125}I in their thyroids (< 2 Bq). A trend was noted towards decreasing internal contamination with time during the period 1977–90 in spite of constant use of ^{125}I. A further decrease in internal contamination during 1991–1996 was attributed to a decrease in the use of ^{125}I (Jönsson & Mattsson, 1998).

An evaluation was made of the doses received by staff working in a nuclear medicine department and by children who may be in close contact with a parent receiving treatment with radionuclides. Dose rates were measured at distances of 10 cm, 50 cm and 1.0 m from the skin surface at the level of the thyroid, chest and bladder of patients undergoing the following procedures: multiple-gated acquisition scans to determine coronary function with ^{99m}Tc-labelled red blood cells, myocardial perfusion scans with ^{99m}Tc-labelled radiopharmaceuticals, lymphoscintigraphy with colloidal ^{99m}Tc (Re) sulfide, bone scans with ^{99m}Tc-labelled oxidronate, ^{111}In-octreotide scans, ^{111}In-labelled leukocyte studies and cardiac re-injection studies with ^{201}Tl. The maximum dose rates at 10 cm were those in myocardial perfusion (one-day protocol, 391.7 μSv/h; two-day protocol, 121.8 μSv/h) and multiple-gated acquisition scans (167.3 μSv/h). The maximum dose received by an infant in close contact with a parent after a nuclear medicine investigation was estimated to be 1.53 mSv, which arose from close contact (approximately 13 h during a 40-h period following treatment) with a parent who had received a ^{99m}Tc myocardial perfusion on a one-day protocol. It is

unlikely that a nuclear medicine technician would receive an annual dose of more than 6 mSv. Likewise, doses received by the nurses of patients treated with radiopharmaceuticals are probably < 6 mSv/year, except perhaps when they are in regular contact with large numbers of helpless patients (Greaves & Tindale, 1999).

Administration of a radiopharmaceutical to a patient gives rise to a radiation hazard to the patient and, possibly, to critical groups exposed to the patient. Estimation of the effective doses for adult and paediatric patients is limited by uncertainties about the biokinetics and the assumption of a uniform distribution of activity in each organ. In the United Kingdom, the effective doses from most nuclear medicine procedures do not exceed twice the annual dose from natural background radiation. Lack of data on human placental transfer is now the main limitation to estimating fetal doses. Internal exposure to radionuclides may occur during breast-feeding of an infant by a mother who has received treatment with radiopharmaceuticals. To ensure that the effective annual dose to the infant does not exceed 1 mSv, interruption of breast-feeding is recommended in some cases (for 25 h after administration of 80 MBq ^{99m}Tc-pertechnetate) and cessation of breast-feeding in others (treatment with ^{32}P-phosphate, ^{131}I-iodide) (Mountford, 1997).

(*k*) *Luminizing*

Luminizing is one of the oldest industrial uses of ionizing radiation. Employment in the luminizing industry in the USA began around 1913, and about 5000 workers are known to have been employed in this industry between 1915 and 1980. While they were not all involved in dial painting, all were at some risk of occupational exposure to the radiation emitted by the radium present at the worksite. Initially, the luminizing paints were enhanced with ^{226}Ra alone, but later some paints contained a mixture of ^{226}Ra and ^{228}Ra. The greatest risk of internal exposure to radium was that of the early dial painters who used to 'tip' and 'point' their brushes between their lips. Before 1925, the daily intake of radioactive substances is estimated to have been 3–48 μg. 'Tipping' was officially banned in the USA in 1926 (Fry, 1998).

The radium body burdens were measured of two groups of female radium-dial workers in the USA, whose first year of employment was either before 1930 (n = 693) or between 1930 and 1949 (n = 561). Measurements were performed by γ-ray spectroscopy of ^{228}Ra *in vivo* and by analysis of radon in exhaled air. The proportions of ^{226}Ra and ^{228}Ra in the paint used in the dial industry before 1930 varied over time and among companies, some factories often using paints very rich in either ^{228}Ra or ^{226}Ra. The estimated total radium intakes of the group employed before 1930 were < 0.5 μCi [about 20 kBq] for 29% of the women, 0.5–4.9 μCi [about 20–200 kBq] for another 29%, 5–50 μCi [about 200–2000 kBq] for 26% and > 50 μCi for 16%. During 1930–49, the radium body burdens were approximately 100-fold lower than before 1930, and ^{228}Ra was not in use during this period. Only 1% of the 561 workers in this group had estimated intakes above 4.9 μCi; 32% had intakes of 0.5–4.9 μCi, and 67% had estimated intakes of < 0.5 μCi (Stebbings *et al.*, 1984).

The United Kingdom radium luminizer survey covered 1110 women who had worked as luminizers between 1939 and the late 1950s. Luminizing was not widespread in the United Kingdom until the Second World War, when there was a demand for luminous aircraft instruments. On the basis of the experience in the USA during the 1920s and 1930s, the intake of radium during painting was more strictly controlled, leading to much lower exposure levels. The body burdens of the 459 women monitored were < 0.01 μCi [370 Bq] ^{226}Ra for 197, 0.01–0.03 μCi [370–1110 Bq] for 202 and > 0.03 μCi for 60 women. From a retention model of alkaline earths in the body, it was estimated that the mean systemic intake of these groups had been 22, 3 and 0.4 μCi [814, 111 and 15 kBq], respectively. If it is assumed that the systemic intake was 0.02 Sv/μCi, the committed doses to the red bone marrow would have been 440, 60 and 8 mSv (Baverstock & Papworth, 1985).

The decay of ^{226}Ra deposited in the bone of workers in the luminizing industry gives rise to formation of ^{210}Pb and ^{210}Po *in situ*, and these radionuclides may be transferred away from the site of deposition of the radium. In one case, the bone of a former dial painter contained ^{226}Ra at about 4000 pCi/kg [148 Bq/kg] and ^{210}Po at 1500 pCi/kg [56 Bq/kg], the ratio of bone:soft-tissue concentration being much higher for ^{210}Po than after direct intake of this radionuclide. The highest concentration of polonium in any tissue in the radium-dial painters was found in hair, one sample containing 25 μCi/kg [925 kBq/kg] (Hill, 1965).

With time, there has been a shift in the luminizing industry from use of radium to use of ^{3}H and, to a lesser extent, ^{147}Pm. The number of workers involved during 1975–94 was small (< 1000). The number of workers monitored during 1990–94 was about 80, and the average annual effective dose was 0.4 mSv (UNSCEAR, 2000).

(*l*) *Radioisotope production and distribution*

Occupational exposure during the production and distribution of radioisotopes for a wide variety of industrial and medical purposes stems mainly from external irradiation. Internal exposure has generally not been included in the exposure data, but when this was reported, e.g. for the United Kingdom from 1985 and for Finland from 1987 onwards, the contribution of internal exposure to the total dose was estimated to be a few per cent. Worldwide, the estimated total number of workers involved in radioisotope production and distribution increased from 57 000 to 88 000 in the period 1975–89 and decreased to 24 000 in 1990–94. This decrease probably reflects rationalization of production and concentration of activities by multinational companies in a limited number of places. The estimated worldwide annual collective effective dose decreased from more than 130 person-Sv in 1975–79 to 47 person–Sv in 1990–94, and the annual effective dose per monitored worker decreased from 2.3 to 1.9 mSv over 1975–94 (UNSCEAR, 2000).

(*m*) *Research centres*

Research workers in universities, polytechnics and research institutes may use radioactive labels, e.g. ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{125}I, and sealed sources containing ^{60}Co or ^{137}Cs. Exposure data are given in Table 21. The apparent doubling of the number of workers monitored in the period 1990–94 may be an overestimate, which can be attributed to the method used, i.e. extrapolation within regions on the basis of gross domestic product. The total annual collective effective dose decreased from 74 to 22 person–Sv in the period 1975–89 and increased to 33 person–Sv over the years 1990–94. The annual average effective dose decreased from 0.55 to 0.11 mSv during 1975–94 (UNSCEAR, 2000).

Table 21. Occupational exposure in educational establishments worldwide

Period[a]	Monitored workers (thousands)	Total annual collective effective dose (person–Sv)	Average annual effective dose (mSv)
1975–79	140	74	0.55
1980–84	180	43	0.24
1985–89	160	22	0.14
1990–94	310	33	0.11

From UNSCEAR (2000)
[a] Data are annual averages over the periods indicated.

1.3 Medical use of radionuclides

The use of radionuclide preparations for medical purposes, referred to as ‘radiopharmaceuticals’, is widely practised throughout the world; ‘nuclear medicine’ is the term used to describe medical diagnostic and therapeutic techniques based on the use of radiopharmaceuticals. Radiopharmaceuticals have been used for therapeutic purposes for more than 60 years, but external beam therapy or encapsulated (sealed) source therapy are by far the most common therapeutic radiation modalities (Carlsson, 1995). This section does not deal with the use of radiopharmaceuticals for analysis of biological specimens, such as blood and urine, in radioimmunoassay procedures but focuses on administration of radiopharmaceuticals for diagnostic and therapeutic reasons in humans.

1.3.1 *Diagnostic use*

(*a*) *Procedures*

Decreased or absent function of an organ, due for instance to the presence of a tumour, can be inferred from a reduced concentration of an appropriate radiopharmaceutical. Tracer tests, scans, renograms, metabolic and haematological examinations are, however, somewhat different from diagnostic radiology, as the results provide information on the physiological process during the short period between administration of the radionuclide and imaging. After administration to a patient, the distribution and localization in the tissue is determined by the pharmaceutical preparation used. Nuclear medical examinations thus give both functional and quantitative information.

One of the characteristics of nuclear medical examinations is that pathological processes can be diagnosed before other diagnostic methods can show morphological alterations; metastases in the skeleton can often be shown months before the first clinical symptom or even before detection at conventional X-ray examinations. The principles of some of the most common nuclear medical examinations are shown in Table 22.

Table 22. Clinical use of common nuclear examinations

Examination	Clinical use
Bone scintigram	Osteoblast activity
Lung scintigram	
Perfusion	Capillary perfusion
Ventilation	Distribution of ventilation
Renogram	Glomerular filtration rate, tubular secretion
Thyroid scintigram	Iodine metabolism
Myocardial scintigram	Myocardial metabolism, circulation and perfusion

Technical developments, computer-assisted imaging techniques and better cameras have improved the quality of diagnostic procedures. In addition to the conventional two-dimension imaging, techniques have been developed to allow emission tomography which shows internal structures in cross-sectional ‘slices’ of a patient. The commonest technique is single-photon emission computed tomography; a more specialized procedure is positron emission tomography, based on simultaneous detection of pairs of photons arising from positron annihilation (Meyer *et al*., 1995; Rigo *et al*., 1996; Schiepers & Hoh, 1998; Ferrand *et al*., 1999; UNSCEAR, 2000).

The latest report from UNSCEAR (2000) included a survey of the use of diagnostic nuclear medicine worldwide. As can be seen from Table 23, thyroid examinations (scans and uptake tests) constituted approximately 28% of all procedures in the countries listed, followed closely by bone scans (26%) and cardiovascular examinations (15%). Some of the commoner examination procedures are described briefly below.

Table 23. Average annual distribution (%) by type of diagnostic nuclear medicine procedure and country, 1991–96

Country or region[a]	Bone	Cardio-vascular	Lung		Thyroid		Kidney	Liver/spleen	Brain
			Perfusion	Ventilation	Scan	Uptake			
Argentina	30	27	2.9	2.3	16	11	7.4	1.2	1.9
Belarus	48	–	–	–	2.4	0.8	35	0.4	0.4
Bulgaria	2.1	2.0	1.4	0.4	38	45	6.8	1.7	1.6
Canada	34	47	0.3	1.5	4.3	4.6	2.5	0.9	2.4
China, Taiwan Province	23	15	2.1	–	4.7	5.3	4.4	20	9.8
Croatia	22	11	2.8	0.3	23	1.5	27	2.4	5.3
Cyprus	27	27	1.8	0	21	0.02	16	0.3	0
Czech Republic	18	8.6	9.5	1.4	9.2	3.5	29	4.1	7.7
Denmark	19	8.5	5.9	3.6	13	2.0	23	0.1	2.2
Ecuador	32	7.2	3.7	1.9	27	21	3.6	2.7	0.2
Finland	39	13	12	2.2	1.7	0.9	17	0.1	2.8
Germany	26	8.3	7.6	–	50	–	4.7	0.1	1.4
Hungary	26	6.5	6.8	0.6	27	4.4	17	2.5	2.2
Ireland	45	5.3	11	2.5	0.8	1.7	24	0.4	0.2
Italy	33	14	4	0.6	23	2.3	12	3.2	3.2
Japan	24	7.0	3.9	–	8.1	–	6.0	5.3	11
Kuwait	7.1	20	2.1	–	31	16	7.7	0.6	0.4
Lithuania	3.2	0.1	0.2	0	16	16	10	1.3	0.01
Netherlands	39	20	7.0	7.3	5.3	3.1	7.6	0.6	1.6
New Zealand	49	7.3	9.0	6.9	7.9	0.3	10	1.0	3.0
Panama	5.2	5.7	5.5	6.5	50	11	7.1	5.0	3.8
Qatar	25	20	3.5	–	12	–	29	1.4	0
Romania	12	–	1.0	–	27	20	9.4	26	3.5

Table 23 (contd)

Country or region[a]	Bone	Cardio-vascular	Lung		Thyroid		Kidney	Liver/spleen	Brain
			Perfusion	Ventilation	Scan	Uptake			
Slovakia	29	2.6	16	–	27	0.05	9.4	6.6	0.5
Slovenia	18	12	7.3	4.0	23	3.4	13	1.5	4.3
Sweden	28	7.9	11	4.4	9.0	3.8	3.1	0.6	0.7
Switzerland	43	5.6	14	6.4	15	–	4.2	0.5	1.8
United Arab Emirates	27	15	2.3	0.3	13	13	19	1.3	0.6
USA	24	13	16	–	–	–	3.2	22	11
Average	26	15	10	2.0	23	5.3	5.0	12	7.3

From UNSCEAR (2000). Since not all procedures are listed, the rows do not add up to 100%.

[a] Health-care level I countries or regions (see Table 25)

(i) *Thyroid examinations*

The possibility of comparing thyroid tissue function (iodine metabolism, hormone synthesis) with an evaluation of the thyroid gland by radionuclide scanning was a milestone for nuclear medicine and endocrinology. Thyroid scans with ^{131}I, ^{123}I or ^{99m}Tc to identify 'hot' and 'cold' nodules are widely used. After clinical examination of the thyroid gland, patients may be referred for a thyroid scan, fine-needle biopsy or ultrasound examination. Ultrasound examination of the thyroid gland has reduced the indications for thyroid scans, but the latter method is still widely used to measure the function of the thyroid gland and to reveal the morphological pattern. Function can also be determined from thyroid hormone measurements, but actual iodine uptakes are used to guide future therapeutic administration of radioiodine. Thyroid scans reveal activity in different parts of the gland, the size and number of pathological findings and atypical thyroid tissue (Carlsson, 1995; Nusynowitz, 1999).

(ii) *Bone examinations*

The second most common use of radiopharmaceuticals for examination is bone scanning for staging of tumours and diagnosis of infectious or inflammatory processes in the skeleton. Skeletal scintigraphy provides information on metabolic changes produced by modifications of bone vascularity and osteoblastic activity. Strontium and fluorine were used for skeletal scintigraphy, but they have been totally replaced by compounds containing ^{99m}Tc, reflecting the ideal properties of this radionuclide for clinical use (Feith *et al.*, 1976; O'Mara, 1976; Carlsson, 1995).

(iii) *Cardiovascular examinations*

For many years, studies of vascular transit and cardiac function were the only nuclear cardiovascular examinations known. Perfusion imaging developed more slowly. In the 1970s, a major breakthrough came with the visualization of myocardial necrosis. The development of single-photon emission computed tomography and positron emission tomography introduced a vast number of perfusion tests, many with the aim of detecting coronary artery disease (Saha *et al.*, 1992; Carlsson, 1995; Lee *et al.*, 2000).

(iv) *Pulmonary perfusion and ventilation tests*

Pulmonary embolism is a potentially fatal complication of deep-vein thromboses, but the clinical presentation of pulmonary embolism is non-specific and additional evaluation with imaging studies is essential for obtaining an accurate diagnosis. Scintigraphic examination of the lungs has been designed to demonstrate patterns of ventilation and perfusion. Pathophysiological conditions are commonly associated with scintigraphically detectable perturbations. Perfusion scintigraphy of the lung is accomplished by microembolization of radionuclide-labelled particles in the pulmonary arterial circulation. Albumin-labelled ^{99m}Tc is commonly used. For ventilation imaging, ^{133}Xe gas is inhaled by the patient. During wash-out, rapid clearance of activity from the lungs is seen, but areas of abnormal ventilation become apparent as hot spots (Taplin, 1979; Carlsson, 1995).

(*b*) *Doses*

Most radionuclides used in the field of nuclear medicine are produced by cyclotron bombardment, reactor irradiation, fission products or generators of secondary decay products from long-lived parent radionuclides. Only a few of the approximately 1700 known radioactive isotopes are suitable for medical purposes, as certain physical and chemical characteristics are required. Low photon energies give images with inferior resolution, whereas high photon energies result in an unacceptably high absorption of energy in the patient. A radionuclide with a long half-life gives a high absorbed dose to the patient, and a short half-life could result in a low concentration of the radionuclide in the organ under examination. The carrier molecule used for transporting the radionuclide must be stable enough to secure measurements characteristic of the organ or the process that is being examined. Electrons and positrons are not particularly helpful in the diagnostic setting, contrary to nuclear medical therapeutic techniques in which localized absorption of ionizing radiation is important (Carlsson, 1995; UNSCEAR, 2000).

Most of the radionuclides used in diagnostic and therapeutic treatments are listed in Table 24. Those most commonly used are ^{99m}Tc and ^{131}I. The half-life of ^{99m}Tc is 6 h, and it emits photons with an energy of 140 keV. Radioiodines have been used for nearly 60 years for diagnostic and therapeutic purposes: ^{131}I (half-life, eight days) gives a high photon energy and is fairly cheap; ^{123}I emits photons with an energy of 159 keV and is therefore well suited for diagnostic purposes; however, it is quite expensive and has a half-life of 13 h which makes it difficult to transport over long distances.

The estimated annual number of nuclear medical examinations in the world in 1985–90 was 24 million, corresponding to a frequency of 4.5 per 1000 individuals. The most recent survey indicated 32.5 million in 1991–96, corresponding to 5.6 examinations per 1000 individuals (UNSCEAR, 1993, 2000). The distribution of examinations is, however, highly dependent on the health care level, and 93% of all examination were confined to the western world (Table 25). When data from different parts of the world are compared, it should be remembered that the averages are often based on small sample sizes, particularly for health care levels III–IV. The contributions to frequency and annual collective dose of the commonest examination procedures are given in Table 26. The much higher collective dose from thyroid examinations in less-developed countries is a reflection of the use of the cheaper and more stable ^{131}I instead of ^{99m}Tc. The estimated annual collective effective dose from nuclear medical examinations in 1991–96 to the world population was estimated to be 150 000 person–Sv (Table 27). Many of the patients exposed are near the end of their lives, and the doses are not distributed evenly in the population; thus, these doses should not be used for assessing adverse effects (UNSCEAR, 2000).

Table 24. Radionuclides used for diagnostic and therapeutic purposes

Radionuclide	γ-ray energy (keV)	Half-life	Characteristics of radiation
^{3}H	–	12.3 years	'Pure' β
^{11}C	511	20.3 min	Positron
^{14}C	–	5730 years	'Pure' β
^{13}N	511	10.0 min	Positron
^{15}O	511	124 sec	Positron
^{18}F	511	109.8 min	Positron
^{32}P	–	14.3 days	'Pure β'
^{51}Cr	322	27.8 days	
^{57}Co	122	271 days	
	136		
^{67}Ga	92	3.2 days	
	184		
	296		
	388		
^{75}Se	121	120 days	
	136		
	265		
	280		
	401		
^{89}Sr	–	51 days	'Pure β'
^{90}Y	–	64 h	'Pure β'
^{99m}Tc	140	6.02 h	Most widely used radionuclide
^{111}In	173	2.8 days	
	247		
^{123}I	159	13 h	
^{131}I	284	8.05 days	High-energy photons, high proportion of β-radiation
	364		
	637		
^{133}Xe	81	5.3 days	β^-
^{153}Sm	70	47 h	β^-, Auger-e^-
	103		
^{165}Dy	95	2.3 h	β^-
^{186}Re	137	91 h	β^-
^{198}Au	412	2.7 days	β^-
^{201}Tl	135	73 h	
	167		
^{211}At	–	7.2 h	α

Table 25. Average temporal trends in annual frequency of diagnostic nuclear medicine procedures per 1000 individuals

Health care level[a]	1970–79	1980–84	1985–90	1991–96
I	11	6.9	16	19
II	0.9	0.1	0.5	1.1
III	0.25	0.25	0.30	0.28
IV	–	–	–	0.02

From UNSCEAR (2000)

[a] Health care level I, one physician per 1000; II, one physician per 1000–3000; III, one physician per 3000–10 000; IV, < one physician per 10 000 persons

Table 26. Contribution to frequency and collective dose of various types of diagnostic nuclear medicine procedures assumed for 1991–96

Procedure	Health care level[a], contribution (%)				
	I	II	III	IV	All
Contribution to total annual frequency					
Bone	24	21	19	8	24
Cardiovascular	14	15	6	0.1	14
Lung perfusion	10	2	2	0.4	9
Lung ventilation	2	1	0.1	0.1	2
Thyroid scan	22	27	59	19	22
Thyroid uptake	5	3	–	42	5
Kidney	5	14	7	13	6
Liver/spleen	11	8	2	1	11
Brain	7	4	4	16	7
All	100	100	100	100	100
Contribution to total annual collective dose					
Bone	25	14	4	2	23
Cardiovascular	27	18	4	0.1	25
Lung perfusion	3	0.6	0.3	< 0.1	3
Lung ventilation	0.4	0.1	< 0.1	< 0.1	0.4
Thyroid scan	10	40	89	28	17
Thyroid uptake	17	10	–	62	16
Kidney	2	6	1	2	2
Liver/spleen	4	2	0.2	0.1	4
Brain	10	4	1	5	8
All	100	100	100	100	100

From UNSCEAR (2000)

[a] Health care level I, one physician per 1000; II, one physician per 1000–3000; III, one physician per 3000–10 000; IV, < one physician per 10 000 persons

Table 27. Estimated doses to the world population from diagnostic nuclear medical procedures, 1991–96

Health care level[a]	Population (million)	Annual per-capita effective dose (mSv)	Annual collective effective dose (person–Sv)
I	1 530	0.081	123 000
II	3 070	0.008	23 000
III	640	0.006	3 500
IV	565	0.0003	200
World	5 800	0.026	150 000

From UNSCEAR (2000)

[a] Health care level I, one physician per 1000; II, one physician per 1000–3000; III, one physician per 3000–10 000; IV, < one physician per 10 000 persons

1.3.2 *Therapeutic use*

External beam radiotherapy (teletherapy) or encapsulated source therapy (brachytherapy) are far commoner modalities of radiotherapy than radiopharmaceuticals. Nuclear medical treatment plays a small but important role in the management of patients with cancer, mainly in the palliative setting, and for a few benign conditions such as hyperthyroidism and arthritis. For several benign disorders, radiopharmaceuticals are an alternative to other treatments, and for the treatment of malignant disorders they combine the selectivity of brachytherapy with that of systemic activity (Hoefnagel, 1991; UNSCEAR, 2000).

Radionuclides should be readily available, penetrate a few millimetres, deliver a sufficiently high dose rate and be cheap. Radionuclides that emit medium-energy β-radiation are currently used (Johansson *et al*., 1984; Volkert *et al*., 1991; Johansson *et al*., 1992; Stabin *et al*., 1999). Small ions or molecules that follow physiological pathways, such as [^{131}I]sodium iodide for the treatment of thyroid carcinoma, [^{32}P]orthophosphate for polycythaemia vera and [^{89}Sr]strontium chloride for skeletal metastases, are in common use (UNSCEAR, 2000). Efficient biological targetting can also be implemented with monoclonal antibodies, but such techniques are not yet used in routine clinical practice (McDevitt *et al*., 1998). Some of the current treatment modalities are listed in Table 28, but it should be emphasized that only the first four examples can be considered to be established treatments (UNSCEAR, 2000).

In a recent survey of nuclear medical practice in 17 European countries, 71% of the therapeutic actions in patients with malignant disorders concerned patients with thyroid cancer, 20% concerned palliation of skeletal metastases, 5% concerned treatment for polycythaemia vera and 2% concerned neural crest tumours (Hoefnagel *et al.*, 1999).

The annual numbers of radiopharmaceutical therapeutic interventions in relation to health care level are listed in Table 29 (UNSCEAR, 2000). The calculations are

Table 28. Therapeutically used radionuclides

Radionuclide	Clinical use
^{131}I	Differentiated thyroid carcinomas
^{32}P	Polycythaemia vera
^{89}Sr	Skeletal metastases
^{131}I	Neural crest tumours
^{153}Sm	Skeletal metastases
^{186}Re	Skeletal metastases
^{32}P	Intracavitary tumours
^{90}Y	Hepatic and various other tumours
^{114m}In	Lymphoma
^{131}I	Hepatic and various other tumours

From UNSCEAR (2000)

Table 29. Annual number of radiopharmaceutical therapeutic treatments per 1000 individuals in 1991–96 worldwide

Disease	Health care level[a]					% contribution to world total
	I	II	III	IV	All	
Thyroid malignancy	0.035	0.01	0.003	0.00001	0.015	23
Hyperthyroidism	0.11	0.019	0.017	0.00035	0.042	65
Polycythaemia vera	0.003	0.0001	0	0	0.001	1
Bone metastases	0.005	0.002	0.001	0	0.002	4
Synovitis	0.007	0.0001	0	0	0.002	3
All treatments	0.17	0.036	0.021	0.0004	0.065	96[b]

From UNSCEAR (2000)

[a] Health care level I, one physician per 1000; II, one physician per 1000–3000; III, one physician per 3000–10 000; IV, < one physician per 10 000 persons

[b] Since not all treatments are listed, the % contribution does not add up to 100%.

based on the distribution of treatments in different countries and average total frequencies for each health care level. As can be seen, the treatment of thyroid disorders comprises nearly 90% of the procedures in the world, and this fraction is even higher in less-developed countries. Almost 75% of the treatments worldwide are performed in economically developed countries, and use of these procedures is more than 400 times commoner in countries with health care level I than in those with level IV. In all countries, therapy for hyperthyroidism predominates (UNSCEAR, 2000).

Table 30 lists the three commonest therapies and the mean administered activity in relation to health care level. In general, the amount of radioiodine administered for hyperthyroidism is one-tenth that for the treatment of thyroid cancer (UNSCEAR,

Table 30. Average activities administered (MBq) in therapeutic treatments with radiopharmaceuticals in relation to health care level, 1991–96, worldwide

Health care level[a]	Thyroid malignancy (^{131}I)	Hyperthyroidism (^{131}I)	Polycythaemia vera (^{32}P)
I	4760	415	170
II	3510	340	148
III	3700	300	–
IV	3500	220	–

From UNSCEAR (2000)

[a] Health care level I, one physician per 1000; II, one physician per 1000–3000; III, one physician per 3000–10 000; IV, < one physician per 10 000 persons

2000). The annual number of nuclear medical treatments was approximately 400 000 in 1991–96 (Table 31), and, as previously stated, most were performed in the western part of the world. The data in Tables 29–31 indicate that the approximate amount of ^{131}I used annually for the treatment of thyroid cancer is only about 3.7×10^8 MBq, while the corresponding figure for hyperthyroidism is about 0.93×10^8 MBq.

A number of national surveys have been undertaken on nuclear medicine practice and are summarized in the latest report of UNSCEAR (2000). The role of therapeutic nuclear medicine is expanding in developed countries, particularly in oncological practice and not only for differentiated thyroid cancer (Kobayashi *et al.*, 1981; Daghighian *et al*., 1995). The full potential of nuclear medicine will not be realized until target-specific carrier molecules, such as antibodies, have been developed; work is in progress to identify DNA-targetting molecules to enhance cytotoxicity.

Table 31. Estimated annual numbers of therapeutic treatments with radiopharmaceuticals in the world, 1991–96

Health care level[a]	Population (millions)	Annual number of treatments (millions)	Annual number of treatments per 1000 individuals
I	1530	0.3	0.2
II	3070	0.1	0.04
III	640	0.01	0.02
IV	565	0.0002	0.0004
All	5800	0.4	0.065

From UNSCEAR (2000)

[a] Health care level I, one physician per 1000; II, one physician per 1000–3000; III, one physician per 3000–10 000; IV, < one physician per 10 000 persons

1.4 Other applications of radionuclides that could lead to exposure

A variety of consumer products and miscellaneous sources of ionizing radiation result in low levels of exposure of human populations. The major source of exposure to radionuclides is from tobacco products. Examples of other sources of internal exposure are gas lantern mantles, transport of radiopharmaceuticals, smoke detectors and tungsten welding rods (Table 32).

Moeller (1996) categorized consumer products in the USA into five groups, depending on the number of people exposed and the associated dose equivalent. Group 1 includes large numbers of people exposed to sources such as building materials, domestic water supplies, mining and agricultural products, combustible fuel (including natural gas heaters and cooking ranges) and road construction materials. Group 2 includes people for whom exposure is limited to parts of the body. The sources include radioluminous products (including watch dials), gas and aerosol (smoke) detectors, spark gap irradiators and thorium products (including fluorescent lamp starters and gas mantles). Group 3 includes a few people exposed to thorium products such as tungsten welding rods and airport luggage scanning systems. None of these sources represents a significant component of the overall collective dose to populations. Group 4 consists of pilots transporting radiopharmaceuticals, and group 5, people exposed to radiation from cigarettes.

Exposure to these consumer products, used in everyday life, can occur in the home, at work and in the general environment. Some of the best-known sources of exposure are luminous-dial watches, smoke detectors, uranium in ceramic colour glazes, thorium in optical glass, potassium in food products, uranium in construction materials and radon in domestic water supplies. While human exposures from consumer products are small in comparison with those from other sources (such as medical radiation or natural background), large numbers of people are nevertheless exposed (National Council on Radiation Protection and Measurements, 1987a; Schmitt-Hannig *et al.*, 1995; Moeller, 1996).

1.4.1 *Products in the home*

Uranium, radium, thorium and potassium can occur naturally in a variety of building materials, thus increasing population exposure to ionizing radiation. Natural gas used to heat homes and for cooking is a source of airborne radon and its decay products. Similarly, water supplies can result in an increased intake of naturally occurring radioactive materials, as radon can be released during showering, washing clothes, washing dishes and flushing toilets. Naturally occurring indoor radon is discussed in section 1.1.4. The commonest types of smoke detectors contain ^{241}Am, a man-made radioactive material, which ionizes the air between two electrodes through α-particle emissions. When smoke passes through the electrode gap, the resistance is decreased or increased and the associated change is amplified to signal an alarm. The exposure of any individual to

Table 32. Examples of sources and doses of radiation from consumer products in the USA

Product	No. of people exposed	Average annual effective dose (μSv)	Annual collective dose (person–Sv per year)
Group 1 — large numbers of people receiving relatively large doses			
Building materials	125 000 000	70	8750
Groundwater supplies	100 000 000	10–100	5000
Agricultural fertilizers	200 000 000	5–50	2000
Natural gas indoors	135 000 000	4–l8	800
Road construction materials	5 000 000	40	200
Group 2 — large numbers of people receiving relatively small doses or limited to a small portion of the body			
Television receivers	250 000 000	≤ 5	≤ 1250
Video display terminals	50 000 000	≤ 10	≤ 500
Luminous watches	50 000 000	0.1–3	150
Gas lantern mantles	50 000 000	2	100
Transport of radiopharmaceuticals (passengers)	14 000 000	2–3	30
Dental products	45 000 000	0.7	30
Smoke detectors	100 000 000	0.08	10
Airport luggage scanning systems (passengers)	50 000 000	< 0.01	0.5[a]
Group 3 — small numbers of people receiving relatively large doses			
Tungsten welding rods	300 000	160	50
Airport luggage scanning systems (operators)	10 000	1000–2000	15
Thickness gauges	15 000	< 1000	< 15
Transport of radiopharmaceuticals (flight attendants)	30 000	35	
Static eliminators	50 000	3–4	0.2
Group 4 — small numbers of people receiving relatively small doses			
Transport of radiopharmaceuticals (pilots)	15 000	0.7	0.01
Group 5 — tobacco products			
Cigarettes	50 000 000	13 000	650 000

From the National Council on Radiation Protection and Measurements (1987a), modified by Moeller (1996)

[a] Based on an annual average of 10 trips for each member of the public in the USA who flies

these products is negligible. Similarly, certain types of porcelain and bathroom tiles in homes are glazed with uranium; ingestion of radioactive materials by people using such porcelain appears to be minimal, but in some instances their use has been discouraged (National Council on Radiation Protection and Measurements, 1987a; Schmitt-Hannig *et al.*, 1995; Moeller, 1996).

1.4.2 *Personal products*

Radioactive materials are found in a number of food products, luminous-dial watches and clocks, eye pieces, false teeth, jewellery and cigarettes, as discussed previously. ^{40}K accompanies nonradioactive potassium in bananas and other vegetables and fruits, and certain agricultural food products contain small amounts of ^{226}Ra, ^{230}Th and ^{238}U owing to use of these radionuclides in the production of phosphorus-containing fertilizers. In the past, ^{226}Ra was incorporated into numerous timepieces, compasses and other products such as military gauges and instrument dials. Most watches containing ^{226}Ra are no longer in use and were last produced in the USA around 1968: It has been estimated that perhaps one million timepieces containing ^{3}H and ^{147}Pm are now sold yearly in the USA. While the dose rates from ^{226}Ra-containing wrist watches might be as high as 3 mSv/year, the watches containing low-energy ^{3}H and ^{147}Pm result in extremely low doses (National Council on Radiation Protection and Measurements, 1987a; Schmitt-Hannig *et al.*, 1995; Moeller, 1996; IARC, 2000).

Eye glasses and eye pieces in optical instruments contain small amounts of uranium and thorium. In the past, slightly increased dose rates to the germinal cells of the cornea of the eye were reported, and manufacturers subsequently reduced the content of radioactive material in optical glass. Eye glasses that were pink or had rose-coloured lenses incorporated the largest amounts of radioactive materials. In the past, uranium salts were added to false teeth to give them a ‘natural’ colour, which could result in increased exposure of the gums of people using such prostheses, but uranium is no longer incorporated into false teeth. Uranium has been also used as a glaze in jewellery, and some topaz gemstones are slightly radioactive after irradiation with neutrons in order to enhance their blue colour. Such jewellery is regulated. Gas lanterns with incandescent gas mantles, mainly used by campers, can result in exposure to radiation from the small amounts of thorium oxide; however, mantles with no radioactive substances are now available (National Council for Radiation Protection and Measurements, 1987a; Schmitt-Hannig *et al.*, 1995).

1.4.3 *Products in the workplace*

Radionuclides can also be used in static eliminators (e.g. ^{210}Po), thickness gauges, thoriated tungsten welding rods, fluorescent lamps (e.g. ^{85}Kr), spark gaps (e.g. ^{60}Co) and other devices. In general, the dose rates are relatively low. Static eliminators are used in industry to reduce the electric charge build-up on materials like printing

presses, photocopying machines, phonograph records and photographic film (National Council for Radiation Protection and Measurements, 1987a; Schmitt-Hannig *et al.*, 1995; Moeller, 1996).

1.4.4 *Exposure to radionuclides in cigarette smoke*

In the 1960s, ^{210}Pb and ^{210}Po were measured in tobacco, in cigarette smoke and in smokers' lungs (Radford & Hunt, 1964; Hill, 1965; Holtzman & Ilcewicz, 1966; Blanchard, 1967). Several radionuclides have been identified in tobacco smoke, such as radium and thorium, but over 99% of the α-activity results from ^{210}Po (Cohen *et al.*, 1980). Radionuclides accumulate in tobacco plants by either root uptake from soils and fertilizers (Tso *et al.*, 1966) or surface deposition of the nuclides through rainfall (Francis *et al.*, 1968).

1.4.5 *Miscellaneous products and sources*

Spacecraft powered by nuclear sources could result in population exposures if a craft were destroyed during launch or re-entry into the earth's atmosphere. While this has occurred in the past, the associated exposure of individuals in the population was low, partly because the radionuclides were widely dispersed on burn-up of the fuel core in the atmosphere (UNSCEAR, 1993).

Thus, while populations are exposed to radionuclides from a variety of consumer products, the associated doses are usually very small, particularly in comparison with the radiation received annually from natural or medical sources; the possible exception is radioactive polonium in cigarette smoke (Table 32).

2. Studies of Cancer in Humans

Knowledge of the carcinogenic effects of internally incorporated radionuclides in humans is derived principally from observational studies of individuals exposed to unusual amounts of radiation, either occupationally, environmentally or medically. The most common study design is that of the cohort study, in which a group of individuals is defined by their employment, by the fact that they have received a certain medical treatment or procedure or by residence in a certain area at a certain time. The group of individuals is then followed forward in time, and the rate at which they develop, or die from, specific types of cancer is documented and compared with the rate that would be expected in the absence of any unusual radionuclide exposure, as defined by the rates in an appropriate external comparison population. Alternatively, internal comparisons can be made between groups of individuals defined and followed forward by the investigator but exposed to radionuclides at a different level, allowing in the most favourable circumstances the construction of a dose–response relationship. In addition to cohort studies, there are a few studies of the case–control design in which individuals who have already developed a certain type of cancer are identified, together with other individuals who are representative of the population from which the individuals with cancer have been drawn, and the past exposure of diseased and non-diseased individuals is compared.

The interpretation of observational studies in this field is often difficult, as the exposed and unexposed groups may differ in ways other than simply their radionuclide exposure. In the ideal situation, information on all likely confounding factors, including age, sex, smoking history and exposure to external radiation would be available, thus enabling their effects to be disentangled from that of the radionuclide. In practice, the circumstances of exposure usually preclude an ideal study design. Nevertheless, humans have been exposed to radionuclides in a wide variety of circumstances, and, as summarized in the following sections, it has in many cases proved possible to characterize the effects of exposure.

2.1 Radon

Radon is a noble gas occurring in several isotopic forms. Only two of these are found in significant concentrations in the human environment: ^{222}Rn and ^{220}Rn (thoron). The major radioactive exposure of public health concern is inhalation of short-lived decay products (^{218}Po and ^{214}Po) of ^{222}Rn (called radon in this section). Underground miners of

uranium and other depositions in igneous rocks have often been exposed to substantial concentrations of radon. Radon is also the most important source of ionizing radiation of the populations of most countries (see section 1). The effects of exposure to radon have been reviewed previously (IARC, 1988; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). With its decay products, it was classified by IARC in Group 1 (carcinogenic to humans). The effects of exposure to ^{220}Rn are discussed in the section on thorium.

2.1.1 *Occupational exposure in underground mining*

In 1987, when the carcinogenicity of radon was first evaluated by an IARC Working Group, eight cohort studies of underground miners exposed to high concentrations of radon gas had been published (IARC, 1988). Since then, additional data have become available for most of these studies, and the results of four additional studies have been published; one study of some 60 000 workers with 1500 lung cancers is still in progress (Kreuzer *et al.*, 1999) and the results are not yet available. These studies are described here briefly and are summarized in Tables 33 and 34.

(*a*) *Lung cancer*

(i) *Mining*

The original references for the reports of these studies are given in Tables 33 and 34. The data from all studies except that carried out in Cornwall, United Kingdom, were compiled by Lubin *et al.* (1995a) and the Committee on Health Risks of Exposure to Radon (BEIR VI) (1999).

The Yunnan (China) cohort study consists of more than 17 000 employees of the Yunnan Tin Corporation in southern China, assembled from an occupational survey in 1976 (BEIR VI). Vital status was determined from occupational and retirement records, and lung cancer deaths were ascertained from a Corporation-operated cancer registry; ascertainment is thought to be complete. Follow-up was performed until 1987. A substantial number of the miners were under the age of 20 at the start of exposure. Data on tobacco use were available for 76% of the cohort but only after 1976; the information on duration and amount of smoking is incomplete. Of the exposed persons, 936 died from lung cancer; 44 lung cancer deaths were found in the unexposed cohort, yielding an excess relative risk (ERR)/WLM of 0.0016 (95% confidence interval [CI], 0.001–0.002) (Lubin *et al.*, 1995a). High concentrations of arsenic were also present in the mine and were associated with the risk for lung cancer.

A cohort study of uranium miners in western Bohemia, Czech Republic, comprised 4320 exposed and 656 unexposed workers (BEIR VI). The main analysis was performed on data for miners who started working in 1948–57. Vital status and disease outcome were obtained from a population registry. The follow-up period covered 1952–90, yielding an average follow-up period of 25.2 years. No data on smoking were available. Among the exposed men, 656 (Lubin *et al.*, 1995a) [701 (BEIR VI)] died

Table 33. Exposure in cohort studies of underground miners occupationally exposed to radon

Study (references)	Type of mine	Person–years		WLM[a]	No. of years exposed[a]
		Exposed	Unexposed		
Yunnan, China (Qiao *et al*., 1989; Xuan *et al*., 1993; Yao *et al*., 1994)	Tin	135 357	39 985	277.4	12.9
Western Bohemia, Czech Republic (Ševc *et al*., 1988, 1993; Tomášek *et al*., 1993, 1994a,b; Tomášek & Darby, 1995; Tomášek & Placek, 1999)	Uranium	103 652	4 216	198.7	7.3
Colorado, USA[b] (Hornung & Meinhardt, 1987; Roscoe *et al*., 1989; Moolgavkar *et al*., 1993; Thomas *et al*., 1994; Roscoe *et al*., 1995; Roscoe, 1997; Hornung *et al*., 1998; Luebeck *et al*., 1999; Stram *et al*., 1999a,b)	Uranium	73 509	7 403	595.7	4.0
Ontario, Canada[c] (Müller & Kusiak, 1989; Kusiak *et al*., 1993)	Uranium	319 701	61 017	30.8	3.0
Newfoundland, Canada (Morrison *et al*., 1988, 1998)	Fluorspar	35 029	13 713	367.3	4.8
Malmberget, Sweden (Radford & St Clair Renard, 1984)	Iron	32 452	841	80.6	17.8
New Mexico, USA (Samet *et al*., 1989, 1991, 1994)	Uranium	46 797	12 152	110.3	7.4
Beaverlodge, Canada (Howe *et al*., 1986; L'Abbé *et al*., 1991; Howe & Stager, 1996; Chambers *et al*., 1999)	Uranium	68 040	50 345	17.2	1.9
Port Radium, Canada (Howe *et al*., 1987)	Uranium	30 454	22 222	242.8	3.2
Radium Hill, Australia (Woodward *et al*., 1991)	Uranium	25 549	26 301	7.6	1.1
France (Tirmarche *et al*., 1993)	Uranium	39 487	4 556	68.7	13.2
All above combined[d] (Lubin *et al*., 1995a)		907 459	242 332	158.0	5.7
Cornwall, United Kingdom (Hodgson & Jones, 1990)	Tin	[2 535]	NR	[65]	[11]

WLM, working-level months; NR, not reported

[a] Means for radon-exposed miners

[b] Totals exclude values > 3200 WLM, including those for 35 lung cancer cases.

[c] Values are given for all uranium miners, including those with previous gold-mining experience.

[d] The data from the original papers, except the study in Cornwall, United Kingdom, were compiled by Lubin *et al.* (1995a). Totals adjusted for 115 workers (including 12 lung cancer patients) who were included in both the New Mexico and Colorado cohorts.

Table 34. Relative risks in cohort studies of underground miners occupationally exposed to radon

Study (references)	Type of mine	Lung cancer deaths		ERR/WLM[a]	95% CI
		Exposed	Unexposed		
Yunnan, China (Xuan *et al*., 1993)	Tin	936	44	0.0016	0.001–0.002
Western Bohemia, Czech Republic (Tomášek *et al*., 1994a)	Uranium	656	5	0.0034	0.002–0.006
Colorado, USA[b] (Hornung & Meinhardt, 1987)	Uranium	292	2	0.0042	0.003–0.007
Ontario, Canada[c] (Kusiak *et al*., 1993)	Uranium	282	2	0.0089	0.005–0.015
Newfoundland, Canada (Morrison *et al*., 1988)	Fluorspar	112	6	0.0076	0.004–0.013
Malmberget, Sweden (Radford & St Clair Renard, 1984)	Iron	79	0	0.0095	0.001–0.041
New Mexico, USA (Samet *et al*., 1991)	Uranium	68	1	0.0172	0.006–0.067
Beaverlodge, Canada (Howe *et al*., 1986)	Uranium	56	9	0.0221	0.009–0.056
Port Radium, Canada (Howe *et al*., 1987)	Uranium	39	18	0.0019	0.001–0.006
Radium Hill, Australia (Woodward *et al*., 1991)	Uranium	32	22	0.0506	0.010–0.122
France (Tirmarche *et al*., 1993)	Uranium	45	0	0.0036	0.001–0.013
All above combined[d] (Lubin *et al*., 1995a)		2 597	109	0.0049	0.002–1.010[e]

ERR/WLM, excess relative risk per working-level month; CI, confidence interval

[a] Means for radon-exposed miners

[b] Totals exclude values > 3200 WLM, including those for 35 lung cancer cases.

[c] Values are given for all uranium miners, including those with previous gold-mining experience.

[d] The data from the original papers were compiled by Lubin *et al*. (1995a). Totals adjusted for 115 workers (including 12 lung cancer patients) who were included in both the New Mexico and Colorado cohorts.

[e] Joint 95% CI based on random effects model

from lung cancer, while there were only five lung cancer deaths in the unexposed cohort, yielding an ERR/WLM of 0.0034 (95% CI, 0.002–0.006) (Lubin *et al.*, 1995a).

The study of Colorado (USA) uranium miners is one of the earliest cohort studies, the first results having been published in the 1960s (Archer *et al.*, 1962; Wagoner *et al.*, 1964, 1965). The cohort consists of 3347 exposed workers in Arizona, Colorado, New Mexico and Utah who had completed at least one month of underground mining and who had had at least one (voluntary) medical examination (BEIR VI). Vital status was ascertained from company records, the State vital statistics office, the National Death Index and by direct contact. The cause of death was determined from State death certificates. Data on smoking for 1950–60 and 1963–69 were obtained from annual censuses and from mailed questionnaires. Among the exposed men, 292 died of lung cancer, while only two lung cancer deaths were observed among the unexposed members of the cohort. The ERR/WLM is 0.0042 (95% CI, 0.003–0.007). The cumulative exposure to radon was among the highest seen in studies of miners (Lubin *et al.*, 1995a).

The cohort study of Ontario, Canada, uranium miners (BEIR VI) covered persons who had had an obligatory medical examination between 1955 and 1984 and who had been employed for a minimum of five years in dusty jobs or for a minimum of two weeks in mining. Vital status and cause of death were determined for 1955–86 through the mortality database of Canada. The cohort consisted of 21 346 exposed male miners with an average duration of exposure of three years and an average length of follow up of 17.8 years. Data on smoking were available from several surveys, and after 1976 smoking history was recorded annually. In the exposed cohort, 282 (Lubin *et al.*, 1995a) [285 (BEIR VI)] men died from lung cancer. Two persons in the unexposed cohort died from lung cancer, yielding an estimated ERR/WLM of 0.0089 (95% CI, 0.005–0.015).

The cohort of Newfoundland, Canada, fluorspar miners comprised men who had worked in one of two local mining companies between 1933 and 1978 and for whom adequate personal identification was available (BEIR VI). Vital status and cause of death were determined for the years 1950–84 from the Mortality Database of Statistics, Canada. Information on smoking was obtained from several surveys but was available for only 48% of the cohort. The average duration of exposure was 4.8 years, and the average follow-up was 23.3 years. The cohort comprised 1751 exposed miners, among whom 112 deaths from lung cancer were observed; as six lung cancer deaths were found in unexposed men, the ERR/WLM was 0.0076 (95% CI, 0.004–0.013) (Lubin *et al.*, 1995a).

The Swedish cohort study covered men who had worked in iron mining in the Malmberget area in the northern part of Sweden (BEIR VI). Men born between 1880 and 1919 and still alive in 1930 and who had worked for more than one year in mining between 1897–1976 were included in the study. Vital status and cause of death were determined for the period 1951–91, and the information is thought to be complete owing to the Swedish system of personal identification numbers. Information on

smoking was obtained from several surveys and was available for all men who had died from lung cancer and for more than half of the men still alive in 1970. The cohort comprised 1294 exposed miners with an average duration of exposure of 18.2 years and an average follow-up of 25.7 years. Of the exposed men, 79 died from lung cancer. The ERR/WLM is 0.0095 (95% CI, 0.001–0.041) (Lubin *et al.*, 1995a).

The New Mexico (USA) cohort represents the most recently employed miners in the USA. Men who had worked for at least one year underground in New Mexico before December 1976 were included in the study (BEIR VI). Vital status was determined from various sources, including the New Mexico vital statistics records and the National Death Index. Death certificates were obtained and causes of death coded by one nosologist. A total of 3457 exposed miners were included in the study, with an average of 5.6 years' exposure and 17 years' follow-up. The follow-up covered the period 1943–85. Medical records were available to categorize the miners into current smokers, former smokers and non-smokers. In total, 68 exposed and unexposed miners died from lung cancer, yielding an ERR/WLM of 0.0172 (95% CI, 0.006–0.067) (Lubin *et al.*, 1995a).

The Beaverlodge uranium mine in Canada began operation in 1949 and was closed in 1982. The cohort study included men who had ever worked at the uranium mine during 1948–80 (BEIR VI). Vital status and causes of death were determined for 1950–80 by searching the Mortality Database of Statistics, Canada. In total, 6895 miners were enrolled in the study, with an average duration of exposure of 1.7 years and an average period of follow-up of 14 years. No information on smoking was available for the members of the cohort. Fifty-six lung cancer deaths were observed in the exposed group and nine in the unexposed, for an ERR/WLM of 0.022 (95% CI, 0.009–0.056) (Lubin *et al.*, 1995a).

The Port Radium, Canada, cohort consisted of 1420 men who had worked in a uranium mine since 1940 and who were known to be alive on 1 January 1945 (BEIR VI). Vital status and cause of death for the period 1950–80 were obtained by searching the Mortality Database of Statistics, Canada. The average duration of exposure was 1.2 years, and the average follow-up was 25.3 years. No data were available on smoking. Overall, 39 lung cancer deaths were observed in the exposed cohort and 18 in the unexposed, giving an ERR/WLM of 0.0019 (95% CI, 0.001–0.006) (Lubin *et al.*, 1995a).

The Radium Hill cohort studies covered 1457 exposed hourly workers who had been employed at the Radium Hill uranium mine in South Australia during 1952–61 (BEIR VI). Vital status was determined from death records for Australia for the period 1960–87; for years prior to 1960, the search was restricted to South Australia. The average duration of exposure was 1.1 years, and the average length of follow-up was 21.9 years. Data on smoking (ever/never) were available for about half of the cohort from a survey carried out in 1984 among cohort members and their next-of-kin. The total numbers of lung cancer deaths were 31 among the exposed men and 22 among unexposed men (ERR/WLM, 0.051; 95% CI, 0.01–0.12) (Lubin *et al.*, 1995a).

The French cohort included uranium miners from three areas in the centre of France and one area on the west coast (BEIR VI). Men who had worked for at least

two years and who had started work between 1946 and 1972 were included in the study. A total of 1769 exposed men were enrolled who had an average duration of exposure of 7.2 years and an average length of follow-up of 24.7 years. Vital status was ascertained from several sources, including company and national records. Causes of death were obtained for 96% of the deceased persons. No data on smoking were available. In the exposed cohort, 45 men died from lung cancer (ERR/WLM, 0.0036; 95% CI, 0.001–0.013) (Lubin *et al.*, 1995a).

A cohort study of tin miners in Cornwall (United Kingdom) comprised 3010 men, of whom 2059 had worked underground (Hodgson & Jones, 1990). Workers had to have been employed for at least one year between 1941 and 1984. Follow-up was performed until the end of 1986 from the records of the United Kingdom National Health system and was successful for 97.6% of the cohort. No data on smoking were used in the analysis. The observed numbers of deaths were compared with those expected on the basis of national death rates. There was a significant increase in the rate of death from lung cancer (standardized mortality ratio [SMR], 1.58 ($p < 0.05$), based on 105 observed cases, 66.6 expected). The rate increased significantly with increasing exposure ($p < 0.001$).

All the studies summarized by Lubin *et al.* (1994a, 1995a) and shown in Tables 33 and 34 found clear evidence of an increasing risk for lung cancer associated with increasing cumulative exposure to radon. In a pooled analysis of the data from these 11 studies, radon-exposed miners with a cumulative exposure of < 50 WLM had 453 604 person–years at risk, and 353 died from lung cancer (Lubin *et al.*, 1997). A separate analysis of 274 161 person–years at risk and 115 lung cancer deaths among unexposed miners showed a significant association between exposure to radon and the risk for lung cancer. The ERR was 0.012/WLM with a 95% CI of 0.002–0.025.

(ii) *Inverse dose-rate effect*

An inverse dose-rate effect is a phenomenon whereby, for a given dose or cumulative exposure, the probability of a cancer being caused per unit dose received increases as the dose-rate is lowered. An inverse dose-rate effect was first reported in analyses of uranium miners on the Colorado Plateau and in western Bohemia, Czech Republic (Hornung & Meinhardt, 1987; Ševc *et al.*, 1988) and was confirmed in more recent publications on these studies (Tomášek & Darby, 1995; Hornung *et al.*, 1998). A similar effect was reported for Chinese tin miners (Xuan *et al.*, 1993). A comparison of published risk estimates from various studies also showed an inverse dose-rate effect (Darby & Doll, 1990). A joint analysis of data on 11 cohorts of miners showed a significant inverse dose-rate effect in all but one of the studies (Lubin *et al.*, 1995b; Table 35). This analysis also showed no inverse dose–rate effect at total cumulative exposures of < 50 WLM. The phenomenon at very high doses is related in part to cell killing. As the lowest concentrations might be experienced in residential settings, the effect is not apparently consistent with biophysical understanding (Brenner, 1994).

Table 35. Numbers of lung cancer cases, estimates of excess relative risk (ERR) per working-level month (WLM) and its modification by continuous exposure rate in working level (WL)

Study cohort	Cases of lung cancer[a]	$\beta \times 100$	γ	p[b]
Yunnan, China	980	0.59	–0.79	< 0.001
Former Czechoslovakia	661	5.84	–0.78	< 0.001
Colorado, USA	294	14.50	–0.79	< 0.001
Ontario, Canada	291	2.40	–0.55	0.002
Newfoundland, Canada	118	5.14	–0.53	< 0.001
Malberget, Sweden	79	1.55	–1.02	0.03
New Mexico, USA	69	6.56	–0.30	0.17
Beaverlodge, Canada	65	7.42	–0.67	0.001
Port Radium, Canada	57	1.15	–0.42	0.24
Radium Hill, Australia	54	5.68	–0.63	0.30
France	45	1.92	0.57	0.57

From Lubin *et al*. (1995b). Background lung cancer rates are adjusted for attained age (all studies), other mine exposures (China, Colorado (USA), Ontario (Canada), New Mexico (USA), France) and indicators of exposure to radon progeny (Beaverlodge, Canada), and ethnicity (New Mexico, USA). In the studies in Colorado, only exposure to < 3200 WLM was considered. The relative risk (RR) is modelled by the form $RR = 1 + \beta \times WLM \times (WL)^{\gamma}$.

[a] Total number of cases is 2701, omitting 12 cases included in both the New Mexico and Colorado studies.

[b] p for test of significance of continuous variation of ERR/WLM by WL (i.e. test of $\gamma = 0$)

(iii) *Effect in lifelong non-smokers*

As a large proportion of the underground miners studied were cigarette smokers, questions have arisen about whether the association between radon and lung cancer seen in the miners is due to confounding by smoking, or whether radon acts as a lung carcinogen only in smokers. A study of Colorado uranium miners who had never smoked (Roscoe *et al.*, 1989), including 14 who had died from lung cancer, showed a highly significant, 13-fold greater risk compared with that of veterans in the USA who had never smoked. Several other studies have also included non-smokers or light smokers and found an increased risk associated with exposure to radon (Radford & St Clair Renard, 1984; Samet *et al.*, 1991a). Further information is available from the pooled analysis of 11 miner cohorts (Lubin *et al.*, 1995a), in which 2798 workers were reported to be lifelong non-smokers. These data cover 50 493 person–years of follow-up and 64 lung cancer cases. The relative risks increased significantly with increasing WLM for both smokers and lifelong non-smokers. The estimated ERR/WLM for the latter was 0.010 (95% CI, 0.002–0.057), just over three times the corresponding value

for smokers. In interpreting this finding, it must be recalled that the baseline rate of lung cancer is lower among non-smokers, so that the absolute risks of non-smokers are lower than those of smokers.

(iv) *Exposure of women and children*

There were virtually no female workers in the mining populations studied, and the exposure of the vast majority of the miners did not start until adulthood. The one exception is the study of Chinese tin miners, in which a substantial proportion of the workforce was aged under 20 at the start of exposure (Yao *et al*., 1994). The data from this study have been analysed by subdividing the group by age at first exposure (Table 36). No significant variation in the ERR/WLM was found.

Table 36. Excess relative risk (ERR) for lung cancer per working-level month (WLM) and its variation with age at first exposure in the study of tin miners in Yunnan, China

Age at first exposure (years)	Cases	Controls	ERR/WLM (%)	p[a]
< 10	35	28	0.38	0.58
10–14	167	185	0.30	
15–19	82	115	0.25	
20–24	38	73	0.18	
≥ 25	59	167	0.30	

From Yao *et al*. (1994). All models were stratified by smoking status, age, source of subject (Gejiu City or Yunnan Tin Corporation) and type of respondent (individual or surrogate).

[a] p for test of homogeneity of ERR/WLM over categories of age at first exposure

(*b*) *Cancers other than lung cancer*

Information on mortality from cancers other than lung cancer was published for some of the cohorts of underground miners exposed to radon (Waxweiler *et al*., 1983; Morrison *et al*., 1988; Tirmarche *et al*., 1993; Tomášek *et al*., 1994b; Darby *et al*., 1995a,b), but for many it was not. Some excesses were reported, but there was no consistent pattern to the findings, and in most cases the small numbers of deaths limited exposure–response analysis and interpretation. The data from the studies of miners were brought together systematically in a pooled analysis of 11 of the 12 studies of miners listed in Table 33 (Darby *et al*., 1995b). The Radium Hill study (Australia) was omitted because follow-up was incomplete for cancers other than of the lung. In addition, the Yunnan cohort could not be included in comparisons of the numbers of deaths observed compared with those expected from regional or national rates because appropriate external rates were not available. However, this study was

included in internal comparisons of the association between specific cancers and cumulative exposure to radon. Except in China, the mortality rate from all cancers other than lung cancer was close to that expected from rates in the areas surrounding the mines (ratio of observed to expected deaths, 1.01; 95% CI, 0.95–1.07, based on 1179 deaths) and did not increase with increasing cumulative exposure. Among 28 individual cancer categories, statistically significant increases in mortality were found for cancers of the stomach (observed/expected, 1.33; 95% CI, 1.16–1.52) and for primary liver cancer (1.73; 95% CI, 1.29–2.28); statistically significant decreases were found in the mortality rates from cancers of the tongue and mouth (0.52, 0.26–0.93), pharynx (0.35, 0.16–0.66) and colon (0.77, 0.63–0.95) (Table 37). The mortality rate from leukaemia was increased in the period < 10 years since starting work (1.93; 95% CI, 1.19–2.95) but not subsequently. The rate was significantly related to cumulative exposure only for cancer of the pancreas (ERR/WLM, 0.07%; 95% CI, 0.01–0.12) and, in the period < 10 years since the start of employment, for other and unspecified cancers (ERR/WLM, 0.22%; 95% CI, 0.08–0.37). [The Working Group noted that the increases in mortality rates from stomach and liver cancers and leukaemia are unlikely to have been due to radon, since they are unrelated to cumulative exposure. The absence of a biological mechanism for radon-induced pancreatic cancer, coupled with the number of comparisons made in this analysis, points to a chance occurrence. This analysis provides considerable evidence that high concentrations of radon in the air do not materially increase the risk for death from cancers other than lung cancer.]

2.1.2 *Residential exposure*

In contrast to the studies of underground miners, which were usually cohort studies, studies of the effects of residential exposure to radon have usually been case–control studies, because detailed residential and smoking histories must be obtained for each subject. In a number of early studies, residential radon concentrations were assessed by indirect measures, such as housing characteristics (for a review, see Committee on Health Risks of Exposure to Radon (BEIR VI), 1999), but in all the more recent studies, the radon concentration was measured directly in the air of the subjects' homes with α-track detectors and imputation of missing values. These measurements were then used to calculate a time-weighted average (TWA) concentration of radon during an appropriate exposure time.

(*a*) *Lung cancer*

These studies were reviewed in detail by the Committee on Health Risks of Exposure to Radon (BEIR VI; 1999). The summaries given below are based on that review and have been updated and modified appropriately; newly published studies are described in similar format.

Table 37. Numbers of deaths observed (O), ratio of observed to expected deaths (O/E) and 95% confidence interval (CI) since first employment for deaths from cancers at selected sites in a pooled analysis of 10 studies of underground miners exposed to radon

Cancer site (ICD-9 code)	O	O/E[a]	95% CI
Tongue and mouth (141, 143-145)	11[b]	0.52	0.26–0.93
Salivary gland (142)	4	1.41	0.39–3.62
Pharynx (146-149)	9[c]	0.35	0.16–0.66
Oesophagus (150)	45	1.05	0.77–1.41
Stomach (151)	217[c]	1.33	1.16–1.52
Colon (152-153)	95[b]	0.77	0.63–0.95
Rectum (154)	60	0.86	0.66–1.11
Liver, primary (155.0, 155.1)	50[c]	1.73	1.29–2.28
Liver, unspecified (155.2)	3	0.43	0.09–1.26
Gall-bladder (156)	19	1.23	0.74–1.92
Pancreas (157)	91	1.05	0.85–1.29
Nose (160)	3	0.69	0.14–2.02
Larynx (161)	38	1.21	0.86–1.67
Bone (170)	10	1.04	0.50–1.91
Connective tissue (171)	5	0.82	0.27–1.91
Malignant melanoma (172)	18	0.92	0.54–1.45
Other skin (173)	9	1.60	0.73–3.03
Prostate (185)	83	0.88	0.70–1.09
Testis (186)	6	0.72	0.26–1.57
Bladder (188, 189.3-189.9)	39	0.85	0.61–1.16
Kidney (189.0-189.2)	44	0.91	0.66–1.22
Brain and central nervous system (191, 192)	52	0.95	0.71–1.25
Thyroid gland (193)	2	0.47	0.06–1.71
Non-Hodgkin lymphoma (200, 202)	36	0.80	0.56–1.10
Hodgkin disease (201)	17	0.93	0.54–1.48
Multiple myeloma (203)	26	1.30	0.85–1.90
Leukaemia (204–208)	69	1.16	0.90–1.47
Leukaemia excluding chronic lymphoid (204–208 except 204.1)[d]	36	1.11	0.78–1.54
Myeloid leukaemia (205,206)[d]	27	1.41	0.93–2.05
Acute myeloid leukaemia (205.0, 205.2, 206.0, 206.2)[d]	12	1.16	0.60–2.02
Other and unspecified	118	1.12	0.93–1.35
All cancers other than lung (140-161, 163-208)	1179	1.01	0.95–1.07

From Darby *et al*. (1995b)

[a] Expected deaths calculated from national or local mortality rates; study in China therefore excluded

[b] $0.01 < p \leq 0.05$

[c] $p = 0.001$ (two-sided tests)

[d] For each study, only the time period for which the 8th or 9th ICD revisions were in use nationally is included.

(i) *New Jersey, USA*

Schoenberg *et al*. (1990) studied cases selected from 1306 histologically confirmed cases of lung cancer diagnosed in women in August 1982 through September 1983 throughout the State of New Jersey. They were identified from hospital pathology records, the New Jersey State Cancer Registry and death certificate files. In the original study, interviews were held with 532 women and 462 next-of-kin, providing data for 994 women (76% of those eligible). For living cases, controls were selected randomly from files of New Jersey driver's licences (age < 65 years) or Health Care Financing Administration files (age ≥ 65 years). For dead cases, controls were selected randomly from death certificates that did not mention respiratory disease. Controls were individually matched by race, age and, for deceased cases, date of death. Data were obtained at interview for 995 control women (69%). Phase I included subjects who had lived in a single index residence for 10 years or more in the period 10–30 years before diagnosis or selection. Phase II broadened the eligibility period to 5–30 years before interview and targeted all houses in which subjects had lived for four or more years in an area of the State with a high radon concentration and seven or more years in the rest of the State. Subjects were restricted to those for whom nine years or more of residence was known. Under these criteria, 661 cases (66% of the 994) and 667 controls (67% of the 995) were eligible. Measurements representing nine or more years of exposure were obtained for 480 cases and 442 controls, and these were included in the study. Radon was measured with a one-year α-track detector, mainly in the living area. The mean radon concentration was 0.5 pCi/L (18.5 Bq/m^3) for both cases and controls. Exposure was estimated for the 5–30 years before the date of case diagnosis or control selection. The relative risks were increased only in the highest category of exposure (148–418 Bq/m^3; 4.0–11.3 pCi/L), which included five cases and one control (RR, 8.7; 90% CI, 1.3–58). The *p* value for linear trend was significant at $p = 0.05$, on the basis of a one-sided test of the null hypothesis (BEIR VI). The results for cumulative radon exposure were similar to those for TWA concentrations of radon (Schoenberg *et al*., 1992). There was no increased risk with increasing exposure for lifelong non-smokers, but the trend was inconsistent for different smoking groups. [The Working Group noted that a one-sided test of the null hypothesis and 90% confidence intervals were reported. Significance would be approximately doubled and confidence intervals wider if the conventional two-sided tests and 95% confidence intervals had been used. As few subjects had appreciable exposure, the power of the study to detect an effect is low. Further, only 50% of the 1306 women with lung cancer contributed to the study.]

(ii) *Shenyang, China*

A study by Xu *et al.* (1989) and Blot *et al.* (1990) included all female residents of Shenyang, China, aged 30–69 years, in whom primary lung cancer was diagnosed between 1985 and 1987 and who were listed in the Shenyang Cancer Registry. All the diagnoses were reviewed. Controls were selected randomly from the general population in five-year age groups, frequency matched to the cases. A total of 308 cases and 356

controls were interviewed personally, and radon was measured with two one-year α-track detectors in current and previous homes (79% of eligible cases and 91% of controls). The median radon concentrations were 2.8 pCi/L [104 Bq/m^3] for cases and 2.9 pCi/L [107 Bq/m^3] for controls. Exposure to radon was estimated for 5–30 years before case diagnosis or control selection. The relative risk for lung cancer, adjusted for age, education, smoking status and an index of indoor air pollution, showed no significant trend with increasing radon concentration. The patterns of relative risk were the same for different levels of an index of indoor air pollution and after adjustment. When the analyses were restricted to women who had lived for more than 25 years in their last residence, the results were similar to the overall results. The overall dose–response relationship was negative, the lowest risk being seen at the higher exposure (28% were > 150 Bq/m^3).

(iii) *Stockholm, Sweden*

Svensson *et al*. (1989), Pershagen *et al*. (1992) and Lubin *et al*. (1994b) studied 210 cases of lung cancer in women in Stockholm County in 1983–85. Two controls were selected per case: 191 hospital controls and 209 population controls were selected randomly from county population registers and frequency matched on age to the cases. Subjects were interviewed in person or by telephone. Radon was measured for 201 cases and 378 controls with two one-year α-track detectors or a thermoluminescence detector in all homes occupied for two years or more since 1945. The values obtained with the thermoluminescence detector were then adjusted empirically to link them with the α-track measurements (Svensson *et al.*, 1988). The mean concentrations were 3.6 pCi/L [133 Bq/m^3] for the cases and 3.7 pCi/L [137 Bq/m^3] for the controls. Exposure was estimated from 1945 to five years before interview. There was a significant ($p = 0.05$) increase in relative risk with increasing TWA radon concentration in a trend test based on the median radon concentration in each category, but this was reduced to $p = 0.46$ when the continuous value for radon concentration was used. The results based on cumulative exposure were similar to those based on TWAs. There were no clear differences in trend for the various histological types; however, the effect was stronger for non-smokers than for smokers. In contrast to the results for underground miners, the apparent risks were higher when exposure had occurred many years in the past, when exposure assessment was uncertain. [The Working Group noted that the discrepancy between the significance level based on the median radon concentration in each category and that based on individual values is surprising. The explanation may lie partly in the fact that the categorical measure gives lower weight to extremely high values, thus effectively correcting in part for measurement error (see below).]

(iv) *Sweden*

Pershagen *et al*. (1994) and Lagarde *et al*. (1997) studied 1500 men and women aged 35–74 years in whom primary lung cancer was diagnosed between 1980 and

1984, who were selected from the Swedish Cancer Registry. The study included all 650 women and a random sample of 850 men who had been living in Sweden in January 1947 and some time during 1980–84. After various exclusions, 586 women and 744 men remained. Two controls were selected: one control group (730 women and 694 men) was derived from a randomly selected sample of population registers, frequency matched on age and calendar year of residence to the cases; and another control group (650 women and 773 men) was similarly selected but was also matched by vital status against the Swedish Cause of Death Registry. Individuals who had died from smoking-related diseases were not included. A total of 1281 cases and 2576 controls were enrolled. Radon was measured with two three-month α-track detectors in all homes occupied for two or more years since 1947. The mean concentration for cases and controls combined was 2.9 pCi/L [107 Bq/m^3]. The results showed a significant ($p < 0.05$) increase in relative risk with increasing radon concentration, and the excess relative risk was 0.10 per 100 Bq/m^3 (95% CI, 0.01–0.22) (Pershagen *et al.*, 1992). No difference in relative risk trends was observed by cell type or by smoking status.

(v) *Winnipeg, Canada*

Létourneau *et al*. (1994) conducted a study in which the eligible cases were all residents of Winnipeg, Canada, 35–80 years old, in whom histologically confirmed primary lung cancer was diagnosed in 1983–90 and who were listed in the Provincial cancer incidence registry. Controls were randomly selected from the Winnipeg telephone directory and individually matched on age within five years and sex. A total of 738 case–control pairs was included. Proxy interviews were held for 257 cases and 78 controls. Radon was measured with two sequential six-month α-track detectors. The mean concentrations in bedrooms were 3.1 pCi/L [115 Bq/m^3] for cases and 3.4 pCi/L [126 Bq/m^3] for controls. Exposure was estimated for 5–30 years and 5–15 years before the date of case diagnosis or control selection. There was no significant trend in relative risk by concentration of radon in bedrooms or basements. The relative risks were similar and showed no increase by cell type. Smoking patterns were used only for adjustment, and the effect of smoking on the relative risks was not evaluated. [The Working Group considered that the authors did not perform analyses based on a suitably weighted average of radon concentrations in bedrooms and basements. This would have reduced the impact of random measurement error.]

(vi) *Missouri, USA (study I)*

Alavanja *et al*. (1994) carried out a case–control study of 618 women aged 30–84 years who had never smoked or who had ceased smoking at least 15 years previously, and in whom primary lung cancer was listed in the Missouri Cancer Registry in 1986–91. Population-based controls (1587) were selected from State driver's licence files or files of the Health Care Finance Administration, frequency matched by age. After refusals and other exclusions, 538 cases (83%) and 1183 controls (78%) for whom at least one home had been measured for radon in the 5–30 years before

enrolment were included. For case subjects, 63% of interviews were conducted with next-of-kin. Radon was measured with two one-year α-track detectors in all homes in Missouri occupied for one year or more 5–30 years before the date of enrolment. The mean value was the same for cases and controls (1.8 pCi/L [67 Bq/m^3]). In about 7% of the homes, the concentration was > 4 pCi/L [148 Bq/m^3]. There was no significant trend in age-adjusted relative risk with increasing radon concentration. The results of analyses of cumulative exposure were similar. No difference in the trend in relative risk with radon concentration was observed between women who had never smoked and former smokers. The study is somewhat unique in including only incident cases of lung cancer in non-smokers and exposure measurements made close to the date of diagnosis.

(vii) *South Finland*

Ruosteenoja (1991) and Ruosteenoja *et al*. (1996) carried out a case–control study of 238 men with primary lung cancer in 19 municipalities in Finland in 1980–85. For 1980–82, cases were obtained from the Finnish Cancer Registry; for 1983–85, cases were obtained from records of treatment hospitals. A population-based random sample served as controls, frequency matched by age category to the cases. On the basis of information on smoking from a mailed questionnaire, a random sample of 50 lifelong non-smokers, 50 ex-smokers and 395 current smokers was selected to serve as controls. Interviews were carried out with next-of-kin for 85% of cases and 16% of controls. Radon was measured with two-month α-track detectors in all homes that had been occupied for one year or more in 1950–75. Exposure was estimated for the 25 years between 1950 and 1975, that is, 5–10 years before diagnosis of the case or control interview. The relative risks increased with increasing radon concentration, but the trend was not significant ($p > 0.05$). No clear differences by histological cell type were observed, and adjustment for smoking had little effect on the pattern of relative risks with radon concentration.

(viii) *Finland*

Auvinen *et al*. (1996, 1998) studied subjects selected from the Finnish Population Registry of persons who had lived in the same single-family house from 1 January 1967 or earlier until the end of 1985. Between 1 January 1986 and 31 March 1992, 1973 cases of lung cancers were diagnosed. For each case, at least one control was matched by birth year, sex and vital status at the time of diagnosis of the case, yielding 2885 controls. Data were obtained from next-of-kin for 85% of case subjects and 10% of control subjects. For the matched analysis, 517 pairs were available. Radon was measured with one α-track detector, which was mailed to each subject with instructions to place it in the bedroom or in the living room. The mean concentrations were 2.8 pCi/L [103 Bq/m^3] for cases and 2.6 pCi/L [96 Bq/m^3] for controls. Exposure was estimated for 38 median years in the index house for cases and 35 median years in the index house for controls. The initial results, reported by Auvinen *et al*. (1996), were

found to be in error, and corrected results were reported by Auvinen *et al.* (1998). There was no significant trend in relative risk with increasing radon concentration. The relative risk patterns were also similar by cell type and within smoking categories.

(ix) *Israel*

Biberman *et al*. (1993) conducted a hospital-based case–control study with two groups of consecutive patients with primary lung cancer at an oncology ward in the Rambam Medical Center in 1985–89. The groups consisted of 35 cases of small-cell carcinoma among both people who had ever and never smoked and 26 cases of non-small-cell carcinoma (16 adenocarcinomas) in people who had never smoked. The case subjects had to have lived in Israel for at least 10 years before diagnosis. The controls were patients without lung cancer matched by sex and five-year age group who were admitted to the same hospital immediately after admission of the case and had lived in Israel for 10 years or more. After exclusions and refusals, only 35 matched pairs (20 small-cell cancer and 15 non-smokers) were available for analysis. Some information was obtained from the subjects themselves and some from proxies, but details were not given. Radon was measured with α-track detectors placed for an average of nine months between June or July 1990 and April 1991. The overall mean concentration was 1.0 pCi/L [37 Bq/m^3]. No limit was defined for exposure estimation, but only measurements obtained in current housing were used: 28 (80%) cases and 19 (54%) controls had lived for 20 years or more in a house in which measurements had been made, and 15 (43%) cases and 13 (37%) controls had lived for 30 years or more in such a house. No significant differences in median radon concentrations were observed between cases and controls.

(x) *Port Hope, Canada*

Lees *et al*. (1987) studied 27 cases of lung cancer diagnosed in 1969–79 in persons who had lived for seven years or more in Port Hope, Ontario, and who had never been employed at the uranium-refining plant. The controls were 49 subjects matched on sex and date of birth who had lived for seven years or more in Port Hope, at least one of these years during the seven-year period before the date of diagnosis of the matched case. One deceased and one live control were matched to each deceased case, and two live controls were matched to each live case. Neither the mean nor the median radon concentration was provided. Exposure to radon progeny was estimated in all homes occupied in Port Hope since 1933, but residences outside the Port Hope area were ignored. The estimates were expressed in WLM and were adjusted by a background exposure of 0.229 WLM/year. The mean WLM values were 2.7 and 0.5 for cases and controls, including 33% and 49% with 'no' WLM (below estimated background exposure), respectively; the mean WLM values for those exposed were 4.1 and 1.0. With adjustment for smoking, a relative risk of 2.36 (95% CI, 0.79–7.11) for exposed (> 0 WLM) versus unexposed (0 WLM) was found. The authors concluded, however, that radon was not a significant contributor to the lung cancer risk of the general

population studied. [The Working Group noted that details of the radon measurement protocol were not given in the final publication.]

The studies described below are not included in the report of BEIR VI (Committee on Health Risks of Exposure to Radon, 1999).

(xi) *South-west England*

Darby *et al*. (1998) studied 982 white men and women aged < 75 years with lung cancer who had lived in Devon or Cornwall for at least 20 years in the period 5–30 years before diagnosis. Two control groups were selected: one comprised 317 persons who were investigated for suspected lung cancer but were found not to have lung cancer or a disease closely related to smoking, plus 1382 hospital patients admitted to the same hospitals as the patients with lung cancer but for diseases that were not closely related to smoking and matched for age and sex to the patients with lung cancer; and the other comprised 1486 population controls matched by age and sex. All subjects were interviewed in person. The refusal or non-participation rates were 12.4% for patients with suspected lung cancer, 4.2% for hospital controls and 19.0% for population controls. Radon was measured with two α-track detectors placed for six months in all residences in Devon or Cornwall. Annual estimates were derived by the method of Pinel *et al*. (1995). The mean concentrations were 58 Bq/m^3 for cases and 56 Bq/m^3 for controls. Exposure was estimated for 5–30 years before the date of diagnosis (cases) or date of interview (controls). The relative risk tended to increase with increasing radon concentration only in the two highest categories. The estimated excess relative risk per 100 Bq/m^3 was 0.08 (95% CI, –0.03, 0.20). There was no heterogeneity in the trend by cell type or by smoking status. For individuals whose exposure to radon had been covered completely, the excess relative risk at 100 Bq/m^3 was 0.14 (95% CI, 0.01–0.29) before and 0.24 (95% CI, –0.01, 0.56) after adjustment for uncertainties.

(xii) *Missouri, USA (study II)*

Alavanja *et al*. (1999) studied 742 women aged 30–84 years with primary lung cancer who were reported to the Missouri Cancer Registry between 1 January 1993 and 31 January 1994. Age-matched population-based controls were randomly selected from files of driver's licences or lists provided by the Health Care Financing Administration. For analyses with α-track measurements, 247 cases and 299 controls were available. For analyses from surface measurements, 372 cases and 471 controls were used. Two radon measurement protocols were used: one-year α-track detectors and surface monitors. Empirically derived correction factors for the glass-based measurements were used in the homes of smokers or where window glass was used (Mahaffey *et al.,* 1996). The mean concentrations of radon with α-track detectors were 58 Bq/m^3 in kitchens and 56 Bq/m^3 in bedrooms; the mean value with surface measurements was 65 Bq/m^3 in kitchens and bedrooms. Exposure was estimated for 5–25 years before diagnosis (cases) or interview (controls). On the basis of the α-track

measurements, and consistent with the earlier study of non-smoking women in Missouri, there was no significant trend in relation to TWA radon concentration. On the basis of surface measurements, there was a significant trend (p = 0.02), and the relative risk for the category ≥ 148 Bq/m^3 was 3.3 (95% CI, 1.5–7.5) when compared with persons exposed to < 37 Bq/m^3. On the basis of surface monitors, the dose–response relationship for each cell type was similar to the overall result. There was no significant heterogeneity in dose–response by cell type or by smoking status. [The Working Group noted that surface measurement has not yet been validated as a better reflection of cumulative exposure than the α-track technique.]

(xiii) *Iowa, USA*

Field *et al*. (2000) studied 413 women 40–84 years old with primary lung cancer, identified from the Iowa Cancer Registry between 1 May 1993 and 30 October 1996. Population-based controls (614) were selected from State driver's licence files or files of the Health Care Finance Administration and were frequency matched by age. No proxy respondents were available for controls, whereas proxy respondents were necessary and available for 31.5% of the cases. Multiple one-year α-track detector measurements were made in the homes, and radon concentrations outdoors and at the workplace were incorporated into the exposure estimates. Retrospective measurements of radon progeny were performed from window glass. Exposure was estimated for 5–19 years prior to diagnosis for cases or prior to time of interview for controls; the median coverage was 32 years. Overall, a positive categorical trend (p = 0.05) was seen with cumulative radon exposure 5–19 years before death. This was strengthened when the analysis was restricted to 283 live patients and 614 live controls (continuous trend, p = 0.03).

(xiv) *Western Germany*

Wichmann *et al.* (1998a,b) and Kreienbrock *et al*. (2000) studied 1449 incident cases of lung cancer in persons aged < 75 years of age in whom the disease was diagnosed during 1990–95 in southern North-Rhine-Westfalia, Rhineland-Palatinate, Saar or eastern Bavaria and who had never worked in the uranium mining industry. The controls consisted of 2297 people interviewed between 1990 and 1996, who were matched to the cases by age, sex and area and selected randomly from official mandatory registries or by random-digit dialling. In the final analysis, 1023 cases and 1626 controls for whom complete radon measurements were available were included. All of the cases were verified histologically. Radon was measured with two α-track detectors placed for one year, one in the living room and one in the bedroom, in present and past residences (up to 35 years previously). The mean concentrations were 49 Bq/m^3 for cases and 50 Bq/m^3 for controls. Exposure was estimated for 5–15 years before interview. There was no significant trend in risk with increasing TWA radon concentration, and the estimated relative risk at 100 Bq/m^3 was 0.97 (95% CI, 0.82–1.14). The results for cases of small-cell carcinoma were similar to the overall results. For areas with radon concentrations of 67 Bq/m^3 (365 cases) and 60 Bq/m^3

(595 controls), a positive association with lung cancer was seen, but this was not statistically significant. Analyses based on concentrations in current homes were similar to those for concentrations 5–15 years earlier.

(xv) *Eastern Germany*

Wichmann *et al.* (1999) carried out a case–control study in Thuringia and Saxony between 1990 and 1997. Data were available for 2110 cases of lung cancer (73% of those eligible) in five clinics in the area and 1927 population controls (45% of those eligible) matched on sex, age and region. Both patients and controls were < 75 years old. Radon was measured with two α-track detectors. The mean concentrations were 87 Bq/m^3 for cases and 90 Bq/m^3 for controls. Among men, 2.4% of the patients and 26.5% of controls were non-smokers while, among women, 52.8% of the cases and 74.9% of controls had never smoked. The adjusted odds ratio for exposure at 100 Bq/m^3 was 1.04 (95% CI, 0.96–1.12). The test for trend was not significant.

(xvi) *Summary*

Table 38 summarizes the chief features of the major studies of residential exposure to radon and lung cancer that included direct, long-term measurements of radon in the homes concerned. The relative risk for exposure at 100 Bq/m^3, calculated by the Working Group on the basis of published data, and its 95% confidence interval are given for each study. When the results of eight studies were combined in a random-effect model, the summary risk estimate, with heterogeneity taken into account, was [1.09; 95% CI, 1.00–1.19)].

Even in studies in which the radon concentration was measured in the subjects' homes, there is considerable uncertainty in its assessment. In most studies, there are inevitably some residences in which radon cannot be measured, for example because the house has been demolished. In order to calculate an appropriate TWA radon concentration for the subject concerned, therefore, the radon concentration in such residences must be imputed. Radon concentrations also vary seasonally so that, unless average radon concentrations over a full year have been measured, approximate seasonal correction factors must be applied. Even when radon has been measured in a home, the measurements are subject to uncertainty in the sense that repeated measurements on the same residence have a coefficient of variation of around 50% (Bäverstam & Swedjemark, 1991; Lomas & Green, 1994; Lagarde *et al.*, 1997; Darby *et al.*, 1998; Bäverstam & Lagarde, 1999). Statistical theory demonstrates that the effect of such measurement errors is to reduce estimates of harmful or beneficial effects unless special analytical methods that take them into account are used (Cox *et al.*, 1999). Two of the case–control studies of residential exposure to radon and lung cancer were analysed by such methods. In the Swedish study, Lagarde *et al.* (1997) found a relative risk for exposure at 100 Bq/m^3 of 1.17 (95% CI, 1.03–1.37), which is considerably higher than the original estimate of 1.10 (95% CI, 1.01–1.22) (Pershagen *et al.*, 1994) in which uncertainties in the assessment of radon concentrations were

Table 38. Estimates of relative risk (RR) of exposure at 100 Bq/m^3 and 95% confidence intervals (CIs) in epidemiological studies of residential exposure to radon and lung cancer based on at least 100 cases of lung cancer and direct measurements of radon with α-track monitors

Study	Reference	Cases		Controls		RR	95% CI
		M	F	M	F		
New Jersey, USA	Schoenberg *et al*. (1990)	–	480	–	442	1.49[a]	(0.89–1.89)
Shenyang, China	Blot *et al.* (1990)	–	308	–	356	0.95[a]	(undefined–1.08)
Stockholm, Sweden	Pershagen *et al*. (1992)	–	201	–	378	1.16[a]	(0.89–1.92)
Sweden	Pershagen *et al.* (1994)	729	552	1317	1259	1.10[a]	(1.01–1.22)
	Lagarde *et al.* (1997)					1.17[b]	(1.03–1.37)
Winnipeg, Canada	Létourneau *et al.* (1994)	488	250	488	250	0.98[a]	(0.87–1.27)
Missouri, USA (I)	Alavanja *et al.* (1994)	–	538	–	1183	1.08[a]	(0.95–1.24)
South Finland	Ruosteenoja *et al*. (1996)	164	–	331	–	1.80[a]	(0.90–3.50)
Finland	Auvinen *et al*. (1996, 1998)	479	38	479	38	1.11[a]	(0.94–1.31)
South-west England	Darby *et al.* (1998)	667	315	2108	1077	1.08	(0.97–1.20)
						1.12[c]	(0.95–1.33)
Missouri, USA (II)	Alavanja *et al*. (1999)	–	247	–	299	0.85[d]	(0.73–1.00)
		–	372[i]	–	471[g]	1.63[d,e]	(1.07–2.93)
Iowa, USA	Field *et al*. (2000)		413	–	614	1.29[d]	(1.20–1.40)
Western Germany	Wichmann *et al.* (1998a,b)	1214	235	1865	432	0.97[f]	(0.82–1.14)
	Kreienbrock *et al*. (2000)					1.09[g]	(0.86–1.38)
Eastern Germany	Wichmann *et al.* (1999)	926	127	1460	207	1.11[d,f]	(1.00–1.27)
						1.27[d,g]	(1.00–1.60)

All the values except for south-west England and western Germany were calculated by the Working Group from data at 150 Bq/m^3.

[a] Calculated by the Working Group from Lubin & Boice (1997). A meta-analysis based on published data for these eight studies showed a relative risk of 1.09 (95% CI, 1.00–1.19) for exposure at 100 Bq/m^3 (calculated from the values given by Lubin & Boice, 1997).

[b] Assuming 50% coefficient of variation in measured radon concentrations

[c] Assuming 50% coefficient of variation in measured radon concentrations and allowing for uncertainties in estimates of missing values

[d] From Lubin (1999)

[e] Analysis based on surface monitoring

[f] Entire study

[g] Areas with high radon concentrations

ignored. Similarly, in the study in south-west England, an analysis that took into account uncertainties in the radon assessment found a relative risk for exposure at 100 Bq/m^3 of 1.12 (95% CI, 0.95–1.33), which may be compared with an estimate of 1.08 (95% CI, 0.97–1.20) when uncertainties were ignored (Darby *et al.*, 1998).

A further problem is that in some countries residential radon concentrations may have changed systematically over time (Hubbard & Swedjemark, 1993), for example because of the tendency to reduce ventilation rates in indoor air. An alternative to measuring the current radon concentration in the air of all the residences of interest is to use surface monitors to measure the cumulative exposure as recorded in household objects made of glass. This method in principle avoids the uncertainty created by this tendency and also those created by missing values and seasonal corrections. It has been used in one study (Alavanja *et al.*, 1999), in which the relative risk for exposure at 100 Bq/m^3 was estimated to be 1.63 (95% CI, 1.07–2.93). As noted earlier, however, the method has not been validated, and the uncertainties are not inconsequential, especially in homes where subjects smoked.

The estimates of risk from the studies of residential exposure are consistent with predictions based on the risks of underground miners occupationally exposed to radon.

The primary lung tumours found in the male population of the USA consist of squamous-cell carcinoma (32%), adenocarcinoma (27%), small-cell carcinoma and/or oat-cell carcinoma (16%), large-cell carcinoma (8%) and other specified types (5%) (Percy & Sobin, 1983). The histology of the lung cancers in the various case–control studies of residential exposure to radon summarized above parallels this distribution, whereas in uranium miners (especially in the 1950s) small-cell carcinomas represented the majority of cases (Saccomanno *et al.*, 1996; Wiethege *et al.*, 1999).

(*b*) *Cancers other than lung cancer*

Five case–control studies of residential exposure to radon and the incidence of cancers other than lung cancer included at least 40 cases of cancer and long-term measurements of residential radon. The first of these comprised 44 men aged 35–80 who had died from myeloid leukaemia during 1980–89 and who had lived in the province of Viterbo, Italy (Forastiere *et al*., 1998). The cases were obtained from the regional mortality register of Lazio. Five controls per case were selected from among men who had died from other causes during the same period, matched for age. Radon was measured with two six-month α-track detectors in the last home in which the man had lived or in the previous home if he had moved within two years. No significant association between residential radon concentration and the risk for leukaemia was found: relative to < 100 Bq/m^3, the odds ratios for exposure categories 100–145, 146–230 and ≥ 231 Bq/m^3 were 0.51 (95% CI, 0.2–1.3), 0.66 (95% CI, 0.3–1.6) and 0.56 (95% CI, 0.2–1.4), respectively.

The second study included children in whom acute lymphoblastic leukaemia had been diagnosed when they were under 15, who had been treated by physicians

associated with the Children's Cancer Group during 1989–93 and resided in one of nine mid-western or mid-Atlantic states of the USA (Lubin *et al.*, 1998). Controls were selected by random-digit dialling and were individually matched to cases on age, race and the first eight digits of the telephone number. A total of 505 cases and 443 controls were included in the study. For children aged under five years, radon was measured in all homes in which the children had lived for at least six months; for children aged 5–14, radon was measured in homes in which the subjects had lived for at least one year in the five-year period before the reference date. Two α-track detectors were placed for one year in each qualifying residence. The mean radon concentration was lower for case subjects (65.4 Bq/m^3) than for control subjects (79.1 Bq/m^3). For categories of radon exposure of < 37, 37–73, 74–147 and ≥ 148 Bq/m^3, the relative risks based on matched case–control pairs and adjusted for sex were 1.00, 1.22 (95% CI, 0.8–1.9), 0.82 (0.5–1.4) and 1.02 (0.5–2.0), respectively. Other methods of analysis gave similar results.

The third study included children aged < 18 years in whom acute myeloid leukaemia or myelodysplastic syndrome had been diagnosed between January 1989 and March 1993 at member institutions of the North American Children's Cancer Group (Steinbuch *et al*., 1999). In order to be eligible, the index child at the time of diagnosis must have had at least one parent in residence and to have lived in a residence with a telephone and an entrance no higher than the floor above street level. Children with Down syndrome were excluded. One or two controls were selected per case by random-digit dialling and selected on age, race and telephone area code. A total of 173 cases and 254 controls were enrolled. No association was observed between exposure to radon and risk for acute myeloid leukaemia. When compared with < 37 Bq/m^3, the relative risks for categories 37–100 and ≥ 100 Bq/m^3 were 1.2 (95% CI, 0.7–1.8) and 1.1 (0.6–2.0), respectively, after adjustment for maternal race, maternal education, family income and age.

A population-based case–control study on risk factors for childhood malignancies was used to investigate a previously reported association between indoor radon concentration and childhood cancer, with special regard to leukaemia (Kaletsch *et al.*, 1999). The patients were all children under the age of 15 with leukaemia or solid tumours (nephroblastoma, neuroblastoma, rhabdomyosarcoma, central nervous system tumours) diagnosed between July 1988 and June 1993 in Lower Saxony (Germany). Two population-based control groups were matched by age and sex to the leukaemia patients. Radon was measured over one year in homes in which children had lived for at least one year, particular attention being paid to those rooms in which they had spent most of the time. Owing to the sequential study design, measurements could be made in these rooms only for 36% (82 cases of leukaemia, 82 cases of solid tumour and 209 controls) of the 1038 families initially contacted. The overall mean indoor radon concentration (27 Bq/m^3) was lower than those measured in other studies. When a pre-specified cut-off point of 70 Bq/m^3 was used, no association with indoor radon concentration was seen for leukaemia (odds ratio, 1.30; 95% CI,

0.32–5.33); however, the risk estimate was increased for solid tumours (odds ratio, 2.61; 95% CI, 0.96–7.13), mainly on the basis of six cases of central nervous system tumours.

A case–control study of 807 cases of acute leukaemia diagnosed between 1991 and 1996 was carried out in the United Kingdom (Law *et al*., 2000), with 1593 controls matched on sex, age and region. The participation rates were 76% for cases and 65% for controls. Two passive radon detectors were placed in the homes for six months, and 1881 measurements were made. The results of logistic regression modelling showed no association between acute leukaemia and exposure to radon.

2.1.3 *Geographical correlation studies*

(*a*) *Lung cancer*

Many geographical correlation studies have been conducted in an attempt to correlate average radon concentrations with average lung cancer rates in specific areas. These analyses, also called 'ecological studies', have been reviewed comprehensively (Stidley & Samet, 1993; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). Such descriptive studies are the weakest form of epidemiological investigation because the cumulative exposure of individuals cannot be estimated, nor can important confounding factors such as smoking be controlled for at the individual level. Ecological bias, namely the difference between associations seen at the group level as opposed to the individual level (Piantadosi, 1994; Morgenstern, 1995), has long been recognized as the principal limitation of geographical correlation studies. Further, in the case of radon, population mobility can lead to problems of dose estimation. In some countries, populations move frequently, and the radon concentration in the residence at the time of death does not reflect the TWA of that experienced over the previous 30 years. In addition, as exposure varies widely within small geographical areas, a single summary average for an area is inadequate as an estimate of current, and much less prior, exposure to radon for all the individuals in the area. Nineteen geographical correlation studies on radon have been conducted (BEIR VI), but the best known is the study of Cohen (1995, 2000) in the USA, who reported an inverse correlation between the background levels of radon and mortality from lung cancer in various areas. The age-adjusted mortality rate from lung cancer among white men and white women during the period 1970–79 was compared with the average radon concentrations in living areas of homes in 1601 counties in the USA. Counties were grouped into 18 categories with average radon concentrations of < 12 Bq/m^3 to 220–260 Bq/m^3. The rate of mortality from lung cancer decreased significantly with increasing radon concentration, in contrast to the increasing trend predicted from the data for underground miners.

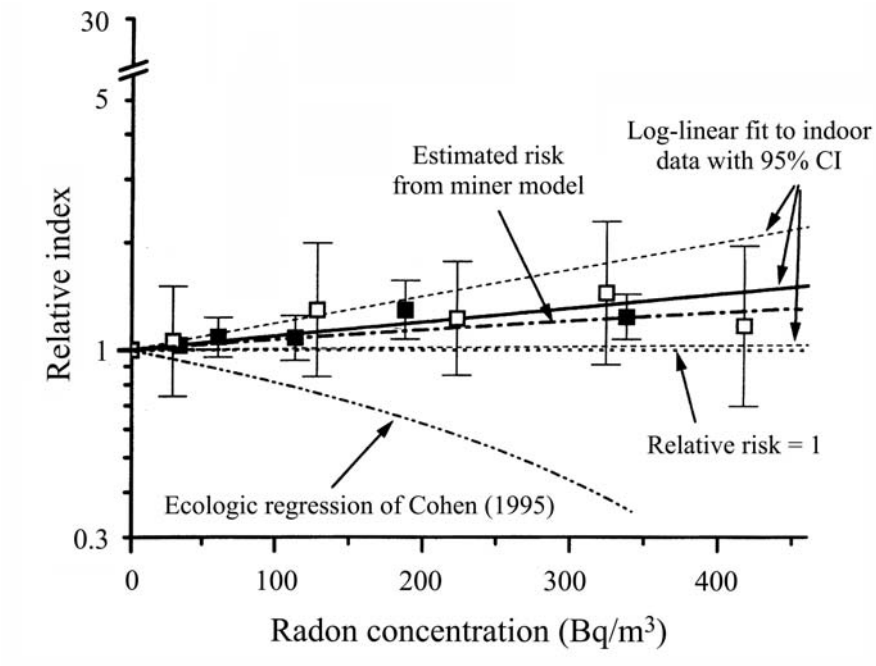
This disparity is striking, and it is not surprising that some researchers have accepted these data at face value, taking them either as evidence of a threshold dose for high-LET radiation, below which no effect is produced, or as evidence that exposure of the lung to relatively high levels of natural background radiation reduces

the risk for lung cancer due to other causes. To those with experience in interpreting epidemiological observations, however, neither conclusion can be accepted (Doll, 1998). Cohen's geographical correlation study has intrinsic methodological difficulties (Stidley & Samet, 1993, 1994) which hamper any interpretation as to causality or lack of causality (Cohen, 1998; Lubin, 1998a,b; Smith *et al*., 1998; BEIR VI). The probable explanation for the correlation is uncontrolled confounding by cigarette smoking and inadequate assessment of the exposure of a mobile population such as that of the USA. It is noteworthy that a positive trend observed in a Swedish case–control study changed to a negative trend when the data were re-evaluated as a geographical correlation study (Lagarde & Pershagen, 1999). Similar differences were noted in Iowa, USA, where Smith *et al*. (1998) reported a negative correlation in the mortality data, which disappeared when incidence data were evaluated, and in southwest England, where substantial ecological bias was observed (Darby *et al.*, 2001). In other words, aberrant dose–response trends in correlation studies disappear when methodologically sounder investigations are conducted within the same geographical regions, based on estimates of individual exposure and control for smoking at the individual level and for other factors that influence lung cancer risk at the geographical level.

It is thus likely that the negative association seen between lung cancer risk and radon concentration in the different areas analysed by Cohen is not due to radon. Uncontrolled confounding by smoking is a probable explanation, as smoking is a predominant cause of lung cancer. Smoking is less prevalent in isolated rural areas of the USA where radon concentrations tend to be higher than in more densely populated areas. Further, confounding is possible because western states include counties with high radon concentrations but low smoking prevalences (Stidley & Samet, 1994). Cohen attempted to allow for differences in smoking by using prevalence data for different states in 1985 and adjusting for changes with time in national data to estimate the prevalence of smoking in the 1970s and then correcting for each county in the states on the assumption that the prevalence varied with the proportion of people living in an urban area and the regression of the lung cancer rate on that proportion. This method of allowing for confounding by smoking is novel but still very crude and inadequate. Even if data on smoking could be obtained for quite small areas, they might still be inadequate for the purpose, as shown by Greenland and Robins (1994), Lubin (1998a,b) and Smith *et al*. (1998). Further evidence for confounding by smoking comes from Gilbert (1994), who noted that other smoking-related cancers were also negatively associated with the radon concentration in Cohen's data.

There is other substantial evidence that contradicts the ecological analyses. The overview of Lubin and Boice (1997), for example, of the results of eight published case–control studies, with individual data on residential exposure to radon and smoking habits, showed a dose–response relationship that was quantitatively similar to that seen for underground miners and statistically incompatible with the negative response reported by Cohen (1995) (Figure 4). That is, when individual exposures to

Figure 4. Summary relative risks from a meta-analysis of case–control studies of residential exposure to radon (open squares) and from a pooled analysis of studies of underground miners (filled squares), restricted to exposures to < 0.175 J h/m^3 (50 WLM)



From Lubin and Boice (1997) and Committee on Health Risks of Exposure to Radon (BEIR VI) (1999)

radon were estimated and smoking was controlled for, there was no evidence of a decreasing lung cancer risk at the concentrations experienced indoors.

It should be stressed that data on radon and the many potential confounders considered in Cohen's correlation studies are averages for geographical areas. Risk estimates from such studies are vulnerable to biases that are not present in estimates based on individual data, such as from cohort or case–control studies. In particular, Greenland and Robins (1994) pointed out that a lack of confounding in group data need not imply the absence of confounding in data for individuals, and vice versa. This is particularly true in the case of indoor radon, since smoking has a much greater impact on lung cancer risk than radon. Furthermore, the data available from correlation studies do not take account of residential history. For example, a person who had just moved into an area from one with a different radon concentration would be categorized solely by the current area of residence rather than by the cumulative or time-weighted average exposure which is obtained in case–control evaluations. Indeed, as mentioned above, residential radon concentrations vary widely, even within geographical areas. While it

is true that the geographical correlation studies have less statistical uncertainty because the numbers are so large, greater statistical precision must be viewed in the context of the greater potential for substantial bias. The estimates of risk may be very precise, but they are nevertheless substantially biased, i.e. incorrect.

The overall evidence and an evaluation of the methodological aspects of the studies indicate that the data on miners provide a sound basis for estimating the risk associated with exposure to radon, at least under occupational conditions (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). The results of the case–control studies of indoor exposure to radon are consistent with the risk estimated from the studies of underground miners (Lubin & Boice, 1997; Figure 4). Geographical correlation studies are of little value in estimating the risks association with exposure to radon because individual exposures are unknown and residential mobility and lack of control of smoking are severe methodological limitations (and probable explanations for the peculiar trend in the low dose range). The weight of evidence is that the ecological analyses of Cohen can be rejected. The interested reader is referred to the lengthy discussions by the BEIR VI Committee in reaching this conclusion (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999).

(*b*) *Cancers other than lung cancer*

BEIR IV (Committee on the Biological Effects of Ionizing Radiations, 1988) and BEIR VI (Committee on Health Risks of Exposure to Radon, 1999) reviewed the ecological studies of exposure to radon and cancers other than of the lung. Both committees concluded that these analyses were too subject to bias to provide much information on the risk of the general population. Further, their results are inconsistent with those of more comprehensive studies of miners, who received substantially higher doses (Darby *et al*., 1995b), and with those of comprehensive case–control studies of indoor exposure to radon and leukaemia in childhood (Lubin *et al.*, 1998) and adulthood (Law *et al*., 2000).

The ecological or geographical correlation units used in these analyses ranged from counties to countries. One of the first reports was that of Lucie (1989), who found a positive correlation between the average radon concentration and the incidence of acute myeloid leukaemia in counties in the United Kingdom. Henshaw *et al*. (1990) then published estimates of the dose of radiation to the red bone marrow and suggested that a significant part of the dose might be from typical indoor concentrations of radon. Positive ecological correlations were shown between the mean exposures of the populations in 15 countries and the incidences of myeloid leukaemia, childhood cancers and other cancers. No positive correlations were found for skin cancer (Eatough & Henshaw, 1992; Harley & Robbins, 1992; Eatough & Henshaw, 1995). The equivalent dose resulting from exposure to radon at 200 Bq/m^3 for one year might be around 100 mSv to the lung and as high as 25 mSv to the skin, in contrast to the dose to red bone marrow of approximately 0.1–1.2 mSv (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999; National Radiological Protection Board, 2000).

There was substantial criticism of the report of Henshaw *et al.* (1990) (Butland *et al*., 1990; Mole, 1990; Peto, 1990; Wolff, 1991). The dosimetric model was questioned (Mole, 1990), and it was noted that even Henshaw's highest estimate of the dose to the red bone marrow from radon would be only 1% of that to the lung (Butland *et al*., 1990; see also Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). Concerns were raised about confounding and biological plausibility, and it was further suggested that the observations might have resulted from confounding by socioeconomic factors.

Muirhead *et al.* (1991) conducted an ecological analysis of childhood leukaemia based on much smaller areas (districts) in the United Kingdom. They reported no significant association with exposure to radon, even though analyses in aggregated areas (counties) showed a significant positive correlation. It was noted that no correlations were found between districts within counties, whereas correlations were found between counties, again indicating the severe difficulties and methodological limitations of ecological analyses, even for small geographical areas.

Further, analytical epidemiological case–control studies have not found a correlation between childhood acute lymphoblastic leukaemia and residential radon concentrations, measured and estimated for individual children who developed leukaemia and for comparable controls (Lubin *et al.*, 1998). In addition, a recent, comprehensive study of adult acute leukaemia based on case–control evaluations also found no evidence that the incidence of leukaemia was related to measured residential radon concentrations (Law *et al*., 2000). In conclusion, the ecological studies have had little success in either directing useful research to identify potential hazards associated with residential radon or providing quantitative evidence for or against an associated risk.

2.1.4 *Estimation of risk*

Epidemiological studies of underground miners have been the primary basis for estimating the risk associated with indoor exposure to radon. The key uncertainties in the data on miners include the heterogeneous risk estimates in the individual studies, which vary by more than a factor of 10, the effects of errors in exposure estimates on these risks, extrapolation to low exposure, the shape of the exposure–response relationship at low exposure, the consequences of exposures other than radon (including known lung carcinogens such as arsenic) in the mines and modification of the effect of radon by smoking. Furthermore, an interesting inverse dose-rate effect (protraction enhancement effect) is demonstrated at very high cumulative exposure levels, but appears to be inconsequential at the lower exposure experienced in the home (see above). Models for risk extrapolation have been used by the Committee on the Biological Effects of Ionizing Radiation (BEIR IV) (1988) and by the Committee on Health Risks of Exposure to Radon (BEIR VI) (1999), which evaluated and combined 11 studies of miners (Lubin *et al*., 1994a, 1995b, 1997). Meta-analyses of the case–control studies have also been conducted in an attempt to quantify the risks

of radon-induced lung cancer (Lubin & Boice, 1997), but so far have been based only on the published studies. Although the results of the analytical case–control studies are consistent with the predicted low risk extrapolated from the studies of miners, the data from the latter studies form the basis for most public health evaluations.

The combined analysis of 12 studies of underground miners is summarized in section 2.1.1. The large numbers of miners studied, the large excess of lung cancers and the long follow-up permitted modelling of the exposure–response relationship. This modelling extends that of the Committee on the Biological Effects of Ionizing Radiations (BEIR IV) (1988) which provided a combined analysis of four data sets: on the Swedish Malmberget iron miners and on the studies of underground uranium miners in the Colorado Plateau and in Ontario and Beaverlodge (Canada). This modelling approach is based on empirical fitting of the data and not on biological end-points, and is used for risk assessment in relation to indoor exposure to radon by the Committee on Health Risks of Exposure to Radon (BEIR VI) (1999).

(*a*) *Risk models*

A linear ERR model has generally been used to analyse the studies of miners:

$$RR = 1 + \beta w$$

where RR is the relative risk, β is a measure of the unit increase in ERR per unit increase in w, and w is the cumulative exposure to radon in WLM (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). The Committee on the Biological Effects of Ionizing Radiations (BEIR IV) (1988) concluded that a relative-risk model based on time since exposure provided the best fit for the data. The age-specific lung cancer mortality rate, *r (a)*, was expressed as:

$$r(a) = r_o(a)\,[1 + 0.025\,\gamma(a)\,(W_1 + 0.5\,W_2)],$$

where $r_o(a)$ is the age-specific background lung cancer mortality rate; $\gamma(a)$ is 1.2 when age a is < 55 years, 1.0 when a is 55–64 years and 0.4 when a is ≥ 65 years. W_1 is the WLM received 5–15 years before age a; and W_2 is WLM received ≥ 15 years before age a. No radon-related lung cancer risk is assumed for exposures received five years before age a. This is a multiplicative model of the background, or naturally occurring, rate, and it is assumed that other factors that determine lung cancer risk, e.g. tobacco use, are multiplicative with those of exposure to radon. This approach allowed the effect of radon exposure to vary within two exposure windows and differs from the so-called 'constant-in-time' relative risk models commonly used for cancer risk estimation in relation to radiation.

The pooled analysis of the 11 studies of underground miners went even further, taking into account that the ERR/WLM varied significantly with other factors (Lubin *et al*., 1994a, 1995b). The ERR/WLM decreased with attained age, time since exposure and time after cessation of exposure, although it was not affected by age at first exposure. The ERR/WLM was seen to increase as the duration of exposure increased

(or as the exposure rate declined) (Lubin *et al.*, 1997). Two models were then developed. Both incorporated time-since-exposure windows and accounted for the modification of the effect of radon by attained age. One incorporated variations in exposure rate (the TSE (time since exposure)/AGE (attained age)/WL (work level)-categorical model), and the other incorporated variations in the duration of exposure (the TSE/AGE/DUR (duration of exposure)-categorical model). These models and their parameters are shown in Table 39.

Table 39. Parameter estimates from recent analysis of pooled data on miners for two summary models

Exposure–age–duration (DUR) model		Exposure–age–concentration (WL) model	
$\beta \times 100$	0.55	$\beta \times 100$	7.68
Time since exposure (TSE) windows		Time since exposure (TSE) windows	
$\theta_{5–14}$	1.00	$\theta_{5–14}$	1.00
$\theta_{15–24}$	0.72	$\theta_{15–24}$	0.78
θ_{25+}	0.44	θ_{25+}	0.51
Attained age (AGE)		Attained age (AGE)	
$\varphi_{< 55}$	1.00	$\varphi_{< 35}$	1.00
$\varphi_{55–64}$	0.52	$\varphi_{35–64}$	0.57
$\varphi_{65–74}$	0.28	$\varphi_{65–74}$	0.29
φ_{75+}	0.13	φ_{75+}	0.09
Duration of exposure (DUR)		Exposure rate (WL)	
$\gamma_{< 5}$	1.00	$\gamma_{< 0.5}$	1.00
$\gamma_{5–14}$	2.78	$\gamma_{0.5–1.0}$	0.49
γ_{15-24}	4.42	$\gamma_{1.0–3.0}$	0.37
$\gamma_{25–34}$	6.62	$\gamma_{3.0–5.0}$	0.32
γ_{35+}	10.2	$\gamma_{5.0–15.0}$	0.17
		γ_{15+}	0.11

From Lubin *et al*. (1997); Committee on Health Risks of Exposure to Radon (BEIR VI) (1999). The fitted model had the form $RR = 1 + \beta (w_{5–4} + \theta_{15–24}\, w_{15–24} + \theta_{25+}\, w_{25+})\, \varphi_{age}\, \gamma_z$, where β is the exposure–response parameter; cumulative exposure is measured in working level months and partitioned into $w_{5–14}$, $w_{15–24}$, and w_{25+} categories defining exposure received 5–14, 15–24 and ≥ 25 years before current age; $\theta_{5–14}$, $\theta_{15–24}$, θ_{25+} are the *relative* contributions from exposures 5–14, 15–24 and ≥ 25 years before, with $\theta_{5–14} = 1.0$; φ_{age} and γ_z denote parameters for multiple categories of attained age; and z represents either exposure rate in WL or exposure duration (DUR).

TSE, time since exposure; AGE, attained age; DUR, duration of exposure; WL, exposure rate in working level

(*b*) *Recent analysis of data on miners*

While the distinct feature of the data on miners is the linearity in response, it has not been clear whether extrapolation to low doses is appropriate because the range of extrapolation is so great. Analysis of the data on low doses suggests that extrapolation from higher doses may not be misleading (Lubin *et al*., 1997).

Another problem was the retrospective assessment of underground exposure to radon and radon progeny. Mines were rarely ventilated and few measurements were made. In many of the newer studies, substantial numbers of miners were exposed to < 100 WLM, and these studies incorporated extensive information on radon concentrations that reduces the potential for bias due to inadequate exposure assessment.

Departures from linearity have also been observed or suggested at the highest and lowest exposure levels. In the study of miners in the Colorado Plateau and some other studies, the risk for death from lung cancer flattened out at the highest concentrations of radon and radon progeny, probably because of errors in dosimetry, bronchial cell killing by α-particles or wasted dose (i.e. after a tumorigenic dose has been delivered, subsequent exposures have no effect). These very high exposures were excluded from the low-dose analysis. In the lower dose regions, however, a convex dose–response relationship adequately described some of the data, although not significantly better than a linear fit. Any such curvilinearity for the relationship between exposure to α-particles and lung cancer would imply less confidence in the assumption that linear extrapolation would be conservative, as is usually assumed for low-LET radiations. While the current analysis does not rule out curvilinearity, the slight departure from linearity would appear to have a minimal impact on risk. For completeness, it should be mentioned that the risk estimates from data on miners exposed to low doses do not take into account their exposure to indoor radon (Lubin *et al.*, 1997). Such considerations suggest that the risks may be overestimated by 10–20%, but the general conclusions are unchanged (Lubin, 1998c).

There is the perplexing observation that the same total exposure delivered over long periods was more strongly carcinogenic than the same cumulative exposure delivered over a shorter period. It is now clear, both epidemiologically (Tomášek *et al.*, 1994a; Lubin *et al.*, 1995b) and radiobiologically (Brenner, 1994), that this phenomenon does not hold or has little influence at the very lowest exposure that might be experienced by most miners today or at residential exposure levels. The absence of an inverse exposure–rate effect at low exposure is perhaps most noteworthy in the study of miners in western Bohemia, Czech Republic, in which the ERR/WLM, after exposure to < 10 WL, did not depend on duration of exposure (Tomášek *et al.*, 1994a).

The recent analysis of the data on miners by Lubin *et al.* (1997) is thus reassuring, in the sense that the estimates of risk based on data for lower doses are not higher than those based on the full range of data. The ‘lower’ exposure range, of course, is not necessarily low in terms of dose to the lung since 50 and 100 WLM probably result in 2.5 and 5.0 Sv, respectively, on the basis of complex assumptions of the conversion of WLM to Gy and of the relative biological effectiveness (RBE) (National Academy of Sciences, 1991).

(*c*) *Generalizability*

The validity of applying estimates of risk from studies of underground miners to the general population, however, relies not so much on the high dose to low dose assumption as on generalizability. Difficulties in generalization include the application

of data on men to women and children; the effects of heavy smoking and mine contaminants such as arsenic, diesel and blasting fumes and silica; differences in breathing rates and attached particles and assumptions of radioactive decay equilibrium (National Academy of Sciences, 1991; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). Because such issues are difficult to resolve, great importance is placed on combining existing and on-going studies of indoor exposure to radon and lung cancer in order to validate the estimates of risk for underground miners. The results of recent meta-analyses of over 4000 lung cancer cases in eight studies are still somewhat equivocal, but the patterns of risk over categories of indoor radon concentrations appear to be remarkably consistent with those estimated from the studies of miners, and a significant dose–response relationship is seen (Lubin & Boice, 1997). The results of subsequent studies in the United Kingdom (Darby *et al*., 1998) and Iowa, USA (Field *et al*., 2000), are generally consistent with those of the early meta-analysis. Although important questions linger about the generalizability of the estimates for miners to the general population, international cooperation between investigators in Austria, Belgium, Canada, China, the Czech Republic, Finland, France, Germany, Italy, Sweden, the United Kingdom and the USA has continued to provide extremely valuable information on lung cancer risks associated with exposure to radon and radon decay products.

2.2 Radium

2.2.1 *Occupational exposure: Radium-dial painters*

The availability of paints made fluorescent by the addition of small amounts of radium salts led to their use on instrument, clock and watch dials in the early 1900s (see section 1.2.2(*k*)). In the USA, almost 5000 workers, the vast majority of them women, were employed in the luminizing industry (Fry, 1998). Employment was greatest between 1915 and 1930 and between 1940 and 1954, and essentially ceased after 1974.

Fluorescence was initially achieved by the addition of ^{226}Ra salts to paint; later, a mixture of ^{226}Ra and ^{228}Ra (mesothorium) was used in some factories (Fry, 1998). Radioactive decay of these isotopes of radium leads to emission of α-particles, β-particles and γ-radiation at various stages in the decay chain. The two isotopes differ, in that ^{226}Ra has a radioactive half-life of 1600 years and decays to ^{222}Rn (radon), a noble gas with a half-life of 3.8 days, whereas ^{228}Ra has a half-life of 5.75 years and decays to the noble gas ^{220}Rn (thoron), which has a half-life of 55.6 s (see section 1).

The dial painters employed during the early years of the industry had the greatest risk for internal exposure because of the common practice of ‘pointing’ the brush tip with the lips, which led to ingestion of radium. Ingested radium retained in the body migrates to bone tissue: first to the endosteal layer and from there into the mineral matrix. Ingestion of radium may also result in exposure of soft tissues, including the stomach, pancreas, lung, liver and colon (Stebbings *et al.*, 1984). The daily intake of

radioactive materials of these workers by ingestion was estimated by Martland *et al.* (1925) to be 3–43 μg; however, the radium intake may have varied substantially among individuals since ingestion was related to personal work habits (Stebbings *et al.*, 1984). Pointing was discouraged from about 1926 because of concern about possible health hazards and the suspicion that occupational exposure led to health problems, notably necrosis of the jaw, among radium-dial painters (Keane *et al*., 1986).

Cohort studies of radium-dial painters in the USA were initially carried out at the Massachusetts Institute of Technology (Evans *et al*., 1969) and the Argonne National Laboratory (Stebbings *et al*., 1984). In 1969, the two studies were combined and transferred to the Argonne Center for Human Radiobiology. Rowland *et al*. (1983) reported on the incidence of bone sarcoma among 3055 female radium-dial workers who entered the industry before 1950. Among 1468 women who survived more than five years after the beginning of employment and whose radium body burdens had been measured, 42 bone sarcomas were seen, with 0.4 expected. About 50% of these workers were identified by themselves or by co-workers (Rowland *et al*., 1978a; Stebbings *et al.*, 1984); some measurements of radium body burden, or exhumation, may have been conducted because cancer was diagnosed. Consequently, concern was raised that diseased workers may have been more likely than non-diseased workers to have been monitored (Rowland *et al*., 1978a). In order to minimize such a possibility, a second analysis was conducted only of cases observed two or more years after the first measurement of body burden. Among 1257 eligible women, 13 bone sarcomas were observed, with 0.2 expected. The two analyses clearly indicate an excess of bone sarcoma among women with measured body burdens of radium.

The bone sarcomas were widely distributed throughout the skeleton, unlike those typically seen in unexposed subjects, and this suggested a causal agent such as radium incorporated in the bone tissue. Cancers of the paranasal sinuses and mastoid process (head) occurred mainly among subjects exposed to ^{226}Ra only, and infrequently among those exposed to both ^{226}Ra and ^{228}Ra. High ^{222}Rn levels were found in the mastoid cavity of subjects whose body burdens were primarily from ^{226}Ra, leading to the conjecture that radioactive decay of ^{222}Rn released into the cavity by decay of ^{226}Ra in the surrounding bone, and subsequent decay of the progeny of ^{222}Rn, were responsible for the excess incidence of head carcinomas. The short half-life of ^{220}Rn would preclude much migration of this isotope, and hence its decay products, into the paranasal sinuses and mastoid process (Evans, 1966). Rowland *et al*. (1978b) noted that a subgroup of 58 subjects estimated to have received at least five times more radioactivity from ^{228}Ra than from ^{226}Ra developed 10 bone sarcomas and no head carcinomas, while a second group of 391 subjects estimated to have received at least five times more radioactivity from ^{226}Ra than from ^{228}Ra developed 13 bone sarcomas and 10 head carcinomas.

In addition to comparisons of mortality among radium-dial painters with rates for the population of the USA, internal analyses were conducted in which cancer rates were examined in relation to estimated internal radiation doses. Statistically significant

dose–response relationships were obtained with the dose–response model (Rowland *et al.*, 1978b):

$$I = (C + \alpha D + \beta D^2)\, e^{-\gamma D},$$

where I is incidence of bone sarcoma per person-year, D is the quantity (in μCi) of radium that entered the blood ('systemic intake'), and C the natural incidence of bone sarcoma in the population. The exponential term represents the competing, 'cell-killing' effect of dose-related damage that precludes further cell division and, thus, cancer. A linear ($\beta=0$) variant of the model, in which D represents microcuries of ^{226}Ra, gave a good fit to the head carcinoma data, whereas a pure-quadratic ($\alpha=0$) variant, where D represents microcuries of ^{226}Ra plus 2.5 times microcuries of ^{228}Ra, gave the best fit to the bone sarcoma data. No bone sarcomas were observed at weighted skeletal doses of < 10 Gy (Rowland, 1997). Similarly, no bone sarcomas were observed in the studies of British dial painters who were exposed to lower doses (Baverstock & Papworth, 1985), none of whom engaged in brush pointing.

Rowland *et al*. (1978b) evaluated the relative effectiveness of ^{226}Ra and ^{228}Ra in inducing bone sarcomas (61 cases) and head carcinomas (21 cases) among 1474 female dial painters employed before 1930, in terms of 'systemic intake', defined as the quantity of radium (in μCi) entering the bloodstream. Systemic intake could be estimated for 524 subjects, of whom 38 had bone sarcomas and 17 had head carcinomas. ^{228}Ra was estimated to be 2.5 times as effective as ^{226}Ra, per μCi, in inducing bone sarcoma. This value is in agreement with previous estimates for beagle dogs exposed experimentally (Dougherty & Mays, 1969, see section 3).

Carnes *et al*. (1997) used multiplicative and additive models to study the relationship of exposures to ^{226}Ra and ^{228}Ra and mortality patterns among 820 women occupationally at risk for exposure to radium before 1930 at geographically separated facilities in the USA. The findings with respect to head carcinoma and bone sarcoma confirmed the main conclusions of previous analyses, except that the dose-specific risk for bone sarcoma was higher among women exposed to ^{226}Ra before the age of 20; both ^{226}Ra and ^{228}Ra contributed significantly and independently to the risk for bone sarcoma. This finding is in general agreement with the patterns of risk with exposure at young ages seen in other irradiated populations, including the Japanese atomic bomb survivors.

The suggested carcinogenic mechanism is migration of ^{222}Rn, a decay product of ^{226}Rn but not ^{228}Ra, to the paranasal sinuses and mastoid process and subsequent exposure to α-particles from ^{222}Rn and its decay products. Associations between ingested radium and other cancers are more tenuous. No excess incidence of leukaemia was observed among dial painters in the USA or among dial painters with measured body burdens (Spiers *et al*., 1983); Stebbings (1998), however, noted that leukaemia occurred early in female dial workers, and an excess of leukaemia was observed among male radium-dial workers. Stebbings *et al*. (1984) reported elevated rates of death among female radium-dial workers from several causes of cancer death, including cancers of the colon (SMR, 1.56) and breast (SMR, 1.44) and multiple myeloma (SMR,

2.79), when the mortality rates were compared with those of the population of the USA. Suggestive positive associations were observed between estimated radium body burden and lung cancer, breast cancer and multiple myeloma. The authors noted that lung cancer and multiple myeloma were associated with duration of employment [a surrogate for cumulative external γ-radiation dose (see IARC, 2000)] as well as with radium body burden. The authors postulated that the association with breast cancer was due to confounding, and that an association with exposure to radium was unlikely to be causal because the excess was as high in women who had started work after 1930 (long after 'pointing' had been stopped) as it was in women who had started earlier and had had average radium intakes approximately 100 times higher (Stebbings *et al.*, 1984; Rowland *et al.*, 1989). Further, women who had worked the longest and had had both heavier exposure to γ-radiation from radium and higher breast cancer rates tended to have chosen not to have children. Thus, nulliparity, an important risk factor for breast cancer, might explain a portion of the excess of breast cancer.

2.2.2 *Iatrogenic exposure*

^{224}Radium, historically known as 'thorium X', is a short-lived α-particle-emitting isotope with a physical half-life of 3.62 days, which deposits preferentially in bone. While the largest radiation doses from internally deposited ^{224}Ra tend to occur at the bone surface, its decay products may accumulate in the liver, kidney, spleen, eye and other organs. Soon after isolation of ^{224}Ra in 1902 (Rutherford & Soddy, 1902), there was great interest in its potential therapeutic use. Medical administration of ^{224}Ra has been used for the treatment of chronic arthritis, ankylosing spondylitis, bone tuberculosis and blood diseases (Bickel, 1913).

Between 1944 and 1951, several hundred German children were treated with repeated injections of ^{224}Ra, mostly for the treatment of bone tuberculosis. This treatment proved ineffective against tuberculosis and was discontinued in children in 1951, but it was used later in Germany and in France for the treatment of adult ankylosing spondylitis (Spiess & Mays, 1979a) up to 1978 (Schales, 1978).

Some patients were given relatively high doses of ^{224}Ra mixed with traces of eosin and colloidal platinum (the latter being presumed to 'guide' the radium to the affected tissue). This compound, known as Peteosthor, was used primarily to treat patients with tuberculosis of the bone or ankylosing spondylitis (Troch, 1949; Spiess & Mays, 1979b). The calculated skeletal dose averaged 4.16 Gy (range, 0.06–57.50 Gy), and the average duration of administration was seven months (Mays, 1988). In the early 1950s, objections were raised to treatment of patients with Peteosthor after ^{224}Ra was found to be deposited in the growing zones of the skeleton, thereby causing severe damage to children and juveniles. In addition to growth retardation, malignant bone tumours were observed in patients treated as children (Rathke, 1954; Spiess, 1956).

Other patients were given lower doses of ^{224}Ra, without platinum or eosin, mainly for treatment of ankylosing spondylitis. This treatment was first used on a large scale

at the Orthopaedic University Hospital in Münster, Germany, and was then adopted by other hospitals. The majority of the patients, most of whom were treated in 1948–75, received one series of 10 weekly injections of approximately 1 MBq of ^{224}Ra per injection. This led to a cumulative α-particle dose of 0.56 Gy to the marrow-free skeleton of a 70-kg man (mean bone surface dose, approximately 5 Gy) (Spiess & Mays, 1970, 1971; Wick *et al.*, 1999).

(*a*) *Studies of patients treated with high doses of radium-224*

In 1944–52, about 2000 patients in Germany, mostly children and juveniles, received repeated injections of Peteosthor (Schales, 1978). From 1954, efforts were made to identify and follow-up these patients. The most recent reports (Spiess, 1995; Nekkolla *et al*., 1999, 2000) describe cancers among 899 patients (621 men, 278 women) who received injections of ^{224}Ra, mainly between 1945 and 1955. This study included most of the patients who were treated with high doses of ^{224}Ra (mean bone surface dose, 30 Gy; mean specific activity, 0.66 MBq/kg). Of these, 455 patients (of whom 214 were under 21 years at the time of treatment) were treated for tuberculosis, 392 adults (one under 21) were treated for ankylosing spondylititis, and the remaining 51 patients were treated for other diseases such as polyarthritis and multiple sclerosis.

In recent follow-up studies, a significant excess of cancers at sites other than the skeleton became apparent. The observed cancer rates were compared with those expected on the basis of incidence rates from the Saarland Cancer Registry for the years 1970–94. In the follow-up to 1998, 188 solid malignancies were observed, four of which occurred less than five years after the first injection of ^{224}Ra. Under the assumption of a minimum latency period of five years, an elevated standardized incidence ratio [SIR, 1.23] was observed for solid malignancies (184 cases observed versus 150 cases expected, $p = 0.004$) (Nekolla *et al.*, 1999).

(i) *Bone sarcomas*

In a follow-up study through September 1998, 219 of these patients were still alive (92 women, 127 men). A total of 56 malignant bone tumours had occurred in 55 patients, one person having developed a secondary bone sarcoma two years after the first. Most of the cases occurred within 25 years of exposure, and only four bone sarcomas have been diagnosed since 1980. According to data from the cancer registries of Saarland and of the former German Democratic Republic, the expected number of bone sarcomas in a group of this size would have been less than one (about 0.3) over the entire observation period. The age at first injection of patients with bone sarcomas was between two and 55 years, and the tumour appearance times peaked at eight years after exposure. Younger age at exposure, particularly at ages of active bone growth, appeared to be associated with a higher risk for radiation-induced tumours. Among patients under the age of 21 years, 37 bone sarcomas were reported, whereas among adults 19 bone sarcomas occurred in 18 patients. In the group of ankylosing spondylitis patients, six bone sarcomas were seen (Nekolla *et al*., 2000).

(ii) *Mammary carcinomas*

A significant increase in the incidence of female breast cancer (28 cases observed, eight cases expected) was a notable finding during the recent follow-up. The excess incidence rate in the group of women treated when under the age of 21 years was particularly large (SIR, 9.4 [17 mammary carcinomas observed versus 1.8 cases expected, data extracted from a figure]). In contrast, in the cohort of female patients treated with ^{224}Ra after the age of 21 years, the rate of breast cancer increased by less than twofold (11 compared with 6.2). Seven cases of breast cancer appeared comparatively early, i.e. before the age of 45. The youngest woman to develop breast cancer (age at diagnosis, 28 years) was only two years old when treated with relatively high doses of ^{224}Ra. It should also be noted that two cases of breast cancer occurred in males (compared with 0.2 cases expected). A control group of 182 tuberculosis patients who had not been treated with ^{224}Ra was also established, consisting of patients treated between 1944 and 1954 at the ages of 8–21 years. Seven mammary carcinomas were observed in this group, with 3.8 cases expected, suggesting that factors other than radiation may have contributed to the breast cancer excess seen in the exposed group. The authors pointed out that, while the excess of mammary cancers is striking, there is no indication of dose-dependence, which raises the question of whether the excess is due to factors other than treatment with ^{222}Ra (Papke *et al.*, 1995; Nekolla *et al.*, 1999).

(iii) *Leukaemia*

Leukaemias were observed in eight patients (3.8 expected; $p = 0.04$); however, one case of acute myeloid leukaemia was diagnosed as early as 1.7 years after the first ^{224}Ra injection. Two of the remaining seven cases were chronic lymphocytic leukaemia, which is considered to be unrelated to exposure to radiation; however, this type is included in the expected numbers as well. The occurrence of the seven cases two years or more after the first injection was not statistically significant ($p = 0.08$), and the finding must be considered only suggestive. No dose–response analysis was reported (Nekolla *et al*., 1999).

(iv) *Cancers at other sites*

The incidences of soft-tissue sarcomas, kidney cancer, urinary bladder cancer, liver cancer and thyroid carcinomas appeared to be significantly increased: seven cases of soft-tissue sarcoma, with 0.9 cases expected; 10 cases of kidney cancer, with 4.2 expected; and 14 cases of urinary bladder cancer, with 7.2 expected. In female patients, the excess incidence of kidney cancer was even more pronounced, four cases being observed with 0.8 expected. Liver carcinomas (four hepatocellular, three cholangiocellular) developed in seven patients, with 2.2 cases expected; three cases were associated with pre-existing liver cirrhosis and one with liver fibrosis. Thyroid carcinomas occurred in five patients, with 0.8 expected, all of whom had been children or young adults (aged 11–22) when they were treated with ^{224}Ra (Nekolla *et al.*, 1999).

(*b*) *Studies of patients treated with lower doses of radium-224*

A study of ankylosing spondylitis patients who were treated with lower doses of ^{224}Ra was begun in 1971 (Schales, 1978; Wick & Gössner, 1983; Wick *et al*., 1986; Wick & Gössner, 1993). The lowest dose to the bone surface associated with an osteosarcoma was 9 Gy (Wick *et al.*, 1999). The most recent report (Wick *et al*., 1999) included 1577 ankylosing spondylitis patients from nine German hospitals who received one series of 10 weekly injections of approximately 1 MBq ^{224}Ra each. In contrast to the patients treated with Peteosthor, these patients were exposed only when adult. The cancer incidence was compared with expected numbers based on the 1970–94 data in the tumour registry of Saarland and the 1945–90 data in the Danish Cancer Registry. A control group of 1462 ankylosing spondylitis patients was established with approximately the same age distribution, to provide comparative information on causes of death and on health problems potentially related to the disease itself or to its treatment with drugs. The control group consisted mainly of patients from a hospital known to have refused use of ^{224}Ra treatment. Patients who showed evidence of having been treated with radioactive drugs and/or X-rays during the course of the study were excluded from further evaluation. At the time of reporting, 649 patients in the exposed group and 762 control patients had died. The cause of death was ascertained for 626 exposed patients and for 725 control patients.

(i) *Bone tumours*

Among patients treated with ^{224}Ra, four cases of malignant primary bone tumour (with 1.3 cases expected from general population statistics) were observed: one fibrosarcoma of the bone, one malignant fibrous histiocytoma, one reticulum-cell sarcoma (malignant lymphoma) of the bone and one medullary plasmacytoma (myeloma), originally observed in the bone marrow of the sternum and pelvis. [The Working Group noted that there were no osteosarcomas.] In the control group, only one case, a medullary plasmacytoma, was observed (Wick *et al.*, 1999).

(ii) *Leukaemia*

Thirteen cases of leukaemia were observed among patients treated with ^{224}Ra (with 4.2 cases expected in the general population; $p < 0.001$). In the control group, seven cases of leukaemia were observed, with 5.4 cases expected ($p = 0.3$). Leukaemia occurred among people over 43 years of age throughout the period of observation. Subclassification of the leukaemia cases in irradiated patients showed a predominance of myeloid leukaemia (eight cases observed, with 1.7 cases expected; $p = 0.001$) in the exposed group, which occurred in people aged 46 and older with no peak in the latency. In the control group, three cases of myeloid leukaemia were found, with 2.2 cases expected (Wick *et al.*, 1999). [The Working Group noted that four cases of lymphoid leukaemia were found among people treated with radium, consisting of one acute and three chronic dysplastic leukaemias.] Inferences are restricted by the generally small numbers of cases and the absence of dose–response analyses (UNSCEAR, 2000).

(iii) *Cancers at other sites*

No significant difference between the observed and expected numbers of cases of cancer of the female breast or of the urinary tract, liver or stomach was found.

In conclusion, bone sarcomas were the major late effect in patients who were treated with high doses of ^{224}Ra. In contrast, treatment of ankylosing spondylitis patients with lower doses of ^{224}Ra resulted in a higher risk of leukaemia than of bone sarcoma.

2.3 Thorium

2.3.1 *Occupational exposure*

Thorium ores and purified thorium materials contain ^{232}Th, ^{228}Th and varying amounts of their radioactive decay products. ^{232}Th is an α-particle emitter with a half-life of 1.4×10^{10} years; ^{228}Ra (half-life, 5.75 years), ^{224}Ra (half-life, 3.62 days) and ^{220}Rn (thoron) (half-life, 55.6 s) are among its decay products (Stehney *et al.*, 1980). ^{228}Th is an α-particle emitter with a half-life of 1.9 years (Albert *et al.*, 1955). Fine particles containing thorium and its progeny nuclides may be inhaled by workers in thorium refineries or in mining monazite and rare earth ores. Ore dust containing thorium and its progeny nuclides absorbed through the respiratory organs was deposited mainly directly in the lungs and surrounding lymph nodes, and little was deposited in the liver, kidney or other inner organs (Table 40) (Stehney, 1999). Until the 1950s, no protection against inhalation of ore dust containing thorium and other radioactive nuclides was available for workers (Stehney *et al.*, 1980), and workers in thorium refineries often inhaled up to 30 Bq/m^3 ^{220}Rn, with a maximum of 2×10^{-11} Ci/L [740 Bq/m^3] contained in ore dust (Albert *et al.*, 1955).

A follow-up study on mortality among workers in a thorium processing plant was carried out at the Lindsay Chemical Company in Chicago, USA. The participants were selected from among 4582 employees and were limited to those who had worked in 1940 or later up to 1973. The first survey in 1975 was limited to analyses of 3039 male workers (Polednak *et al.*, 1983), but the second survey in 1982 was extended to 3796 workers (3119 men, 677 women; Liu *et al.*, 1992). The exposure of 84 men to α-particle irradiation from airborne thorium in 1952 was calculated to be [0.1–7.1 Bq/m^3 (mean 0.7 Bq/m^3)] (Stehney *et al.*, 1980). Job classifications and duration of employment were used to provide information on exposure to thorium, and individual doses were not available. In the first survey in 1975, an increased mortality rate from lung cancer was observed, although it was not statistically significant (SMR, 1.44; 95% CI, 0.98–2.02) (Polednak *et al.*, 1983). In the second survey in 1982, which included 3119 male thorium workers, the SMR for lung cancer was significantly increased (SMR, 1.36; 95% CI, 1.02–1.78), but Poisson regression analyses showed no significant effect of selected factors on mortality from lung cancer (Table 41) (Liu *et al.*, 1992). These findings suggest that some etiological factor other than radioactivity from the thorium decay

Table 40. Adjusted concentrations of ^{232}Th (mBq/g) in autopsy samples of former thorium workers[a] and their controls

Subject	Years on job	Lung	Pulmonary lymph nodes	Compact bone	Liver	Kidney
Thorium worker A	6.8	1.74	5.40	0.70	0.17	NR
Thorium worker B	22.9	67.1	1210.0	0.58	0.15	NR
Thorium worker C	23.8	12.1	30.5	NR	0.68	0.066
Thorium worker D	3.1	0.23	3.64	0.15	0.013	0.007
Normal samples[b]	–	0.0125	0.22	0.0039	0.0015	0.0018

From Stehney (1999). NR, not reported

[a] Workers at the thorium refinery of the Lindsay Chemical Company

[b] Geometric mean concentrations in samples from men in two general populations

series and the effects of ore dust are the cause of the significant increase in mortality from lung cancer among male workers. Unfortunately, data on smoking were not available (Stehney *et al*., 1980; Liu *et al*., 1992).

In the Baiyan Obo rare-earth and iron mine in China (see section 1.2.2(*h*)), the total number of miners and staff members in 1994 was 7558 (Chen *et al*., 1986, 2000), of whom about half were exposed to thorium in ore dust. An epidemiological study was begun in 1980 on 2072 miners who had inhaled ore dust containing thorium and its progeny nuclides and about 2000 controls consisting mainly of miners who had inhaled dust-free air. The study was expanded until 1993 to include 2903 miners and 4655 controls and is continuing (Chen *et al*., 1989, 1993, 1999, 2000). The numbers of deaths from lung cancer among 2903 miners who had inhaled thorium in ore dust and 4655 controls were 17 among exposed miners (3.30 expected) and 8 (3.48 expected) among controls. The mortality rate from lung cancer among miners who had inhaled ore dust containing thorium decay series was significantly higher than that of the male population of China (SMR, 5.15; 95% CI, 3.36–7.89); however, the rate in controls was also increased (SMR, 2.30; 95% CI, 1.17–4.51). Therefore, the ratio of the two SMRs, 2.24, was not significantly increased. The significantly higher mortality rate from lung cancer in the two groups than in the Chinese male population was due mainly to the high rate of smoking among the Baiyan Obo miners (80%) (Chen *et al.*, 1999).

2.3.2 *Iatrogenic exposure*

(*a*) *History*

Use of thorium dioxide-containing X-ray contrast media for splenography was introduced into clinical practice in the late 1920s, simultaneously in Japan (Oka, 1930) and in Germany (Radt, 1930). Thorotrast, which was marketed in 1931 (Muth, 1989), is the trade name of a medium consisting of a stabilized 250 g/L (19–20% w/w)

Table 41. Standardized mortality ratios for all malignant tumours and lung cancer among male thorium workers according to selected study parameters

Study parameter	All malignant tumours			Lung cancers		
	No. of deaths	Standardized mortality ratio	95% confidence interval	No. of deaths	Standardized mortality ratio	95% confidence interval
Job classification[a]						
Group 1 (mean, 7.1 Bq/m^3)	113	1.23	1.01–1.47	39	1.38	0.98–1.89
Group 2 (0.9–2.0 Bq/m^3)	19	1.44	0.86–2.24	6	1.37	0.50–2.99
Group 3 (0.1–0.5 Bq/m^3)	21	1.28	0.79–1.96	5	1.12	0.36–2.62
Duration of employment (months)						
≤ 1	55	1.38	1.04–1.80	22	1.80	1.13–2.73
2–12	44	0.99	0.72–1.33	15	1.10	0.62–1.81
≥ 13	29	1.44	1.08–1.88	13	1.16	1.62–1.99
Time since first employment (years)						
< 15	57	1.40	1.06–1.82	17	1.73	1.01–2.77
15–29	67	1.21	0.94–1.54	21	1.17	0.73–1.80
≥ 30	29	1.12	0.75–1.61	12	1.29	0.67–2.25
Year at first employment						
1915–1954	115	1.27	1.05–1.53	33	1.24	0.85–1.74
1955–1973	38	1.21	0.85–1.65	17	1.65	0.96–2.64
Total	153	1.26	1.07–1.47	50	1.35	1.00–1.78

From Liu *et al.* (1992). Involved 2999 selected male workers in the thorium refinery at Lindsay Chemical Company, because the job classification or duration of employment was unknown for 120 workers.

[a] Airborne α-particle activity concentration (see also Stehney *et al.*, 1980)

colloidal solution of ThO_2, 16–19% (w/w) dextrin and 0.15% methyl *para*-hydroxybenzoate as a preservative (Council on Pharmacy and Chemistry, 1932; Andersson, 1997).

Thorotrast was used by instillation or injection for various radiological purposes but was used mainly for roentgenological visualization of vascular structures after intravascular injection. Its most important application was for cerebral arteriography (angiography), for which it was introduced in the early 1930s (Moniz, 1932). It gained widespread usage in most of Europe, Japan and North America until it was replaced by other agents around 1950. It can be estimated from the amounts produced that more than 2.5 million (probably 10 million) people have been exposed (Abbatt, 1979).

(*b*) *Distribution of Thorotrast after intravascular injection*

Intravascularly injected Thorotrast is cleared from the blood in animals within a few hours (see also section 4) (Harrington & Huggins, 1939; Müller, 1968), and in humans most is distributed after < 20 days (Kaul *et al.*, 1986). Only about 1% of injected ^{232}Th and its decay products are excreted in human faeces and urine up to one year after injection. The biological half-life has been estimated to be > 400 years (Hursh *et al.*, 1957).

Injected colloidal Thorotrast is cleared from blood by phagocytosis by macrophages of the reticuloendothelial system, mostly in liver, spleen, bone marrow and lymph nodes. After its initial distribution, Thorotrast tends to aggregate in conglomerates, which amplify with time after injection and with increasing amounts of Thorotrast injected (Kaul & Muth, 1978).

(*c*) *Dosimetry* (see also section 1)

The dosimetry of Thorotrast is relatively well established in comparison with that of other internally deposited radionuclides, mainly because ^{232}Th, once incorporated, is not easily removed from the body. Several measurements are possible, including whole-body counting and measurements of exhaled ^{220}Rn in the breath and ^{232}Th and its progeny in tissues obtained at surgery and autopsy. Many biophysical investigations have been conducted in various countries, the most recent ones in Germany and Japan (Kaul & Noffz, 1978; Ishikawa *et al.*, 1993a,b, 1999). Estimates of the absorbed dose in tissues after Thorotrast injection are based on the amount of ^{232}Th deposited in the target organs, the steady-state activity ratios in the organs of interest, consideration of so-called self-absorption of α-particle energy within conglomerates and the distribution of Thorotrast to organs after injection. These factors and other uncertainties have been taken into account.

Uncertainties about the recorded volume of injected Thorotrast have been noted. In order to improve the dosimetry, parts of the cohorts in the German and Japanese studies were monitored by whole-body counting and/or breath measurement as well as by tissue measurements.

It is well known that a proportion of the Thorotrast injected may be spilled at the injection site, leading to the formation of granulomas with dense fibrosis, called thorotrastomas. In the German study, 245 of 899 patients screened by X-ray for cerebral arteriography developed thorotrastomas at the site of injection, and there are further reports in the literature of 147 cases (van Kaick *et al.*, 1995; Andersson, 1997). However, malignant lesions have been reported only rarely to be thorotrastomas (Liebermann *et al.*, 1995).

The distribution of Thorotrast in the organs, especially the ratio between liver and spleen, does not seem to be a linear function of the injected volume. After injection of larger amounts, a higher fraction is stored in the liver (van Kaick *et al.*, 1984; Ishikawa *et al.*, 1989), but this has not been considered in any of the studies in which risks were estimated.

Through biological processes, Thorotrast particles accumulate and form conglomerates of various sizes within a few years, resulting in non-uniform distribution of the nuclide and radiation dose (Dalheimer & Kaul, 1989). This factor is considered by use of a formula developed by Rundo (1958). Therefore, the distribution and dose of Thorotrast are heterogeneous, although mean organ doses have been adopted in all studies. The mean local dose in the region of potential target cells for tumour deve-lopment has been calculated for various organs with little storage of Thorotrast (Dalheimer *et al.*, 1995) and showed a surprising similarity between mean cellular dose and mean organ dose.

Decay products of ^{232}Th deposited in organs with major deposits can be transferred to other organs. In order to take this phenomenon into account, the steady-state activity ratios of the decay products in relation to the parents must be known for each organ of interest. Extensive work has been done (Rundo, 1956; Hursh *et al.*, 1957; Kaul, 1965; Parr, 1968), and there are no major discrepancies between the ratios from older compilations (Kaul, 1973; Kaul & Noffz, 1978) and more recent ones (McInroy *et al.*, 1992; Ishikawa *et al.*, 1993b). Hence, the ratios compiled by Kaul and Noffz (1978) are now used in dosimetric studies.

Little is known about the intervals in tumorigenesis between establishment of malignant cells and clinical manifestation of the tumour. For long-term irradiation from internally deposited radionuclides, the dose absorbed during the interval between initiation of the malignant process and diagnosis may be irrelevant in terms of carcinogenesis and may be considered ‘wasted’ dose in calculations of the cumulative dose needed for cancer induction (Mays, 1982). Ultrasonographic studies of the growth rate of liver tumours showed great variability (Sheu *et al.*, 1985). The interval corresponding to ‘wasted’ dose for primary liver cancer is assumed to be 10–15 years (Andersson *et al.*, 1994; van Kaick *et al.*, 1995; Mori *et al.*, 1995).

The distribution of injected Thorotrast to different organs is important because it is critical for estimation of α-particle dose and the associated risks in epidemiological studies. Kaul and Noffz (1978) estimated the organ distribution in 7–34 cases in the published literature to be 59% to liver, 29% to spleen, 9% to red bone marrow and 3%

to other organs. However, as pointed out later (Ishikawa *et al*., 1989), although the spleen of patients given Thorotrast undergoes severe fibrosis and its weight is thus significantly reduced, the estimates are based on the organ masses of the standard man, resulting in overestimation of spleen deposition and subsequent underestimation of bone-marrow deposition. A revised organ distribution has been published (Ishikawa *et al*., 1999), with a new averaging method and revised organ masses, on the basis of more cases. Risk estimates were based on those of Kaul and Noffz (1978) adjusted with additional estimates based on the new organ partition.

(*d*) *Epidemiological studies*

The long-term effects of injected Thorotrast have been studied in a number of cohorts. The methodological details of these studies are summarized below and in Table 42, while the results are presented together in the next section. More than 5000 persons injected with Thorotrast during 1929–56 have been followed, but only 198 persons were still alive at the end of the follow-up period.

The largest study was initiated in Germany in 1968, where hospital records from almost 50 hospitals in western Germany revealed approximately 5000 Thorotrast-injected patients in 29 hospitals. Of these, 916 could not be traced, while 1917 had died < 3 years after the injection and were excluded from the study, leaving 2326 patients. Of these, 1427 had died before 1968 and had not been examined. They were followed-up with regard to cause of death in hospital records, doctors' reports, pathology reports and death certificates. The remaining 899 patients have been followed by means of regular clinical examinations and certain para-clinical tests including measurements of external γ-radiation in order to estimate the body content of ^{232}Th (van Kaick *et al*., 1984, 1986a,b, 1989, 1991). Of 5151 controls, 1890 hospital patients who were alive three years after hospitalization, matched by age and sex but not by index disease, were identified and followed; 662 had been examined (van Kaick *et al*., 1991). Approximately 70% of the case patients had received injections of Thorotrast for cerebral angiography, while the remainder underwent angiography of the limbs. The cohort has been followed-up regularly, the latest follow-up being in 1998 (van Kaick *et al*., 1999). The dosimetry is based on whole-body measurements of γ-radiation in a large proportion of the patients and on information about the injected volume of Thorotrast for the rest. Data on the risk for cancer are presented as internal risk ratios.

A study was set up in Denmark in 1949 in which patients who had undergone cerebral angiography with Thorotrast were identified at two neurosurgery departments, resulting in about 1000 patients. A control group of 1480 patients who had undergone cerebral angiography with contrast agents other than Thorotrast was identified, but they were not matched to cases for age, sex or calendar period. Thorotrast-treated patients and controls have been followed up with regard to cause-specific mortality by linkage with the Danish Cause of Death Register and with regard to site-specific cancer incidence by linkage with the Danish Cancer Registry (Andersson *et al*., 1994, 1995a). Furthermore, Thorotrast-treated patients have been followed-up by review of hospital

Table 42. Methodological considerations in five cohort studies of patients treated with Thorotrast

Methodological consideration	Germany (van Kaick *et al.*, 1984, 1986a,b, 1999)		Denmark (Andersson *et al.*, 1994, 1995a)		Japan (Kido *et al.*, 1999; Mori *et al.*, 1999a,b)		Portugal (dos Santos Silva *et al.*, 1999)		Sweden (Martling *et al.*, 1999)	Total	
	Thorotrast-treated	Controls	Thorotrast-treated	Controls	Thorotrast-treated	Controls	Thorotrast-treated	Controls	Thorotrast-treated	Thorotrast-treated	Controls
Period of treatment	1937–47	1937–47	1935–47	1946–63	1931–45	1930–45	1929–55	1930–55	1932–50		
Start of study	1968		1949		1963		1961		1963		
Initial cohort size	5159	5151	1095	1480	412	1649	1931	2258	1117	9714	10538
Eligible for study	2326[a]	1890	999	1480	412	1630	1131	1032	509[b]	5377	6032
Ratio men:women	2.82	2.91	1.23	0.92	Men	Men	1.65	1.43	1.3		
Information available for dosimetry	1163[c]		[990][d]		412[c]		1131[d]		306[d]	4002	
Volume of Thorotrast injected, mL, mean	24		18.7–18.8		10–19		26.3		15.4		
Mean age at injection (years)	29 or 36[e]		37.4		> 20		34.1		35		
Year of end of follow-up	1998		1992		1998		1996		1993		
No. of patients still alive	48	239	40	422	37	481	38	173	35	198	1296

[a] Not including patients who died within the first three years after injection

[b] Not including patients who died within the first year after injection or those who died before 1 January 1952

[c] Dose estimated from information about injected volume of Thorotrast or from biophysical measurements (1 mL of Thorotrast contains 0.2 g (~ 810 Bq) of ^{232}Th)

[d] Dose estimated from information about injected volume of Thorotrast

[e] 29 years, mean age at injection in those who developed liver tumours; 36 years in others

records and other sources relevant for diagnoses of liver cancer (Andersson *et al*., 1994), leukaemia (Andersson *et al*., 1993) and lung cancer (Andersson *et al*., 1995b). For the dosimetry, recorded or estimated volumes of injected Thorotrast were used (individual mean dose to the liver, 3.9 Gy; Andersson *et al*., 1994). The rates of mortality and incidence are given as age-, sex- and calendar period-matched SMRs and SIRs (in comparison with the rates of the general population) and as ratios of the two (SMR:SIR ratios for Thorotrast-treated and control patients).

An epidemiological study was started in Japan in 1963 in which 262 male wounded soldiers were injected intravascularly with Thorotrast and were followed up. An age- and sex-matched control group consisting of 1630 ex-servicemen wounded during the same period was also identified. In addition, 370 patients known from autopsies between 1945–92 to have received Thorotrast have also been analysed (Mori *et al*., 1995). Another series of 150 wounded, Thorotrast-treated ex-servicemen known to have been alive on 1 January 1979 has since been established and followed-up. Men in the control group of the first series who were alive on 1 January 1979 served as the control group (Kido *et al*., 1999). Follow-up was conducted through hospital records. The dosimetry was based on information about the injected volume of Thorotrast and, in some cases, on biophysical examinations. Data on the cause-specific mortality are given as internal age-adjusted rate ratios (Mori *et al*., 1999a,b).

A study was started in Portugal in 1961. Of 2436 persons given Thorotrast, 1052 who received intra-arterial injections (80% for cerebral angiography) were followed-up by means of death certificates and hospital records. Of a control group identified in 1972, consisting of 2086 persons matched for age, sex and index disease who had undergone arteriography with other contrast agents, only 924 had been traced at the time of the last follow-up in 1976 (da Silva Horta *et al*., 1978; Cayolla da Motta *et al*., 1979). The study has recently been reactivated and follow-up extended to the end of 1996. The study now consists of 1931 patients treated with Thorotrast systemically and 2258 unexposed controls. Of these, 1131 (705 men, 426 women) Thorotrast-treated cases and 1032 (607 men, 425 women) controls were successfully traced. The amount of injected Thorotrast was recorded in the hospital records for 90.3% of the patients and varied considerably. The cause of death was obtained at post-mortem examination (25.5% of Thorotrast-treated cases, 10.4% of controls), clinical records and death certificates (dos Santos Silva *et al*., 1999). Data on cause-specific mortality are given as internal age-adjusted rate ratios.

In Sweden, a cohort of 431 patients who had undergone cerebral angiography with Thorotrast was identified, but follow-up has been rudimentary until recently (Blomberg *et al*., 1967). The cohort has now been expanded and followed-up for an additional 30 years (Martling *et al*., 1999). The total cohort consists of 1117 Swedish patients with neurological disorders who received Thorotrast for cerebral angiography during the period 1932–50. A total of 608 patients were excluded from further analyses mainly because of death within one year of examination, leaving 509 patients in the study. Survival through 1 January 1952 was required to allow computerized linkage of the

cohort to the Swedish Cause of Death Register, which was established in that year and contains information on all deaths in the country. Data on cause-specific mortality are presented as SMRs calculated as the ratio of the number of cases observed in the cohort to that expected in the general population. No control group was described. Cancer incidence was analysed by linkage to the Swedish Cancer Registry, but the results of this analysis are not yet available.

In the USA, Janower *et al*. (1972) identified 724 persons who had received Thorotrast for cerebral angiography and a control group of 315 persons who had been exposed to other contrast agents. The cohorts were followed-up only recently, when the study was reactivated, and the results have not yet been published. Smaller groups of Thorotrast-injected patients have been identified and followed for shorter periods in the United Kingdom (Boyd *et al*., 1968) and Canada (Berrett & McRae, 1958).

Numerous case reports of long-term sequels after administration of Thorotrast have also been published.

[The Working Group noted that differences may be seen between the studies since the underlying disease for which Thorotrast was injected varied. In Japan, only wounded soldiers received Thorotrast, whereas in Denmark only neurological patients were treated, and in Germany patients with a variety of diseases were examined. Furthermore, the criteria for matching of controls varied between the studies.]

(*e*) *Mortality from and incidence of cancer*

In general, the cancer risk of Thorotrast-treated cohorts for cancer or death from cancer was increased by three- to fourfold.

(i) *Liver tumours*

The most consistent finding was that the incidence of and mortality from liver cancer in all the studies was highly significantly increased by up to more than 100-fold (Table 43; Andersson, 1997; van Kaick *et al.*, 1999). Almost 800 cases of Thorotrast-related primary liver cancer have been reported in the cohort studies, and approximately 400 cases, not included in the cohort studies, have been reported (Andersson *et al*., 1994). The difference in the relative risk in the Japanese study (36 for mortality) and in the three European studies (71–129; two of mortality and one of incidence) may reflect the fact that the mortality rate from liver cancer is much higher in Japan (annual age-standardized rate per 10^5 among men in 1990, 21) than in Europe (Germany, 4.4; Portugal, 4.1; Denmark, 2.2), and the values for incidence are: Japan, 27.6; Germany, 3.4; Portugal, 4.0; Denmark, 3.9 (IARC, 1998). Liver cancers are usually diagnosed 15 years after Thorotrast administration, and they continue to be the leading cause of death among such patients. In the Danish (incidence), German and Japanese studies, the histological distribution of liver cancer was approximately two-thirds carcinoma (predominantly cholangiocarcinoma) and one-third haemangiosarcoma, which is usually an extremely rare tumour (van Kaick *et al.*, 1986a; Andersson *et al.*, 1994; Mori *et al.*, 1999b). [The Working Group noted the remarkable finding that a similar

Table 43. Numbers and relative risks with 95% confidence intervals (for definitions of relative risk, see footnotes) for cancer at selected sites plus cirrhosis of the liver and all causes of death in five cohort studies of Thorotrast-treated patients

Cancer site	Germany (van Kaick *et al.*, 1999)		Denmark (Andersson *et al.*, 1993, 1995a,b)		Japan (Mori *et al.*, 1999b)		Portugal (dos Santos Silva *et al.*, 1999)		Sweden (Martling *et al.*, 1999)	
	No.	RR[a] (risk)	No.	RR[b]	No.	RR[a] (rate)	No.	RR[a] (rate)	No.	SMR[c]
Liver cancer	454	129[*d]	84	SIR = 121[*] (97–150)	143	36[*] (24–53)	104	71[*] (20–251)		
Cirrhosis of the liver	372	6.0[*]	32	SMR = 7.5[*] (5.1–11)	26	6.9[*] (4.0–12)	50	5.7[*] (3.1–10)	18	13[*] (7.6–20)
Cancer of the bile ducts	29	7.8[*]					3[e]	1.4 (0.4–5.6)		
Gall-bladder cancer	13	2.7	15	Ratio = 17[*] (4.9–110)						
Mesothelioma	9	[f]	7[g]	Risk = 2.5%						
Pancreas	18	2.4[*]	5	2.2 (0.6–7.9)						
Acute myeloid leukaemia	40	4.6[*]	16[g]							
Acute lymphoid leukaemia	2	[f]	1[g]							
Non-chronic lymphoid leukaemia			20	20.35[*] (5.9–127)	10[h]	13[*] (4.5–35)	11	15[*] (1.3–182)		
Myelodysplastic syndrome	30	6.1[*]	7[g]							
Non-Hodgkin lymphoma	15	2.5	2	1.5 (0.2–8.9)						
Hodgkin disease	2	0.8	1	1.6 (0.1–40)						
Myeloma	10 (plasma-cytoma)	4.1	4	4.3 (0.9–31)						
Bone sarcoma	4	3.3	0	–			16	7.1[*] (1.7–30)		
Cancer of the larynx	7	1.9	1	SIR = 1.1 (0.0–6.2)						
Lung cancer	53	0.7	21	1.6 (0.9–2.9)	11	2.0[*] (1.0–3.9)	10	4.7 (0.2–92)		
Cancer of the kidney	10	0.8	5	2.6 (0.7–10.6)						

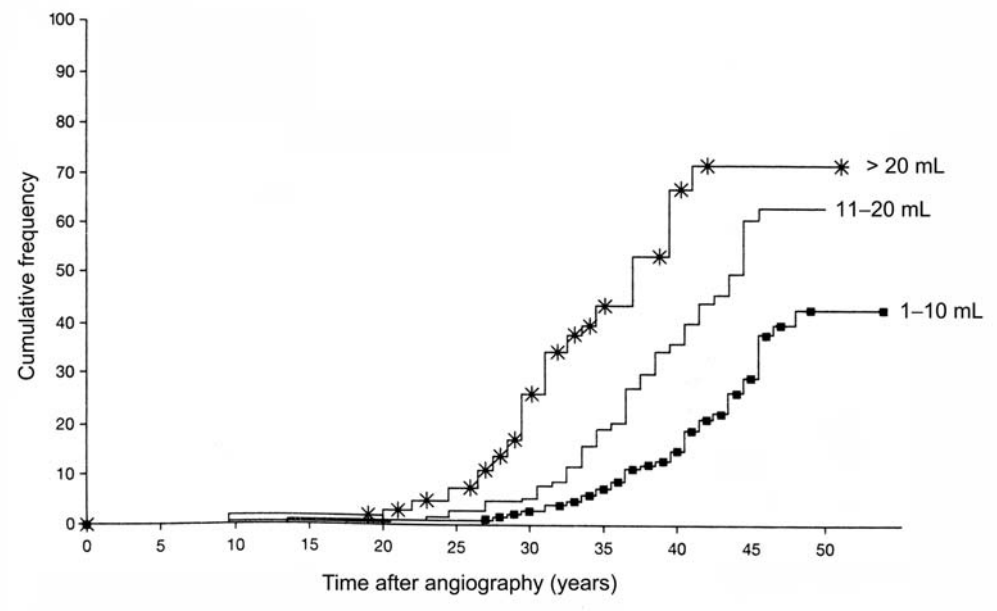
Table 43 (contd)

Cancer site	Germany (van Kaick *et al.*, 1999)		Denmark (Andersson *et al.*, 1993, 1995a,b)		Japan (Mori *et al.*, 1999b)		Portugal (dos Santos Silva *et al.*, 1999)		Sweden (Martling *et al.*, 1999)	
	No.	RR[a] (risk)	No.	RR[b]	No.	RR[a] (rate)	No.	RR[a] (rate)	No.	SMR[c]
Cancer of the urinary bladder	10	1.2	5	0.75 (0.2–2.0)						
Prostate cancer	21	0.9	6	2.98 (0.9–12)						
Central nervous system cancer	19	1.1	21	3.2* (1.6–6.6)			290	1.8 (0.8–4.1)		
All sites of cancer			315	3.2* (2.7–3.9)			509	6.0* (4.4–8.3)	164	4.2* (3.6–4.9)
All causes of death			751	SMR = 3.5* (3.2–3.7)	375	2.5* (2.2–2.8)	988	2.4* (2.0–2.7)	474	2.8* (2.5–3.0)

* $p < 0.05$
[a] Mortality rate (risk) ratio
[b] Ratio of standardized incidence ratios of SIRs (SIR of Thorotrast-treated/SIR of controls, unless otherwise stated)
[c] Standardized mortality ratio
[d] 12.9 in the paper
[e] Bile duct plus gall-bladder
[f] No. in controls, 0; therefore, no RR
[g] Non-register-based data (Andersson *et al.*, 1993)
[h] All leukaemia

histological distribution, with a large number of hepatic haemangiosarcomas, was observed among Russian nuclear workers who inhaled plutonium (see section 2.4.3).] All three studies show a clear relationship between the injected volume of Thorotrast (taken to be equivalent to the dose-rate) and the risk for liver cancer (Figure 5), and it can be assumed that the documented volumes of injected Thorotrast in the hospital records are reasonably appropriate for dose estimation, at least for liver tumours. The cumulative risk estimates calculated from the number of excess liver tumours at the end of these studies agree well. If a 10-year 'wasted' dose is assumed, i.e. patients who died within the first 10 years after Thorotrast injection were excluded since they had no chance to develop liver malignancies, the cumulative risk estimates are 510 per 10^4 person-Gy (Andersson, 1997) in the Danish study, 607 per 10^4 person-Gy (405 with the new dosimetry) (van Kaick *et al.*, 1999) in the German study and 523 per 10^4 person-Gy (Mori *et al.*, 1999a) in the Japanese study. [With a radiation weighting factor of 20 for α-particles, the expected risk for low-LET radiation would be 25.5–30.3 cases per 10^4 person–Sv]. Thompson *et al.* (1994) estimated that the average risk for liver cancer incidence among survivors of the atomic bombings, who were exposed mainly to external radiation, was 1.64 (95% CI, 0.54–2.91) per 10^4 person–years per Sv. [If an exposure period of 30–40 years is assumed, the estimate would be 49–66 cases per 10^4 person–Sv.] These values are similar to those in the

Figure 5. Cumulative frequency of liver tumours with time after angiography in relation to the volume of Thorotrast injected (Kaplan-Meier estimates, log rank test: $p < 0.0001$)



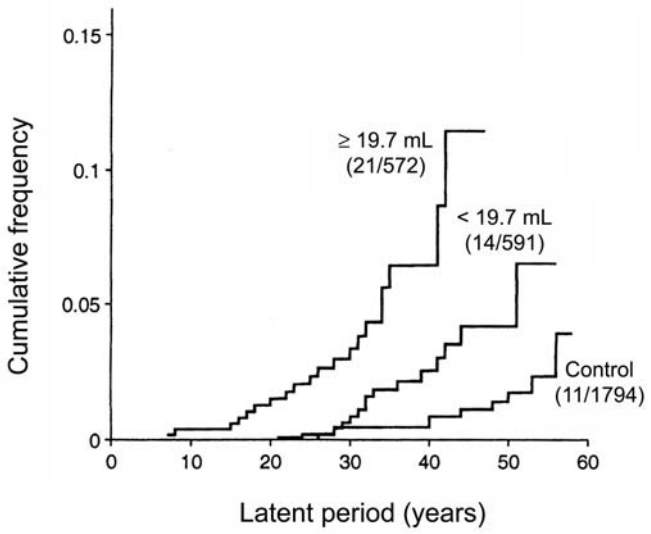
From Andersson (1997)

Thorotrast-treated patients. With a radiation weighting factor of 20, the cumulative risk estimate for liver cancer in the German study was calculated to be 40 per 10^4 person-Sv (van Kaick *et al.*, 1999).

(ii) *Haematological malignancies*

Similarly, the incidence of and mortality from non-chronic lymphoid leukaemia and myelodysplastic syndrome is increased 5–20-fold in Thorotrast-treated individuals, whereas the risk for chronic lymphoid leukaemia was not increased in any study. More than 80 cases of Thorotrast-related non-chronic lymphoid leukaemia were reported in the cohort studies, and more than 40 other cases have been reported (Andersson *et al.*, 1993). An association between the risk for leukaemia and the amount of Thorotrast injected was described in the German study (van Kaick *et al.*, 1999; Figure 6) but not in the Danish study (Andersson *et al.*, 1993, 1995a). Leukaemia was diagnosed approximately five years after exposure. In many studies, most of the cases of acute myeloid leukaemia consisted of erythroleukaemia. The cumulative risk estimates for non-chronic lymphoid leukaemia were 140 cases per 10^4 person-Gy in the Danish study, 135 cases per 10^4 person-Gy in the German study and 129 cases per 10^4 person-Gy in the Japanese study, assuming a 5-year 'wasted' dose. [With a radiation weighting factor of 20 for α-particles, the expected risk for low-LET radiation would be 6.4–7

Figure 6. Cumulative frequency of haematopoietic malignancies (myeloid leukaemia and myelodysplastic syndrome) among persons injected with Thorotrast



The numbers in parentheses are the number of malignancies per number of patients. Note that the frequency and the latency are related to the injection volume (i.e. dose rate) (van Kaick *et al.*, 1999).

cases per 10^4 person–Sv.] Preston *et al.* (1994) estimated that the excess absolute risk for leukaemia among atomic bomb survivors was 2.7 cases per 10^4 person–years per Sv. [If an exposure period of 20–30 years is assumed, the estimate would be 54–81 cases per 10^4 person–Sv.] In contrast to the situation for liver cancer, there is no agreement if a radiation weighting factor of 20 is assumed. [If the fractional deposition of Thorotrast in the bone marrow is assumed to be 25%, as proposed by Ishikawa *et al.* (1999), instead of 9% (Kaul & Noffz, 1978), the risk would be lowered by about 2.5.]

[The Working Group noted that the estimates of the risk for liver cancer associated with exposure to Thorotrast are generally as expected from experimental studies of the RBE of high-LET neutrons (IARC, 2000). High-LET radiations are generally more effective in inducing cancer than low-LET radiations, by a factor of 5–40, and a radiation weighting factor of 20 is used to compute equivalent dose for radiation protection purposes. The estimated risk for leukaemia, however, rather suggests a RBE of 1–2. It should be noted that the difference between low-LET and high-LET in the induction of leukaemia in experimental animals is not as great, and RBEs closer to 1 than to 20 have been reported (Upton *et al.*, 1970; IARC, 2000). It is recognized, however, that RBE is a complex function related to dose, end-point and the radiation qualities and energies being compared.]

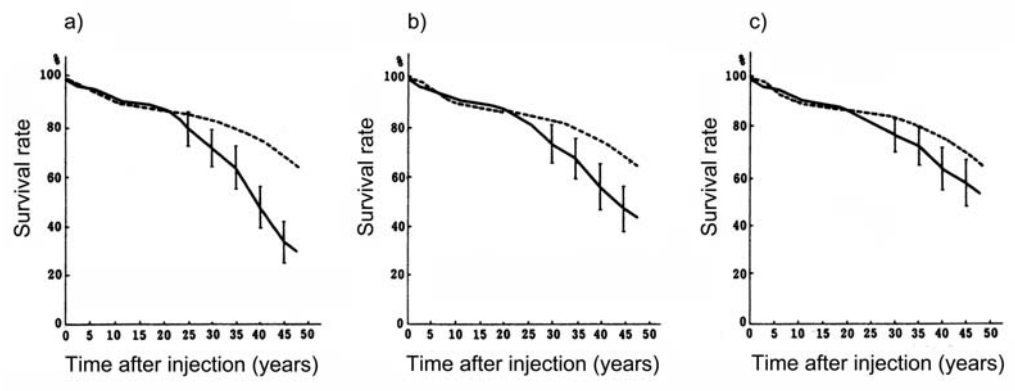
(iii) *Cancers at other sites*

The risks for cancers at other sites were not consistently significantly increased. In some studies, however, significantly increased risks for cancers of the extrahepatic bile ducts, gall-bladder and pancreas and malignant mesothelioma have been reported (Andersson *et al.*, 1995b; van Kaick *et al.*, 1999; see Table 43). Elevated risks for tumours of the central nervous system observed in some studies are presumed to result from selection bias (pre-existing lesions). Although some studies have reported excess frequencies of lung cancer, there is no consistent evidence of an increase in Thorotrast-treated patients, despite the fact that they exhale extremely high concentrations of ^{220}Rn (Grillmaier & Muth, 1971; Kato & Ishikawa, 1992). Interpretation of these data is hampered by lack of information on smoking. The spleen, abdominal lymph nodes and areas with perivascular deposits receive substantial doses, but no increase in cancer risk has been observed.

A significantly elevated increase (6–13-fold) in the rate of mortality from non-malignant liver disorders (cirrhosis) was reported in all these studies (see Table 43).

The German and Japanese studies showed a statistically significant decrease in survival, even after exclusion of the major Thorotrast-related causes of death, liver cancer, liver cirrhosis and haematopoietic malignancies including myelodysplastic syndrome (van Kaick *et al.*, 1989; Mori *et al.*, 1989, 1999b; Figure 7). The implications of this phenomenon have not been interpreted fully yet, but might be explained by slight, but not significant, increases in cancer mortality in various organs and tissues such as the pancreas and pleural and peritoneal membranes.

Figure 7. Survival curves for persons injected with Thorotrast and controls



From Mori *et al.* (1989)
a) All causes; b) excluding mortality from malignant hepatic tumours; c) excluding mortality from malignant hepatic tumours, liver cirrhosis, blood diseases, sarcoma at the injection site, necrotic thorotrastomas, bone sarcoma, lung cancer and epilepsy. Note that the survival rate is still significantly decreased after exclusion of these diseases.

2.4 Plutonium

Studies of workers exposed to plutonium have been conducted in the the United Kingdom and the USA, and studies in the Russian Federation have recently become available. In this section, the word 'plutonium' and the symbol ^{239}Pu refer specifically to the combination of the α-particle emitters ^{239}Pu and ^{240}Pu. ^{239}Pu is the major component of the dose in most circumstances. Smaller contributions to the dose from ^{238}Pu (α-particle emitter) and ^{241}Pu (β-particle emitter, including its decay product, ^{241}Am (α-particle emitter)) are frequently ignored. No epidemiological studies have been conducted on ^{238}Pu or ^{241}Pu. ^{239}Pu has a very long half-life, over 24 000 years, and decays by emitting an α-particle. As α-particles are densely ionizing radiations that penetrate only a few cells before coming to a halt, cells adjacent to the site of deposition of the plutonium receive most of the imparted dose. The distribution of plutonium in the body is such that it concentrates mainly in the liver and skeleton and also in the lung, if inhaled. Experimental studies and knowledge of dose distribution indicate that internally incorporated plutonium would increase the risks for cancers of the lung, bone and liver.

2.4.1 *United Kingdom*

A major study was performed on all 14 319 workers (11 635 men) employed at the Sellafield fuel reprocessing plant of British Nuclear Fuels between 1947 and 1975 (Omar *et al*., 1999), which is on the Cumbrian coast of the United Kingdom and which was originally designed for the production of plutonium for nuclear weapons. Later, plutonium was produced during commercial reprocessing of spent nuclear fuel and has

been stored on the site. The mortality of these workers was studied up to the end of 1992, and cancer incidence was examined from 1971 through 1986. The study included 5203 workers who were monitored for exposure to plutonium, of whom 4609 were assessed for dose. The body burden of most workers was estimated to be < 50 Bq, and only a few had > 1 kBq. The age-, sex- and cause-specific deaths rates for the population of England and Wales were used for comparison. For incidence analyses, cancer registration rates were obtained for both England and Wales and for Cumbria. In addition, rate ratios were calculated for plutonium workers in comparison with other radiation workers, and for all radiation workers in comparison with non-radiation workers. The results of the cancer mortality study are summarized in Table 44. The data in the Table are only for specific cancer sites for which a statistically significant excess (pleura, breast) or deficit (liver and gall-bladder) of deaths was found and deaths from leukaemia and lung and bone cancer. Liver, lung and bone are principal deposition sites for about 90% of plutonium in the body. Leukaemia is included because of its status as a marker disease for exposure to external radiation. [In this cohort, the average cumulative doses from plutonium were 712 mSv to bone surfaces, 194 mSv to lung, 91 mSv to liver and 58 mSv to red bone marrow; a radiation weighting factor of 20 was applied to the absorbed doses to compute equivalent doses in mSv.] The doses to other organs were relatively low. The doses for each worker were calculated by the company by dosimetric models based on the distribution of plutonium activity between organs and its clearance, as recommended by the ICRP (1986) (Riddell *et al.*, 2000). Plutonium workers were defined as those who had ever provided a urine sample for a plutonium assay. As many of these workers were never exposed to plutonium, the dose distribution and average dose are skewed towards low doses.

Assessments of plutonium uptake in the Sellafield study were divided by three to compensate for differences previously observed between the results of urine bioassays and autopsy studies. In Table 44, the number of deaths from all cancers in plutonium workers is not excessive when compared with the death rates in England and Wales (SMR, 1.00). The overall death rates from cancer were also similar when plutonium workers were compared with other radiation workers (rate ratio, 1.05) and when radiation workers were compared with non-radiation workers (rate ratio, 1.06). The numbers of deaths from cancers of the liver, lung and bone were not in excess, but there were significant excesses of deaths among plutonium workers when compared with the rates in England and Wales from cancer of the pleura (SMR, 4.71; $p < 0.001$), breast cancer (SMR, 2.36; $p < 0.05$) and cancers of ill-defined and secondary sites (SMR, 1.44; $p < 0.05$). All the significance tests in this study were one-sided in the direction of the observed difference or trend (Omar *et al.*, 1999).

Eight deaths from malignant pleural mesothelioma occurred in plutonium workers and six deaths in other radiation workers. The increased risk among plutonium workers (SMR, 4.71; $p < 0.001$) and other radiation workers was of similar magnitude (SMR, 3.90; $p < 0.05$) (rate ratio for plutonium and for other radiation workers, 1.15).

Table 44. Observed and expected numbers of deaths from cancers at specific sites among plutonium workers at Sellafield, United Kingdom, rate ratios relative to other radiation workers, and a comparison of all radiation workers with non-radiation workers

Cancer site	Plutonium workers			Rate ratio	
	Observed	Expected	SMR	Pu versus other radiation	Radiation versus non-radiation
Liver and gall-bladder	1	5.17	0.19**	0.85	0.34
Lung	133	145.78	0.91	1.12	0.98
Pleura	8	1.70	4.71***	1.15	∞*
Bone	0	1.10	0.0	–	1.12
Breast	6	2.55	2.36*	7.66**	1.35
Prostate	22	21.36	1.03	0.95	2.21*
Ill-defined and secondary (195–199)[a]	29	20.13	1.44*	1.90*	0.96
Leukaemia	7	9.86	0.71	0.79	1.27
All neoplasms	384	385.10	1.00	1.05	1.06
Person–years at risk		134 817.2			

From Omar *et al.* (1999). Only sites at which significant risks were found and organs with large plutonium deposits are included. SMR, standardized mortality ratio

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] ICD, 8th rev.

Non-radiation workers had no cancers of the pleura (Omar *et al.*, 1999). In an earlier study of workers exposed to external radiation at Sellafield, an increased death rate from cancer of the pleura ($n = 9$; SMR, 4.25; $p < 0.001$) was found. Four more cancers of the pleura were reported among radiation workers (Douglas *et al*., 1994). All nine cancers of the pleura were malignant mesotheliomas (Carpenter *et al*., 1998). Exposure to asbestos is known to be a strong risk factor for pleural mesothelioma, and mesothelioma is pathognomonic for asbestos exposure until proven otherwise. The extent of exposure to this material of employees either at the plant or in other work settings is unknown.

The plutonium workers had higher death rates from breast cancer than other radiation workers (rate ratio, 7.66; $p < 0.001$), but the rate in other radiation workers was significantly lower than that of the population of England and Wales (SMR, 0.34; $p < 0.05$). There were six deaths in plutonium workers and two in other radiation workers (Omar *et al.*, 1999), all among women. A urine sample was taken from one woman for plutonium analysis because of her diagnosis, and she was included among

the plutonium workers' deaths. When this case is excluded from the analysis, the mortality rate from breast cancer among plutonium workers was not significantly greater than that in England and Wales, and the excess in comparison with other radiation workers was of reduced significance ($p < 0.05$).

The mortality rate for ill-defined and secondary cancers in plutonium workers was significantly higher than that in other radiation workers (rate ratio, 1.9; $p = 0.04$), but there was no significantly increased incidence rate nor a relationship between risk and estimated cumulative radiation dose. Trend analyses for plutonium workers related the risk for death from organ-specific cancers to the estimated organ-specific radiation doses from exposures to plutonium and external radiation combined. The only statistically significant finding ($p < 0.05$) was a negative trend between the risk for death from all malignant neoplasms and cumulative radiation dose, assuming no lag period. Analysis of the cancer incidence data revealed no significant increases for plutonium workers when compared with registrations for all neoplasms or all organ-specific cancers in England and Wales. The incidence rate of all neoplasms was the same for plutonium workers and other radiation workers (rate ratio, 0.99). Trend analysis was performed on cancer incidence among plutonium workers in relation to organ-specific plutonium dose plus cumulative external radiation dose. The only statistically significant findings ($p < 0.05$) were positive trends with cumulative dose for all lag periods considered (0, 10 and 20 years), for all lymphatic and haematopoietic neoplasms combined. However, grouping these malignancies with such different characteristics and causes has little biological meaning. The authors concluded that their findings provide no evidence that plutonium increases the risk for cancer in this worker population, who are exposed to relatively low levels (Omar *et al.*, 1999).

Deaths from cancer among 40 761 employees of three United Kingdom nuclear industry facilities, the Atomic Energy Authority, the Atomic Weapons Establishment and the Sellafield plant of British Nuclear Fuels, who had been monitored for exposure to external radiation were examined according to whether the employees had also been monitored for possible internal exposure to tritium (^{3}H), plutonium or other radionuclides (Carpenter *et al*., 1998). For the first two facilities, information was available for the actual years each worker was monitored, while the data from Sellafield were limited to the first year the worker was monitored for ^{3}H and plutonium. Information on individual doses was not available. Among the 12 498 workers monitored for plutonium, 581 died from a malignant neoplasm, giving a significantly lower mortality rate than national rates (SMR, 0.89; two-sided *p* value, 0.005). The SMR for cancers of the pleura ($n = 9$, all mesotheliomas) was significantly elevated (SMR, 3.57; two-sided *p* value, 0.002). None of the other organ-specific cancers in workers monitored for plutonium occurred significantly more frequently than in national rates, and none of the rates differed significantly from those of workers who were not monitored. The lack of dosimetry for internal doses and possible confounding by exposure to external radiation weaken the reliance that can be placed on the relative absence of excess cancer rates in workers monitored for plutonium.

2.4.2 *USA*

The longest medical follow-up study of plutonium workers involved 26 white men who were exposed at Los Alamos, New Mexico, in 1944–45 while working on the Manhattan Project during the Second World War. This Project, for the design and building of the first atomic bomb, involved chemical and metallurgical research on plutonium and fabrication of plutonium-containing parts (Voelz & Lawrence, 1991; Voelz *et al*., 1997). The workers were exposed to very pure ^{239}Pu because the ^{241}Am was removed (the Am content was 2–5% of that in a comparable amount of plutonium processed in the 1980s). Inhalation of plutonium was the main pathway of exposure of these workers. Their effective doses, through 1994 or year of death, range from 0.1 to 7.2 Sv with a median value of 1.25 Sv (mean, 2.08 Sv [assuming a radiation weighting factor of 20 because of α-particle emission, see IARC, 2000). The dose of plutonium deposited by 1994 or year of death ranged from 50 to 3180 Bq, with a median value of 565 Bq (mean, 970 Bq). The doses of external radiation in 1944–45 were not measured, as no personal dosimeters were used until the end of 1945, but were believed to be low. Medical examinations and dosimetry were performed at roughly five-year intervals from 1952. The results of a study of deaths through 1994 are given in Table 45. The rate for all causes of death was significantly decreased in these workers when compared with national rates, due primarily to a low rate of death from diseases of the circulatory system. The mortality rate ratios for these workers were also compared with those of 876 unexposed Los Alamos workers hired on comparable dates. The rate ratio for death from all causes was 0.77 (95% CI, 0.36–1.6) and that from all malignant neoplasms was 1.5 (95% CI, 0.46–4.9). One bone sarcoma was observed in these workers, which originated in the sacrum and became symptomatic in 1988, about 43 years after exposure. The individual, a chemist, had received an effective dose of plutonium of 1.3 Sv, essentially the median dose for this cohort. The amount of plutonium deposited at the time of death, calculated from urinary excretion, was 580 Bq; the cumulative dose to the bone surfaces is estimated to be 0.44 Gy two years before appearance of the tumour. Three cases of lung cancer (with one death) were also observed, but among heavy smokers. Although the health of this cohort has been monitored for 50 years, the group is too small to allow precise estimates of risk.

Deaths among 5413 workers employed at the Rocky Flats, Colorado, nuclear weapons facility were investigated in order to estimate the risks from exposure to plutonium and external radiation (Wilkinson *et al.*, 1987). The cohort consisted of all white men who had been employed at this facility for at least two years between the beginning of operations in 1952 and 1979. In comparison with death rates for the USA, significantly fewer deaths from all causes, all cancers, lung cancer, circulatory system diseases and accidents, poisonings and violence were observed (see Table 46). The three deaths from cancers of the liver and gall-bladder did not result in a statistically significantly elevated SMR (1.39; 90% CI, 0.38–3.59). No bone tumours occurred in this cohort. A significant excess of benign and unspecified neoplasms was found; all

Table 45. Standardized mortality ratios (SMRs) of 'Manhattan Project' plutonium workers through 1994 in comparison with rates for white men in the USA

Cause	Observed	Expected	SMR	95% CI
All	7	16.3	0.43	0.17–0.88**
All malignant neoplasms	3	4.0	0.75	0.15–2.18
Lung cancer	1	1.5	0.68	0.01–3.79
Prostate cancer	1	0.3	3.42	0.04–19.04
Bone cancer	1	0.01	96.4	1.26–536**
All diseases of circulatory system	2	7.7	0.26	0.03–0.93*
All respiratory diseases	1	1.2	0.83	0.01–4.64
All external causes	1	1.3	0.79	0.01–4.40

From Voelz *et al*. (1997); CI, confidence interval
* One-sided *p*-value, < 0.05
** One-sided *p*-value, < 0.01

Table 46. Standardized mortality ratios (SMRs) for selected causes of death among white male workers in Rocky Flats compared with the death rates in the USA

Cause of death[a]	Observed	Expected	SMR	90% CI
All	409	656.21	0.62	0.57–0.68
All cancers	95	134.21	0.71	0.59–0.84
Lung cancer	30	46.57	0.64	0.46–0.87
Benign and unspecified (210–239)	7	1.86	3.76	1.77–7.07
All circulatory system (390–458)	193	315.02	0.61	0.54–0.69
Accidents, poisonings and violence (800–998)	55	85.11	0.65	0.51–0.81

From Wilkinson *et al*. (1987); CI, confidence interval
[a] ICD, 8th rev.

seven cases were intracranial tumours. In a case–control study of the brain tumours at Rocky Flats (Reyes *et al*., 1984), no statistically significant association was found with exposure to either external radiation or plutonium. Plutonium-exposed workers at Rocky Flats were defined as those employees with plutonium deposits ≥ 74 Bq, the detection limit of the urine bioassays. The mortality rates of plutonium-exposed workers were compared with those of unexposed workers (< 74 Bq) after a 2-, 5- and 10-year lag. The rate ratios for only two categories — all causes of death and all lymphatic and haematopoietic neoplasms combined — were significantly increased on the basis of 90% confidence intervals. The rate of all causes of death was increased with a 5-year lag (n = 74; rate ratio, 1.33; 90% CI, 1.05–1.68) and a 10-year lag

(*n* = 40; rate ratio, 1.39; 90% CI, 1.04–1.87). The incidence of all lymphatic and haematopoietic neoplasms combined (*n* = 4) was elevated with a 2-year lag (rate ratio, 7.69; 90% CI, 0.99–72.93) and a 5-year lag (*n* = 4; rate ratio, 9.86; 90% CI, 1.26–94.03). The four neoplasms in this combined category were all of different cell types: lymphosarcoma (reticulum-cell sarcoma), non-Hodgkin lymphoma, multiple myeloma and myeloid leukaemia. It seems unlikely that these different diseases are related biologically, although they are commonly grouped in studies of limited numbers of cases. The small number of cases in this study (four or fewer in each organ-specific category) resulted in wide confidence intervals and limited the precision of results. In trend analyses with individual doses from external radiation and deposited plutonium independently, no overall dose–response relationship was found.

A cohort study was conducted through 1990 of deaths among 15 727 white men who had been employed by the Los Alamos National Laboratory during 1943–77. The laboratory has been an important nuclear weapons research and design laboratory since the Second World War (Wiggs *et al*., 1994). Mortality rate ratios were calculated for 303 plutonium-exposed workers, defined as persons with internal deposition of plutonium ≥ 74 Bq, in comparison with 3472 unexposed workers monitored for plutonium (< 74 Bq); plutonium deposits measured after 1980 were not included in the analysis because a 10-year tumour induction period for plutonium was assumed. The rate ratios for deaths from all causes and all cancers were close to 1.0. No statistically significant increases or deficits in rate ratios were observed. The rate ratio for lung cancer (eight cases in plutonium-exposed persons) was 1.78 (95% CI, 0.79–3.99). One case of osteogenic sarcoma was observed among the plutonium-exposed workers. The characteristics of this case, described by Voelz and Lawrence (1991), are discussed above.

The studies conducted in the United Kingdom and the USA on plutonium workers provide no evidence of excess risks of either lung cancer or liver cancer. One bone cancer in a plutonium-exposed person was identified in these studies, and its causation should remain questionable until confirmatory evidence of risk to the bone is obtained from other studies. As these studies have limited power, they provide little convincing evidence that the exposure to plutonium at relatively low levels experienced in these occupational settings is associated with an increased risk for cancer.

2.4.3 *Russian Federation*

The first Russian nuclear complex is now known as the Mayak Production Association. It is located in the southern Urals, about 100 km from Chelyabinsk (now called Ozyorsk) (Koshurnikova *et al.*, 1997a). This nuclear complex, which included an industrial nuclear (uranium–graphite) reactor, a plant for radiochemical separation of plutonium from irradiated nuclear fuel in the reactor (radiochemical plant) and a plant for the production of standard plutonium (plutonium production plant), was put into operation between June 1948 and March 1949. There are two other nuclear complexes

in the Russian Federation (near Tomsk and Krasnoyarsk), in which workers could be exposed to plutonium, but no data were available on health effects in these workers.

Clinical studies and studies of working conditions were begun at Mayak practically at the inception of its operation; however, because of the regime of secrecy, the results of these studies were summarized as classified reports or were published in classified journals. The first publication available in the open literature, which described working conditions, levels of exposure to radiation and some early and late health effects, appeared only in 1990 (Nikipelov *et al*., 1990). This paper provides information on mortality from cancer among workers who had started working at Mayak between 1948 and 1958. The paper also mentioned for the first time that the cancers in the Mayak workers might have been induced not only by external exposure to γ-radiation but also by internal exposure to deposited plutonium. Although this paper does not provide evidence for the carcinogenicity of plutonium, it was a catalyst for subsequent publications directly relevant to the carcinogenic effects of plutonium and for declassification of papers published earlier in the classified journals.

Studies on the metabolism and dosimetry of plutonium and the health effects of exposure to this element were conducted at Branch No. 1 of the First Institute of Biophysics (FIB-1). The distribution of plutonium in the human body was found to be highly non-uniform, regardless of the route of intake, although after inhalation it was deposited mainly in the lung, liver and skeleton. Post-mortem radiometry showed that the distribution of inhaled plutonium compounds in the human body was determined by its physical and chemical properties (Plotnikova, 1965; Khokhryakov & Kudryavtseva, 1985; Khokhryakov *et al*., 1990, 1998). On the basis of 34 autopsies, Plotnikova (1965) showed that larger amounts of inhaled soluble plutonium compounds were transferred from the lung to the skeleton than to the liver, while most of the plutonium in insoluble compounds was retained in the lung. On the basis of post-mortem radiometry for 177 cases, Khokhryakov and Kudryavtseva (1985) and Khokhryakov *et al.* (1990) studied the distribution and secondary deposition in various organs of plutonium absorbed into the bloodstream. They showed that, regardless of the solubility of inhaled compounds, extrapulmonary plutonium accumulated mainly in the skeleton (about 60%) and liver (about 30%). Khokhryakov *et al.* (1998) reported that retention of plutonium in the lung varied over time, was strongly dependent on the solubility of inhaled aerosols and represented about 2.5% of the total body burden of soluble compounds and 23% of the burden of plutonium compounds with low solubility.

Since studies in both humans and experimental animals show that inhaled plutonium is deposited mainly in the lung, liver and bone, studies were conducted at the FIB-1 to evaluate the risks for cancer in these organs.

(*a*) *Lung cancer*

Cases of lung cancer among Mayak workers who were exposed to plutonium were described in the early 1970s (Yakushina *et al.*, 1972; Koshurnikova *et al*., 1973), and lung cancer incidence was first studied by Moroz (1976). The incidence in workers

who received cumulative doses of external γ-radiation higher than those permissible at the time (most received doses > 100 roentgen [about 1 Gy] and > 0.02 μCi [740 Bq] plutonium to the lung) 20 years after the beginning of exposure was significantly higher than that in workers exposed to the same types of radiation within permissible dose limits or in those who had never worked at Mayak.

Since that time, three epidemiological studies have been conducted at FIB-1: a cohort study by the epidemiology department, a cohort study by the internal dosimetry laboratory and a case–control study by the clinical department. These studies are based on partially overlapping material.

(i) *Cohort study by the epidemiology department*

In the study by the epidemiology department, mortality was followed-up for about 19 000 male and female workers (Table 47) who had been hired at the nuclear reactor and radiochemical and plutonium production plants between 1948 and 1972 (regardless of duration of employment). The number of subjects in the cohort varied slightly over time as details of occupational histories became available and duplicate records were found. The findings have been reported for successive follow-up intervals. The most detailed description of the cohort is that of Koshurnikova *et al.* (1999). Vital status was ascertained in address bureaus and in some cases from relatives of the cohort members; the fact of death was obtained from the address bureau and the cause of death from vital statistics departments. As of 31 December 1994, 90% of the cohort had been traced, and the cause of death was known for 97% of the deceased cohort members. Cause of death was determined from death certificates (45%), autopsy records (43%), other medical documents (5%) and reports from relatives (7%). Workers in all the facilities were exposed to external γ-radiation, and those in the radiochemical and plutonium production plants had potential internal exposure as a result of inhalation of plutonium aerosols. For the analysis, those who had worked at more than one Mayak plant were assigned to one plant according to the following scheme: plutonium production plant:

Table 47. Numbers of workers by sex, period of hire and plant at the Mayak nuclear complex, Russian Federation

Plant	Sex	Period of hire				Total
		1948–53	1954–58	1959–63	1964–72	
Reactor	M	1757	643	609	436	3445
	F	672	154	66	77	969
Radiochemical	M	2339	1741	1227	584	5891
	F	1329	289	243	158	2019
Plutonium production	M	1467	980	1309	986	4742
	F	910	238	311	305	1764

From Koshurnikova *et al.* (1999)

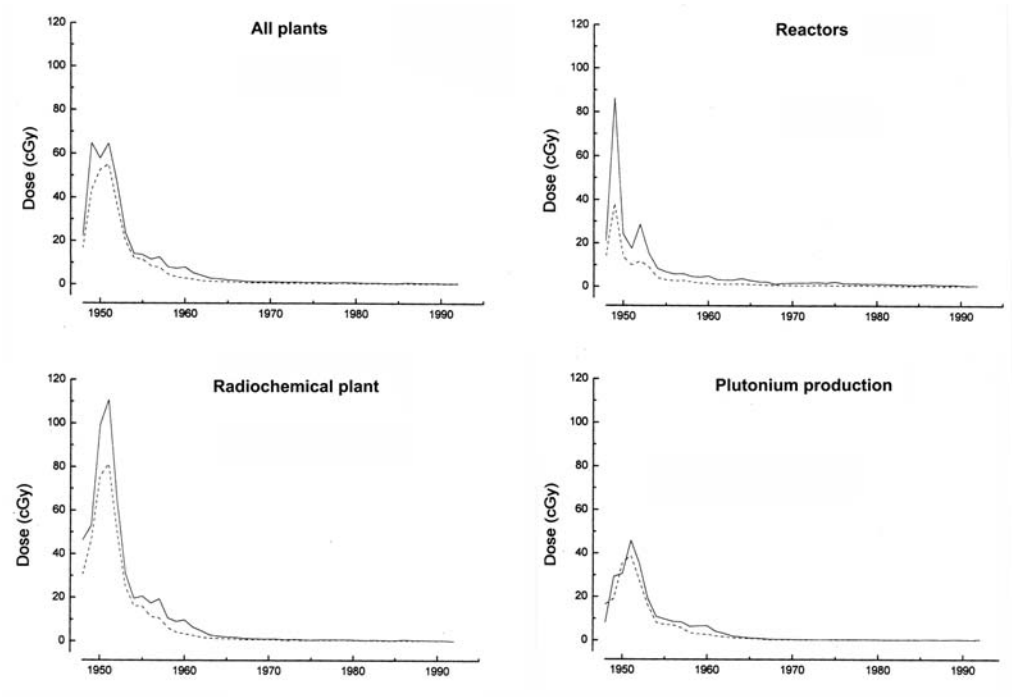
ever worked in the plutonium production plant; radiochemical plant: ever worked in the radiochemical plant and never in the plutonium production plant; nuclear reactors: worked only in nuclear reactors. The assignment was based on the degree of occupational exposure to plutonium. Working conditions at the plutonium production plant were considered to be the most unfavourable because of the highest potential exposure to plutonium.

Individual monitoring for exposure to external radiation at Mayak was conducted from the inception of operations of the main Mayak plants in 1948, when the Radiation Safety Department began to keep individual film-badge measurements of external γ-radiation doses. About 83% of the workers in the study cohort had been monitored. In general, workers were not monitored when they were considered to have little or no likelihood of external exposure. The highest doses of external γ-radiation were received by the workers in the late 1940s to early 1950s, many of the cumulative doses exceeding 1 Gy. From the mid-1950s, the annual doses decreased considerably. Workers assigned to the radiochemical plant had the heaviest exposure to external γ-radiation (Figure 8). During 1948–53, dosimeters were changed for each working shift. By 1953, the daily doses were considerably reduced, and workers were placed on weekly or, in some departments, monthly exchange schedules. By 1960, dosimeters were changed monthly in almost all departments. The body burden of plutonium and doses from deposited plutonium were estimated at the FIB-1 dosimetry laboratory. The algorithm for estimating plutonium content and dose developed at this laboratory was approved as an obligatory standard for all nuclear industry plants in the Russian Federation. The body burdens of Mayak workers were evaluated by this method from measurements of plutonium in urine from the late 1960s. Thus, only about 30% of the cohort members with potential exposure to plutonium (radiochemical and plutonium production plant workers) were monitored for plutonium body burden according to the standard method.

Mortality from lung cancer was analysed only for workers who were hired during the first decade of operations at Mayak (1948–58) (Koshurnikova *et al*., 1992, 1996, 1997a,b, 1998), when there was extensive exposure to external γ-radiation and high concentrations of plutonium aerosols in the air of the working premises. The average cumulative whole-body dose of external γ-radiation of workers who started work during this period was 1.28 Gy for men and 1.11 Gy for women. The average dose of internal α-particle radiation to the lung for workers with a measured plutonium body burden was 6.56 Sv for men and 12.61 Sv for women, assuming a radiation weighting factor of 20 for plutonium as an α-particle emitter (Koshurnikova *et al*., 1997a). As only limited information was available on smoking (ever/never), mortality from lung cancer was analysed separately for men (most of whom were smokers at the time of the study) and women (mostly non-smokers).

Koshurnikova *et al.* (1998) analysed mortality from lung cancer during 1948–93 among 1479 male workers with an average dose of external γ-radiation of 1.78 Gy and an average equivalent dose to the lung from plutonium of 6.56 Sv, of known vital

Figure 8. Average annual doses of external γ-radiation in the Mayak nuclear complex by year and plant



From Koshurnikova *et al.* (1999). Solid lines, men; dashed lines, women

status, who had started working at the radiochemical and plutonium production plants in 1948–58 and who were examined for their body burden of plutonium. The equivalent dose to the lung (radiation weighting factor, 20) accumulated from the time of the first occupational contact with plutonium to the end of follow-up or to the date of death was used as a measure of exposure to plutonium. The expected number of deaths was calculated on the basis of age-specific lung cancer mortality rates for men in the Russian Federation averaged over the period 1970–86 and in comparison with an 'internal control group'. This comprised 3333 individuals of known vital status who had started work at the same plants during the same period and met the following criteria: average external γ-radiation dose over 20 years did not exceed the maximum permissible dose of 0.05 Gy/year (average external γ-radiation dose, 0.38 Gy), and the body burden of plutonium did not exceed the maximum permissible value of 1480 Bq (average equivalent dose to the lung from plutonium, 0.13 Sv). [The Working Group noted that exposed persons in this study had a body burden of plutonium of 1480 Bq, a level rarely exceeded by workers employed in the United Kingdom or the USA.] Since the workers included in the Mayak cohort were exposed not only to plutonium but also to external γ-radiation, an additional comparison group was used in the

analysis which consisted of workers at the nuclear reactors (1841 individuals of known vital status) who were exposed to external γ-radiation (1.02 Gy) but not to plutonium. The person–years of the cohort were calculated from 1970 (the year in which systematic monitoring of plutonium body burden was begun) and those of the comparison cohorts from the year of hire. The number of lung cancer deaths observed in the cohort was 105, and the expected numbers calculated from national statistics and for the internal control group were 42.18 and 40.67, respectively. The risk for lung cancer increased with the total dose of α-particles to the lung (Table 48). [Since the results based on national statistics and those based on the internal control group were similar, only the former are given here.] The rate of death from lung cancer was not increased among workers at the nuclear reactors when compared with the national average (47 observed versus 56.23 expected deaths), and no association was detected between death from lung cancer and the whole-body dose of γ-radiation.

A significantly elevated rate of mortality from lung cancer over the national average was also reported by Koshurnikova *et al*. (1997a) among 666 women hired at the radiochemical and plutonium production plant in 1948–58 and examined for their body burden of plutonium (Table 49). The person–years of the study group were computed from 1970. The end of follow-up was 31 December 1993. The expected numbers of deaths were calculated from age-specific rates in the Russian Federation averaged over the period 1970–86 (Koshurnikova *et al.*, 1998). The number of observed cases (15) was significantly higher than that expected (2.57), and the risk for cancer mortality was associated with the total dose of α-radiation to the lung. Most of the deaths occurred among workers with the highest equivalent dose of α-particles to the lung (> 100 Sv).

[The Working Group noted that the analyses described above have the following limitations: no adjustment for the possible effects of γ-radiation and smoking, although there was little evidence in the cohort of an independent effect of long-term exposure to γ-radiation on lung cancer risk; the dose of α-particles was not treated as a time-dependent variable; and secular changes in the baseline rates were not explicitly accounted for in the analysis. In addition, the possible contribution of neutrons was not estimated. Furthermore, the dose to the lung was averaged over the entire lung whereas in fact the dose distribution was inhomogeneous. Computation of person–years in the study cohort from 1970 might lead to underestimation of person–years, as would exclusion of person-years for people lost to follow-up. In contrast, assignment of workers who had worked at more than one plant to the ‘most dangerous’ plant might have led to overestimation of the person–years for the plutonium production plant and underestimation of the person–years for the nuclear reactor plant.]

Kreisheimer *et al*. (2000) analysed mortality from lung cancer among men in the same cohort hired during 1948–58 and employed in plutonium and reprocessing plants for a longer follow-up period (1948 to end of 1995). The analysis differed from that of Koshurnikova *et al*. (1998): the dose of α-particles from plutonium and the external dose of γ-radiation were treated as time-dependent variables and the baseline

Table 48. Mortality from lung cancer in men in the Mayak nuclear complex as a function of α-particle dose to the lung

	Equivalent dose (Sv, assuming radiation weighting factor of 20)										
	< 0.5	0.5–1.7	1.8–3.9	4.0–6.9	7.0–12.9	13.0–19.9	20.0–29.9	30.0–59.9	60.0–119	≥ 120	Total
Average dose (Sv)	0.27	1.03	2.75	5.36	9.51	16.17	24.64	39.9	81.35	260.7	6.56
Persons	360	474	268	143	89	45	45	28	18	9	1479
Person–years[a]	7875	10 482	5716	3104	1807	999	856	465	275	114	31 693
Observed lung cancer deaths	13	14	13	11	12	9	13	7	8	5	105
Expected deaths	9.47	14.01	7.97	4.43	2.43	1.37	1.24	0.7	0.42	0.14	42.18
SMR (95% CI)	1.37 (0.60–3.13)	1.0 (0.48–2.07)	1.63 (0.69–3.88)	2.48 (0.84–7.29)	4.95 (1.28–19.04)	6.25 (1.14–37.59)	10.51 (1.74–63.4)	9.95 (0.91–109.0)	19.07 (0.92–396)	34.8 (0.2–∞)	2.49 (1.75–3.53)
SR (cases per 10^5 person–years)	99.4 ± 35.5	72.4 ± 26.3	118.2 ± 45.4	179.6 ± 76.0	358.1 ± 140.5	474.3 ± 217.4	760.8 ± 297.0	720.0 ± 392.1	1380.3 ± 703.6	2520 ± 1468	180.2 ± 23.8

From Koshurnikova *et al.* (1998). SMR, standardized mortality ratio; CI, confidence interval; SR, standardized rate. Expected numbers of deaths calculated on the basis of national statistics. The mortality rate for all people over 20 combined was 72.4 cases per 10^5 person–years.

[a] Person–years were calculated from 1970, when systematic monitoring of workers for plutonium body burden by urinary excretion was begun.

Table 49. Mortality from lung cancer among women in the Mayak nuclear complex in whom the body burden of plutonium was measured

Deaths	Average equivalent dose (Sv)[a]			
	1.2	8.3	116.2	Total (12.5)
Observed	2	3	10	15
Expected	0.90	0.49	0.18	2.57
Observed/expected	1.05	6.13	55.7	5.84*

From Koshurnikova *et al*. (1997a)
* Significant ($p < 0.05$)
[a] Dose of α-particle to the lung with a radiation weighting factor of 20

rate of death from lung cancer was not taken from national statistics but from the cohort itself. For both α-particles and γ-radiation, the results of the analysis are consistent with linear dose-dependence. The estimated excess relative risk per unit organ dose equivalent in the lung due to plutonium α-particles at age 60 was equal to 0.6/Sv (95% CI, 0.39/Sv–1.0/Sv), with a radiation weighting factor of 20 for α-particles. For the γ-radiation component, the analysis suggested an excess relative risk for death from lung cancer at the age of 60 of 0.20/Sv, but the confidence interval was very wide (from –0.04/Sv to 0.69/Sv).

(ii) *Cohort study by the internal dosimetry laboratory*

Another cohort study was conducted at the FIB-1 internal dosimetry laboratory (Khokhryakov *et al*., 1988; Khokhryakov & Romanov, 1992, 1994, 1996; Khokhryakov *et al*., 1998). Khokhryakov and Romanov (1992, 1994) reported the findings for the period 1970–89 for the cohort of 2346 workers (1832 men, 514 women) and 45 deaths from lung cancer. Later reports (Khokhryakov & Romanov, 1996; Khokhryakov *et al*., 1998) were based on a cohort consisting of 4279 workers (3316 men, 963 women or 3309 men, 970 women) followed during 1970–89 and 80 lung cancer deaths. [The Working Group noted that the criteria for inclusion in the cohort and procedures for determining vital status and cause of death were not described.]. The mean dose of γ-radiation to the lung of these workers was 0.9 Gy, and the mean dose of total α-particles was 0.15 Gy (3 Sv) (Khokhryakov *et al*., 1998). The computations were not aimed at separating the effects of γ-radiation and α-particles. Information on smoking was not available. The analyses were based on the constant relative risk model with a least-squares fit to the cumulative incidence in calendar years. Estimates of the expected number of death were based on age- and sex-specific mortality rates in the former USSR in 1986. Secular changes in the baseline rates were not considered in the analysis.

Khokhryakov and Romanov (1996) reported 80 lung cancer deaths, while 48.17 were expected (31.83 excess deaths). All the excess deaths were concentrated in the dose category > 4.0 Sv (Table 50). For doses < 4 Sv, the authors found fewer lung cancer deaths than expected, which indicated to them that the 'spontaneous' rate of lung cancer in the study cohort was lower than the national average rate, perhaps due partly to a 'healthy worker' effect. In order to account for the difference between the 'spontaneous' lung cancer rate in the study cohort and the national average, the authors introduced the ratio of the two, estimated to be 0.229. Introduction of this parameter increased the estimate of the number of excess ('radiation-induced') lung cancers to $80 - 48.17 \times 0.229 = 68.97$. Khokhryakov *et al.* (1998) investigated the effect of the choice of the numerical fitting procedure on the results. The estimates of the number of 'radiation-induced' lung cancers were high with all the procedures, being in the range 49.9–66.42 depending on the procedure chosen.

Table 50. Expected and observed numbers of deaths from lung cancer by dose among workers at the Mayak nuclear complex

	Equivalent dose category (Sv)[a]				
	0–0.25	0.25–1.00	1.00–4.00	> 4.00	All
No. of exposed	1119	1001	1302	857	4279
Observed cases	1	5	16	58	80
Expected cases	5.23	8.87	18.1	16.0	48.2
Ratio	[0.19	0.56	0.88	3.63	1.66]
95% confidence interval	[0.02–1.65	0.19–1.71	0.45–1.74	2.07–6.34	1.16–2.38]

Adapted from Khokhryakov and Romanov (1996). Ratio and 95% CI calculated by the Working Group. Doses were calculated to 31 December 1989 or the time of death. Expected numbers were calculated on the basis of age-specific lung cancer mortality rates for the urban population of the former USSR during 1986.

[a] A radiation weighting factor of 20 was applied.

(iii) *Case–control study by the clinical department*

The results of the case–control study of lung cancer in Mayak workers conducted at the FIB-1 clinical department have appeared in several publications (Tokarskaya *et al.*, 1993, 1994, 1995, 1996a,b, 1997a,b). The cases were those of individuals who had ever worked at the main plants of Mayak and who developed histologically confirmed lung cancer between 1966 and 1991 (162 persons: 148 men and 14 women). The controls (338 persons: 296 men, 42 women), matched for sex, year of birth (± 5 years), year of hire (± 2 years), occupation and workplace (department, sector), were workers at the same plants who did not develop lung cancer during this period. Quantitative data on smoking were obtained by direct interviews conducted by medical experts on the basis of a standard questionnaire. A smoking index (product of the number of years of

smoking and the average number of cigarettes smoked daily) was used. Data on previous pulmonary disease were abstracted from medical documents. Estimates of the body burden of plutonium and the dose to the lung from deposited plutonium were provided by the FIB-1 internal dosimetry laboratory. Data on the doses of external γ-radiation measured from film badge dosimeters were provided by the Mayak Radiation Safety Department. Odd ratios were calculated by logistic regression, and univariate analysis was used to estimate crude odds ratios. Multiple logistic regression with stepwise selection of independent variables based on the maximum likelihood method was used for multivariate analysis. The odds ratio for each variable was adjusted for all other variables. Tokarskaya *et al.* (1994, 1995) evaluated 11 potential risk factors for lung cancer and identified six significant ones. One was plutonium deposition in body. In later reports, Tokarskaya *et al.* (1996a, 1997a) evaluated the three most important factors: smoking, plutonium deposition and external γ-radiation (Table 51). The dose–response relationship was evaluated in terms of plutonium body burden, absorbed dose of plutonium to the lung and equivalent dose of external and internal radiation. Both the crude and the adjusted odds ratios were significantly elevated in the two highest ranges of exposure, whether exposure was expressed as plutonium level or total exposure (Table 51). For γ-radiation, the crude odds ratios were elevated at doses > 2 Gy, but, after adjustment, none of the odds ratios was statistically significant. There was a strong association between lung cancer and smoking, both the crude and the adjusted odds ratios being significantly elevated with smoking indices above 0. [The Working Group noted that the case–control analysis confirmed the finding that high doses of plutonium cause lung cancer, and the attempt to control for the strong effect of smoking was important. However, the shapes of the dose–response curves in the cohort and the case–control analyses differed. One possibility is that the findings in the cohort study were confounded by smoking, but since the analysis was primarily of men, it seemed unusual to expect that smoking history might vary by plutonium dose. Another possibility in the case–control study is that the lung doses of female workers were much higher than those of males, whereas virtually all of the male patients and only one of the female patients were smokers. Khokhryakov *et al.* (1998) suggested that the curvilinearity in the dose–response curve in the case–control study may be an artefact due to combining two subgroups with different characteristics, whereas the cohort findings are based exclusively on data for men. Other methodological concerns include the possibility of overmatching in the case–control analysis, i.e. the controls were matched to cases on calendar year of hire, occupational title and workplace (shop, sector), essentially forcing the potential plutonium exposure to be similar. The possible distorting effect of matching dead cases mainly with living controls was also noted.]

(iv) *Cancer location and histopathological analysis*

Attempts were made to determine whether the lung cancers found in plutonium-exposed individuals had specific characteristics. A number of reports describe the location within the lung and the distribution by histological type of the lung cancers

Table 51. Dependence of the risk for lung cancer on the values of various risk factors among workers at the Mayak nuclear complex

Factor	Value		Frequency		Crude odds ratio	Adjusted odds ratio		Trend	
	Range	Mean	No. of cases (cancer)	No. of controls		Point estimate	95% confidence interval	χ^2	*p*
^{239}Pu body burden (kBq)	0–0.148	0.01	44	86	1.0	1.0			
	0.149–0.59	0.34	16	52	0.60	0.56	0.28–1.12	4.9	< 0.05
	0.60–2.29	1.18	28	97	0.56**	0.59*	0.32–1.04		
	2.30–8.99	4.2	24	71	0.66	0.83	0.45–1.57		
	9.0–35.6	16.5	33	30	2.15**	2.48**	1.28–4.82	16.1	< 0.001
	35.7–140.6	54.2	17	2	16.6**	59.3**	11.2–314		
Absorbed lung dose (Gy)	0	0	31	69	1.0	1.0			
	0–0.10	0.042	48	118	0.91	0.84	0.45–1.5	2.9	< 0.1
	0.11–1.0	0.353	33	116	0.63**	0.71	0.39–1.3		
	1.01–2.0	1.38	13	18	1.6	2.0	0.80–5.0		
	2.01–5.2	3.30	21	15	3.1**	3.7**	1.60–8.7	10.3	< 0.01
	5.21–17.0	9.70	16	2	17.8**	96.0**	16.2–571		
Summary equivalent dose to the lung (Sv)[a]	0–0.8	0.31	27	59	1.0	1.0			
	0.81–6.0	2.91	60	167	0.79	0.75	0.45–1.4	1.1	> 0.1
	6.1–20.0	10.2	24	73	0.72	0.76	0.38–1.5		
	20.1–50.0	31.4	19	26	1.6	1.83	0.83–4.3		
	50.1–107	73.2	14	11	2.8**	4.0**	1.43–11	12.7	< 0.001
	108–344	187	18	2	19.7**	65.3**	13.5–317		

Table 51 (contd)

Factors	Value		Frequency		Crude odds ratio	Adjusted odds ratio		Trend	
	Range	Mean	No. of cases (cancer)	No. of controls		Point estimate	95% confidence interval	χ^2	p
Total γ-radiation (Gy)	0–1.0	0.30	62	168	1.0	–	–		
	1.01–2.0	1.42	40	77	1.4	–	–		
	2.01–4.0	2.70	56	88	1.7**	–	–		
	4.01–9.99	5.40	4	5	2.2*	–	–		
Smoking index	0	0	14	93	1.0	1.0			
	1–500	300	41	94	2.9**	5.36**	2.2–12.8	27.7	< 0.001
	501–2000	930	107	151	4.6**	9.35**	4.1–21.4		

From Tokarskaya *et al*. (1997a)
* ($p < 0.1$)
** ($p < 0.05$)
[a] From internal α- and external γ-radiation

in Mayak workers (Koshurnikova & Nifatov, 1978; Tokarskaya *et al.*, 1993; Koshurnikova *et al.*, 1995; Tokarskaya *et al.*, 1995, 1996b).

Tokarskaya *et al.* (1993) studied the distribution of lung cancers by lobe in 131 male workers at Mayak and in 178 men who had never worked at Mayak. As the average age of the study group (56.7 years) was lower than that of the control group (61.7 years), an additional, smaller control group (97 subjects) of an average age of 56.3 years was used. Of the 131 Mayak workers, 24 were exposed only to external γ-radiation (average dose, 0.58 Gy) and constituted an additional control group. Only 1% of the study subjects had never smoked, 14% had stopped smoking more than five years previously, and 85% were current smokers. The study and control cases were examined in the same pathology laboratory. The authors noted that the lung cancers in the study subjects were located in the lower lobe more frequently (45%) than in either of the control groups (25%), although the lung content of plutonium is higher in the upper lobe of the lung (Plotnikova, 1965).

Tokarskaya *et al.* (1995, 1996b) described the distribution of lung cancers by histological type in Mayak workers (168 cases: 154 men, 14 women) and in unexposed population controls (157 control cases: 144 men, 13 women). All the cases (both study and control) occurred between 1966 and 1991, and the age range was similar. The study cases were divided into two groups, consisting of 125 cases in workers with a plutonium body burden of ≤ 11.0 kBq, and 43 workers with a plutonium body burden of > 11.0 kBq. All cases were examined histologically at the same laboratory. In doubtful cases, the histological type was determined by two or three pathologists at the laboratory. Histological types were classified in the WHO classification (WHO, 1982). The percentage of adenocarcinomas was higher in the workers (46%) than in the unexposed population (33%) (Table 52), and the highest percentage of adenocarcinomas (74%) was found among workers with plutonium body burdens of > 11.0 kBq.

Table 52. Distribution of histological types of lung cancer in exposed and unexposed workers at the Mayak nuclear complex

Histological type	Unexposed population (control)	Exposed workers		
		Group 1 (≤ 11.0 kBq)	Group 2 (> 11.0 kBq)	Total
Adenocarcinoma	52 (33%)	46 (37%)	32 (74%)	78 (46%)
Squamous-cell	54 (34%)	42 (34%)	5 (12%)	47 (28%)
Small-cell	36 (23%)	29 (23%)	3 (7%)	32 (19%)
Large-cell	15 (10%)	8 (6%)	3 (7%)	11 (7%)
Total	157	125	43	168

From Tokarskaya *et al.* (1995, 1996b)

Tokarskaya *et al.* (1995, 1996b) also evaluated the associations between different histological types of lung cancer and a number of radiation- and non-radiation-related factors. They reported that plutonium-related factors were most strongly associated with adenocarcinoma: the adjusted odds ratio for plutonium deposition was 4.0 (95% CI, 2.1–7.6) and that for plutonium-associated pulmonary sclerosis was 2.9 (95% CI, 1.0–8.4). The authors indicated that the latter condition was highly correlated with the level of plutonium deposition and that it was difficult to discriminate between the effects of these two factors. By excluding pulmonary sclerosis from the model, they obtained an adjusted odds ratio for plutonium deposition of 6.9, (i.e. the sum of the odds ratios for the two variables). The adjusted odds ratios for smoking and exposure to external γ-radiation were 4.3 (95% CI, 1.9–9.9) and 1.9 (95% CI, 0.99–3.5), respectively. For squamous-cell carcinoma, the association with plutonium-related factors was weaker. The adjusted odds ratio for plutonium deposition was 4.2 (95% CI, 1.4–12.8), and the association with pulmonary sclerosis was not statistically significant. The adjusted odds ratio for smoking was 6.8 (95% CI, 1.2–39).

Koshurnikova and Nifatov (1978) evaluated autopsy records for Mayak workers who had died over a period of 27 years. The records were divided into two groups: those of 408 deceased individuals (341 men, 67 women) who had been exposed to plutonium and external γ-radiation, and those of 337 individuals (290 men, 47 women) who had been exposed only to γ-radiation. The number of lung cancer deaths was 31 in the first group and 15 in the second, and the percentage of cancers located in the lower lobe of the lung was 29% in the first group and 13% in the second. The percentage of adenocarcinomas was higher in the first group (42%) than in the second group (27%). Koshurnikova *et al.* (1995) studied the distribution by histological type of lung cancers that occurred in workers at the radiochemical and plutonium production plants and in workers at the nuclear reactors. They found that the proportion of adenocarcinomas was higher among workers at the radiochemical and plutonium production plants (43.3%) than among reactor workers (23.8%); however, the percentage of adenocarcinomas in the control group of workers exposed to external and internal radiation within the radiation protection limits was almost as high as that in the radiochemical and plutonium plants workers (40.8%). [The Working Group noted that the numbers of histologically confirmed cases, on which the percentages are based, are not listed in the paper.] The authors also reported that the degree of differentiation of lung cancer was dose-dependent: poorly differentiated adenocarcinomas were diagnosed in individuals exposed to doses to the lung of > 10 Sv (a radiation weighting factor of 20 was used), while highly differentiated adenocarcinomas were diagnosed in individuals with an average dose to the lung of 2.35 Sv. Poorly differentiated squamous-cell carcinomas developed after a dose to the lung of 6.9 Sv and highly differentiated keratinizing squamous-cell carcinomas after a dose of 0.4 Sv. [The Working Group noted that no numbers were provided to support these statements.]

(*b*) *Bone tumours*

A case of osteosarcoma in a female worker at the plutonium production plant was described in 1964 by Z. Bukhtoyarova [cited by Pesternikov *et al*. (1972)]. The tumour was detected in the rib and femur 12 years after the first exposure to plutonium. The plutonium content estimated *post mortem* was 7.25 μCi [268.3 kBq] in the body and 5.61 μCi [207.6 kBq] in the skeleton. The dose to the rib was estimated to have been 320 rad [3.2 Gy], that to the spongy bone of the femur metaphysis, 204 rad [2.04 Gy], and that to the compact bone of the femur, 307 rad [3.07 Gy]. Another case was described by Pesternikov *et al.* (1972) in a woman who had worked at the plutonium production plant for nine years and who had been exposed to both soluble and relatively insoluble plutonium compounds. The woman had left her job after pulmonary sclerosis was diagnosed, and the tumour in the rib was diagnosed 11 years after the end of occupational exposure and 20 years after the first exposure to plutonium. The tumour was described histologically as a combination of a spindle-cell sarcoma and a malignant 'osteoblastoclastoma' [perhaps a fibroblastic spindle-cell sarcoma]. The plutonium content was estimated to be 2.6 μCi [96.2 kBq] in the body and 2.2 μCi [81.4 kBq] in the skeleton, and the estimated dose to the bone was 430 rad [4.3 Gy].

A report by Koshurnikova *et al*. (1973) included the two cases described above and a newly diagnosed case. Additional information on the two cases described previously revealed that the total dose of external γ-radiation had been 3.8 Gy in the first case and 1.7 Gy in the second. In the second case, the tumour recurred 1.5 years after surgical removal, resulting in death, and was found to be a spindle-cell sarcoma. The third case occurred in a female worker at the plutonium production plant 22 years after her first occupational exposure to plutonium. The tumour was located in the upper part of the shin and was an osteoblastic sarcoma mainly of the osteolytic type. The plutonium content was 2.55 μCi [94.4 kBq] in the body and 1.9 μCi [70.3 kBq] in the skeleton, and the absorbed dose to the skeleton was 640 rad [6.4 Gy]. Histoautoradiography showed diffuse tracks of α-particles in the endosteum and bone marrow in all three cases. In the cortical bone, the tracks were oriented around haversian canals. In the third case, the remains of the old bone plates were seen in the tumour tissue, and on the autoradiograms the diffuse tracks of α-particles corresponded to these plates. Some diffuse tracks were found in the connective tissue surrounding tumour nodules. No tracks of α-particles were found in the tumour cells.

All cases of malignant bone neoplasm detected in the cohort of Mayak workers between 1948 and 1996 were summarized by Koshurnikova *et al.* (2000). The authors based their analysis on the cohort of about 11 000 workers initially employed in one of the main Mayak plants in 1948–58. The procedures for determining vital status and cause of death and the sources of information on exposure to radiation in this cohort are described in the section on lung cancer. Statistical analyses were conducted by Poisson regression methods. During 1948–96, 27 cases of malignant neoplasms (bone and soft-tissue tumours; ICD-9 codes, 170–171) occurred, 19 of which were bone and cartilage

neoplasms (16 osteosarcomas, three chondrosarcomas) coded 170; the other eight cases were soft-tissue neoplasms (ICD-9 code 171), comprising one fibrosarcoma, three synovial sarcomas and four myosarcomas. In three cases, the bone tumour was not the underlying cause of death described on the death certificate, and these three cases were excluded from comparisons with national statistics. [The Working Group noted that the high rate of autopsy of deceased Mayak workers, in contrast to national rates, makes comparisons, even when based on death certificate information, problematic because of diagnostic bias.] Finding an appropriate external control group was difficult, since age- and sex-specific mortality rates from bone cancer (ICD 170) in the Russian Federation were available only for 1990–94 and were combined with the rates for soft-tissue cancers (ICD 171). Three approaches were used. Deaths in which bone or soft-tissue cancer was given as the cause on the death certificate were compared with those expected calculated from both Russian rates (age- and sex-specific for 1990–94) and rates in the USA (age-, sex- and calendar year-specific) for the combined category of bone and soft-tissue cancer. Deaths in which bone cancer was given as the cause on the death certificate were compared with those expected calculated from bone cancer rates in the USA. Partly because of the limitations of external rates and the possibility of diagnostic bias, internal comparisons by plant, external dose and body burden were also carried out. For these analyses, deaths in which bone cancer was considered to be either the underlying or the contributing cause were included. In addition, four deaths in which soft-tissue cancer in tissue very close to the bone (three synovial sarcomas, one fibrosarcoma) was an underlying or contributing cause (one death) were included. The analyses consisted of evaluations of the effects of exposure to plutonium with adjustment for the possible effects of external dose. The excess number of cases resulting from exposure was estimated by the linear relative risk model. Analyses of the effects of exposure to plutonium were limited to cases in which the body burden had been estimated, expressed in kBq. Of 8048 radiochemical and plutonium plant workers of known vital status, 2772 were monitored for exposure to plutonium. These workers and workers in the reactor plant, who had no potential exposure to plutonium, were considered to have ‘known’ plutonium body burdens, while the remaining workers were considered to have ‘unknown’ body burdens. The distribution of workers and bone tumours by plutonium body burden and external dose of γ-radiation is shown in Table 53. With all three external comparisons, the SMRs were significantly elevated for men and women: for codes 170–171, 1.8 (95% CI, 1.2–2.6) based on Russian rates and 3.1 (95% CI, 2.0–4.6) based on rates in the USA, for ICD 170, 6.6 (95% CI, 3.9–10) based on rates in the USA. The highest risk for bone cancer was noted among plutonium plant workers, with a SMR of 2.7 (95% CI, 1.4–4.7), while the SMR for the reactor plant workers was 1.3 (95% CI, 0.5–2.9), and that for the radiochemical plant workers was 1.4 (95% CI, 0.6–2.6). The SMRs for women were more than twice those for men, due, according to the authors, to the fact that both the Russian rates and rates in the USA for women were lower than those for men. The results of the internal comparisons by plant and level of exposure are shown in Tables 54 and 55. The relative

Table 53. Numbers of workers, numbers of bone tumours and mean external dose by category of plutonium monitoring and external dose among workers at the Mayak nuclear complex

Exposure	All workers		Men		Women	
	No. of workers (bone tumours [a])	Mean dose[b] (Sv)	No. of workers (bone tumours[a])	Mean dose[b] (Sv)	No. of workers (bone tumours[a])	Mean dose[b] (Sv)
Plutonium body burden (kBq)						
Known						
0	3314 (4, 0)	0.81	2418 (3, 0)	0.93	896 (1, 0)	0.51
> 0–1.48	1297 (0, 2)	1.55	856 (0, 2)	1.48	441 (0, 0)	1.68
1.48–7.40	659 (1, 0)	1.74	495 (0, 0)	1.95	164 (1, 0)	1.10
≥ 7.40	251 (3, 0)	2.24	180 (1, 0)	2.36	71 (2, 0)	1.93
Subtotal	5521 (8, 2)	1.16	3949 (4, 2)	1.24	1572 (4, 0)	0.96
Unknown[c]						
Radiochemical	3134 (6, 0)	1.35	2262 (5, 0)	1.40	872 (1, 0)	1.22
Plutonium	2142 (6, 1)	0.40	1465 (2, 0)	0.40	677 (4, 1)	0.40
Subtotal	5276 (12, 1)	0.96	3727 (7, 0)	1.01	1549 (5, 1)	0.86
External dose[b] (Sv)						
Unmonitored	1416 (2, 0)	0.00	836 (1, 0)	0.00	580 (1, 0)	0.00
> 0, < 0.1	1182 (0, 1)	0.04	814 (0, 1)	0.04	368 (0, 0)	0.04
0.1–1	4290 (6, 0)	0.47	3093 (4, 0)	0.47	1197 (2, 0)	0.45
1–3	2955 (8, 1)	1.79	2203 (3, 1)	1.80	752 (5, 0)	1.77
≥ 3	954 (4, 1)	4.35	730 (3, 0)	4.38	224 (1, 1)	4.29
Total	10 797 (20, 3)	1.07	7676 (11, 2)	1.13	3121 (9, 1)	0.91

From Koshurnikova *et al.* (2000)

[a] The first number is the number of bone tumours indicated as the cause of death on the death certificate; the second is the number of bone tumours indicated as a contributing cause of death on the death certificate.

[b] External γ-radiation dose; the dose for the two years preceding the end of follow-up was excluded.

[c] Workers in the radiochemical and plutonium plants who had not been monitored before 1996; 493 of these workers were monitored in 1996 or later.

Table 54. Numbers of person–years and bone tumours and relative risks (with 95% confidence interval [CI]) by plant at the Mayak nuclear complex

Plant	No. of person–years (no. of bone tumours)	Relative risk[a] (95% CI)
Reactor	110 043 (4)	1.0
Radiochemical	193 421 (8)	1.2 (0.4–4.6)
Plutonium	124 036 (11)	2.4 (0.8–8.8)

From Koshurnikova *et al*. (2000)
[a] Stratified by age, calendar year and sex

Table 55. Numbers of person–years and bone tumours and relative risks (with 95% confidence interval [CI]) by category of plutonium body burden at the Mayak nuclear complex

Plutonium exposure and/or type of plant	No. of person–years (no. of bone tumours)	Relative risk[a] (95% CI)
Body burden (kBq)		
0–1.48	162 540 (6)	1.0
1.48–7.40	15 614 (1)	0.9 (0.05–5.5)
≥ 7.40	4 410 (3)	7.9 (1.6–32)
Unknown		
Radiochemical	149 878 (6)	1.4 (0.4–4.7)
Plutonium	97 058 (7)	4.1 (1.2–14)

From Koshurnikova *et al*. (2000)
[a] Stratified by age, calendar year and sex and adjusted for external dose as a linear variable

risks by plant (Table 54), not adjusted for external dose or plutonium exposure, suggest higher risks for workers in the plutonium plant. The analyses of relative risks by category of plutonium body burden, adjusted for external dose by its inclusion as a linear variable, indicated elevated risks among workers with estimated body burdens > 7.4 kBq (Table 55). The three cases of bone tumours in which the body burdens of the patients exceeded 7.4 kBq (47.8, 93.7 and 114.0 kBq) had estimated doses to the bone surface of 35, 60 and 78 Gy, respectively. An elevated risk was also found for plutonium plant workers who were not monitored for exposure to plutonium, some of whom may also have had large but unmeasured burdens. There was little evidence of an elevated risk for workers who were not monitored for plutonium in the

radiochemical plant. On the basis of the results of the external and internal comparisons, the authors concluded that the risks for bone tumours in the Mayak worker cohort were related to exposure to plutonium.

(*c*) *Liver tumours*

The first report on malignant liver tumours in Mayak workers exposed to plutonium appeared in 1978 (Migunova *et al*., 1978). The authors described three cases of liver haemangiosarcoma in female workers at the plutonium production plant (Table 56). In view of the high body burdens of plutonium, the high absorbed doses to the liver in all three cases and information from the literature on liver haemangiosarcomas in Thorotrast-treated patients (see section 2.3.2(*a*)), the authors concluded that these tumours had been induced by α-particles from deposited plutonium.

Shilnikova *et al.* (1995), in the study described in detail on the section on lung cancer, reported the mortality rate from malignant liver tumours in the Mayak worker cohort of 11 847 persons (8399 men, 3448 women) who started work at the nuclear reactor, the radiochemical plant and the plutonium production plants between 1948 and 1958. As of 1 January 1993, the vital status was known for 10 151 individuals (85.7%). Forty-eight persons had died from liver tumours (32 men, 16 women). Thirty-six of these 48 persons had worked at the radiochemical and plutonium production plants and had potential exposure to plutonium. A total of 2412 individuals (1662 men, 750 women) were monitored for plutonium: the average equivalent dose of α- and γ-radiation to the liver was 7.25 Sv for men and 11 Sv for women. For the 1888 persons exposed to doses < 7.5 Sv, the contribution of α-particles and γ-radiation was almost equal, while for the 524 persons exposed to doses > 7.5 Gy, α-particles contributed about 80% of the total equivalent dose to the liver. Eighteen deaths from liver neoplasms occurred among workers monitored for plutonium (eight men, 10 women). The expected numbers of deaths were calculated on the basis of age- and sex-specific mortality rates in the group of 9695 workers whose average annual doses were lower than those permitted at the time. [The Working Group noted that this group is not clearly defined. Since only 20% of the workers were monitored for plutonium, some individuals with a high, but unmeasured plutonium body burden might be included in this group. The annual dose of external radiation averaged over several years does not reflect the actual annual dose, which could be much higher than the maximum permissible dose in the early years of operation at the Mayak nuclear complex.]

The relative risk for liver neoplasms was significantly increased only among female workers at the plutonium production plant (Table 57). [The Working Group noted that one explanation for this finding is that women have fewer liver cancers than men.] The authors reported that female workers at the plutonium production plant had the highest doses from plutonium, with an average dose to the liver of 20.5 Sv, while the dose of male workers at the same plant was 8.8 Sv. The average doses to the liver of male and female workers at the radiochemical plant were 6.5 Sv and 5.0 Sv, respectively. These doses apply only to workers who were monitored for plutonium, who were those in jobs

Table 56. Characteristics of three cases of liver haemangiosarcomas among women at the Mayak nuclear complex

Duration of contact with plutonium (years)	Dose of external γ-radiation	Plutonium body burden	Dose to the liver from plutonium (Gy)	Age at death (years)	Time between first exposure and death (years)	Diagnosis
6	218 rad [2.2 Gy]	1.8 μCi [66.6 kBq]	5.64	57	24	Haemangiosarcoma of the liver
5	149 rad [1.5 Gy]	5.8 μCi [214.6 kBq]	5.62	46	23	Haemangiosarcoma of the liver
5	94 rad [0.94 Gy]	2.1 μCi [77.7 kBq]	5.42	49	22	Haemangiosarcoma of the liver and spleen

Data from Migunova *et al*. (1978)

Table 57. Mortality from malignant liver tumours among workers at the Mayak nuclear complex

Deaths	Sex	Plant			Total
		Reactor	Radiochemical	Plutonium production	
Observed	M	10	13	9	32
	F	2	2	12	16
Expected	M	6.90	8.73	6.29	21.9
	F	1.08	2.05	1.50	4.61
Observed/expected	M	1.45 (0.55–3.81)	1.49 (0.63–3.51)	1.43 (0.52–3.96)	1.46 (0.85–2.51)
(95% confidence interval)	F	1.86 (0.18–19.3)	0.98 (0.14–6.86)	8.01 (1.47–43.7)	3.47 (1.23–9.76)

From Shilnikova *et al*. (1995)

with the greatest likelihood of exposure to plutonium. Thus, if all the workers at the plutonium production and radiochemical plants were examined, their average doses would be lower, but the ratio of doses by sex and plant would be similar. Histological diagnoses were available for 30 of the 48 cases of liver tumours: 53% were hepatocellular carcinoma, 16.7 % were cholangiocellular carcinoma and 26.7% were haemangiosarcoma. Of the eight haemangiosarcomas, six were diagnosed in female workers. The haemangiosarcomas occurred only in persons who were exposed to plutonium. The average dose to the liver in these cases was 150 Sv.

The most recent report (Gilbert *et al*., 2000) was based on a cohort of about 11 000 workers who had started working at the Mayak nuclear complex in 1948–58. The methods of analysis used are similar to those of Koshurnikova *et al.* (2000). A total of 2207 workers (1531 men, 676 women) were monitored for plutonium and had detectable body burdens. The mean dose to the liver for these workers was 0.60 Gy (0.47 Gy for men, 0.88 Gy for women). The highest doses to the liver were received by female workers at the plutonium plant, with a mean of 1.74 Gy. The mean dose for male workers at the plutonium plant was 0.72 Gy, and those for female and male workers at the radiochemical plant were 0.24 Gy and 0.33 Gy, respectively. Sixty cases of liver tumours occurred during the period 1948–96, 13 in reactor workers, 19 in radiochemical plant workers and 28 in plutonium plant workers. In four cases, liver cancer was not recorded as the underlying cause of death on the death certificate. Since mortality rates from liver cancer in the Russian Federation were not available, comparisons were made with the incidence rates for 1990–94. Since liver cancer is nearly always fatal, the authors considered that the incidence rates should not differ greatly from the mortality rates. As the comparisons were based on incidence rates, the analyses included all liver cancers, regardless of whether they were considered to be the cause of death. [The Working Group noted that Mayak workers who died were more likely to have been autopsied and the causes to have been better diagnosed than for the general population, so that some bias due to surveillance is possible.] The internal comparisons also included all diagnoses. There was clear evidence of an excess risk for workers at the plutonium plant (SMR, 2.8; 95% CI, 1.9–3.9) and for the 23 workers with detectable plutonium burdens (SMR, 3.4; 95% CI, 2.2–5.0). The SMR for all women (n = 19) (3.0; 95% CI, 1.9–4.6) was twice that for men (n = 41) (1.5; 95% CI, 1.1–2.0). In the authors' opinion, the difference in risk between men and women might result from the larger plutonium burdens and lower baseline risks of women than of men. The authors noted that comparing mortality from liver cancer with the Russian incidence rate might have introduced bias, although they considered that bias could not explain the elevated SMRs entirely. The results of the internal comparisons also showed an excess risk for liver tumours in plutonium-exposed workers (Tables 58 and 59). The relative risks by plant (Table 58), not adjusted for external dose or exposure to plutonium, indicated an elevated risk for workers at the plutonium plant; the risk for women at this plant was higher than that for men. The analyses of relative risks by category of plutonium body burden, adjusted for external dose by including it as a

Table 58. Numbers of person–years, liver tumours and relative risks (with 95% confidence interval [CI]) by plant at the Mayak nuclear complex

Plant	All workers		Men		Women	
	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)
Reactor	110 043 (13)	1.0	80 108 (11)	1.0	29 935 (2)	1.0
Radiochemical	193 421 (19)	1.0 (0.5–2.1)	131 925 (17)	1.2 (0.6–2.7)	61 496 (2)	0.5 (0.06–4.1)
Plutonium	124 036 (28)	2.1 (1.1–4.1)	81 144 (13)	1.3 (0.6–3.0)	42 891 (15)	5.2 (1.5–33)

From Gilbert *et al*. (2000)

[a] Stratified by age, calendar year and sex

Table 59. Numbers of person–years, liver tumours and relative risks (with 95% confidence interval [CI]) by category of plutonium body burden at the Mayak nuclear complex

Plutonium body burden (kBq)	All workers		Men		Women	
	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)
Known						
0–1.48	162 540 (16)	1.0	112 996 (14)	1.0	49 544 (2)	1.0
1.48–7.40	15 614 (4)	1.5 (0.4–4.2)	11 278 (2)	0.9 (0.1–3.2)	4 336 (2)	7.1 (0.9–59)
≥ 7.40	4 410 (16)	17 (8.0–36)	3 159 (7)	9.2 (3.3–23)	1 252 (9)	66 (16–453)
Unknown						
Radiochemical	147 878 (10)	1.0 (0.4–2.2)	101 801 (9)	1.1 (0.5–2.6)	46 078 (1)	0.6 (0.03–6.1)
Plutonium	97 058 (14)	2.8 (1.3–6.2)	63 944 (9)	2.0 (0.8–4.8)	33 114 (5)	13 (2.4–94)

From Gilbert *et al*. (2000)

[a] Stratified by age, calendar year and sex and adjusted for external dose as a linear variable

linear variable (Table 59), indicated elevated risks among workers with estimated body burdens > 7.4 kBq; this relative risk was also larger for female than for male workers, and an elevated risk was found for female plutonium plant workers who were not monitored for exposure to plutonium. Information on histological type was available for 44 of the 60 tumours: 24 were hepatocellular carcinoma, eight were cholangiocellular carcinoma, 10 were haemangiosarcoma and two were tumours of an undifferentiated cell type. All 10 of the haemangiosarcomas occurred among workers with detectable plutonium burdens, and eight of them occurred in women. On the basis of external and internal comparisons, the authors concluded that the increased risks for liver tumours in Mayak workers were related to exposure to plutonium.

2.4.4 *Americium*

All plutonium contains some americium-241 (^{241}Am; half-life, 432.2 years), which contributes to the overall dose. It is a product of neutron interactions with ^{241}Pu that has not been totally separated from ^{239}Pu or ^{238}Pu. For example, ^{239}Pu often contains 5–15% ^{241}Am by activity. The radiation doses from ^{241}Am, if significant, are calculated separately from those of plutonium and are usually not included with the doses of plutonium in epidemiological studies. Chemically, ^{241}Am is more soluble and is transported more rapidly from wounds or the lung to the liver or bone than plutonium. Accidental exposure to essentially pure ^{241}Am has occurred, the most notable being an accident at the nuclear weapons site in Hanford, Washington, USA, involving a chemical explosion in a glove box (Toohey & Kathren, 1995). A 64-year-old chemical operator received massive percutaneous exposure to ^{241}Am from contaminated glass shards and nitric acid. A four-year intensive course of calcium trisodium diethylenetriamine pentaacetate (DTPA) and then of the zinc salt of DTPA prevented deposition in the internal organs of 99% of the ^{241}Am that entered the blood. The total amount of ^{241}Am excreted in his urine and faeces was 41 MBq (Breitenstein & Palmer, 1989). The cumulative absorbed doses to the bone, bone surface, liver and lung were 18, 520, 8 and 1.6 Gy, respectively (Toohey & Kathren, 1995). The health problems attributed to this radiation dose were thrombocytopenia and leukopenia. The man died 11 years later from pre-existing cardiovascular disease (see also section 1.2.2(i)).

2.4.5 *Summary*

Studies of plutonium workers in the United Kingdom and the USA provide little evidence that exposure to this radionuclide is carcinogenic to humans, largely because of the relatively low levels of exposure of these working populations, i.e. only a small proportion of workers had measured body burdens of plutonium > 1 kBq. In contrast, clear excesses of cancers of the lung, bone and liver were reported among Russian men and women who worked at the Mayak nuclear complex in the southern Urals. The risk was concentrated among workers who had first been employed in 1948–58 and who

had inhaled or ingested large quantities of plutonium, a significant number of workers having body burdens > 3 kBq. The estimated equivalent dose to the lung for some workers, for example, was > 80 Sv (assuming a radiation weighting factor of 20). There was little evidence that significant effects occurred at doses below about 3 kBq, but statistically significant risks were seen at the higher exposure levels. While the risks are difficult to quantify because of limitations in dosimetry and incomplete ascertainment of vital status and information on important confounders such as smoking, the demonstration of dose–response relationships for different cancer types over a broad range of doses in both men and women provides strong evidence that exposure to plutonium at sufficiently high levels is associated with an increased risk for cancer.

2.5 Uranium

Uranium is a radioactive heavy metal which occurs commonly in small amounts in all rock, soil and other natural materials. Naturally occurring uranium consists of a mixture of three radioactive isotopes, ^{234}U (0.006%), ^{235}U (0.72%) and ^{238}U (99.27%), which have half-lives of 2.4×10^5, 7.0×10^8 and 4.5×10^9 years, respectively. Natural uranium decays mainly through emission of α-particles (see Table 7 of General Remarks). The very long half-life of ^{238}U, the most abundant isotope, results in a very low decay rate per unit mass of uranium. Because of the high percentage of ^{238}U and its slow decay rate, naturally occurring uranium is, in fact, one of the least radioactive of the unstable isotopes.

Uranium is mined from natural deposits containing concentrations ranging from 0.05% to tens of per cent by mass. These deposits, called uranium ore, are typically found in sandstone formations.

Several studies have been conducted of uranium millers and of individuals involved in other uranium processing operations. Study of these individuals is often complicated by external exposures, and even in cases where there may be internal deposition, internal exposure has not always been estimated. These workers are not exposed to high concentrations of radon gas in air but may be exposed to α- and β-particles from inhaled or ingested uranium dust. Inhalation of insoluble uranium particles is the major pathway for exposure of the lung. As these studies involve persons selected for employment, their mortality rate might be expected to be lower than that of the general population (i.e. the 'healthy worker effect'. [The Working Group noted that the SMRs of an exposed cohort is about 0.7–0.9 when compared with a general population which includes some disabled or ill persons who would not be in an employed population.])

In a retrospective cohort study of mortality in 995 white men who had been employed for more than 30 days at a uranium processing facility in upstate New York, USA, between 1943 and 1949, the association between an increase in mortality rates and long-term occupational exposure by inhalation to uranium compounds was investigated (Dupree *et al*., 1987). Two comparison groups were used: the white male population of the USA and the white male populations of the New York counties of Erie and

Niagara. Vital status was known for 94.3% of the men through 31 December 1979. When the national comparison group was used, statistically significantly increased SMRs were observed for all causes of death (SMR, 1.18; 95% CI, 1.07–1.30, 429 deaths), laryngeal cancer (SMR, 4.47; 95% CI, 1.44–10.43; five deaths), all circulatory disease (SMR, 1.18; 95% CI, 1.04–1.35, 227 cases), arteriosclerotic heart disease (SMR, 1.19; 95% CI, 1.01–1.39, 159 cases), all respiratory disease (SMR, 1.52; 95% CI, 1.04–2.14, 32 cases) and pneumonia (SMR, 2.17; 95% CI, 1.26–3.47, 17 cases). No association was found with length of employment or work in the most hazardous areas of the plant. The rate of death from lung cancer was not increased (SMR, 0.97; 95% CI, 0.60–1.48, 21 cases). The internal doses from uranium were given only for the lung: 40% of the cohort received 10–100 mSv/year and 38% received > 100 mSv/year; the remainder of the cohort received < 10 mSv/year, or the value was unknown. The comparison with regional rates gave similar results.

Polednak and Frome (1981) described the mortality rates in a cohort of 18 869 white men who had been employed between 1943 and 1947 at a uranium conversion and enrichment plant in Oak Ridge, Tennessee, USA, and followed-up until 1974. Workers in certain departments (especially chemical workers) were exposed to high average air concentrations of uranium dust (up to 500 $\mu g/m^3$ of air in 1945). In comparison with mortality rates for white men in the USA, the SMRs for various causes in the entire cohort were generally < 1.00. After correction for unascertained deaths and missing death certificates, the SMR for lung cancer was 1.22 (95% CI, 1.10–1.36). Adequate data on smoking habits were not available in this study. The SMRs for various causes, including lung cancer, did not tend to be higher among 8345 workers who were employed in areas where uranium dust was present or among 4008 of these 8345 workers who were employed for one year or longer at the plant. The SMRs for other causes of death, such as bone cancer, leukaemia and diseases of the respiratory and genitourinary systems were not significantly increased. [The Working Group noted that no estimates of dose were included in the analyses.]

A retrospective cohort study was conducted among 6781 white male employees who had worked at the Oak Ridge Y-12 nuclear material fabrication plant for at least 30 days during 1947–74; vital status was determined for 6477 workers, and the cohort was followed-up until the end of 1979 (Checkoway *et al.*, 1988). Among 3490 monitored workers, the mean cumulative α-particle dose to the lung was 82 mSv (range, 0–3.1 Sv), and the mean cumulative external whole-body penetrating dose from γ-radiation was 9.6 mSv (0–4.3 Sv). When compared with the rates for white men in the USA, the mortality rates from all causes combined, cardiovascular diseases and from most site-specific cancers were decreased. Increased rates of cancers of the lung, brain and central nervous system were seen in comparison with national and State rates. Dose–response trends were detected for death from lung cancer with respect to cumulative exposure to α-particles and γ-radiation, the most pronounced trend being found for exposure to γ-radiation among workers who received ≥ 0.05 Sv of α-particles. These trends became smaller when a 10-year latency was assumed.

When no latency was assumed, the rate ratio for death from lung cancer associated with exposure to both types of radiation at ≥ 0.05 Sv compared with < 0.01 Sv was 4.60 (95% CI, 0.91–23.4), while the corresponding result when a 10-year latency was assumed was 3.05 (95% CI, 0.37–24.8). No dose–response trend in mortality from brain or central nervous system cancer was found.

The association between exposure to uranium dust and death from lung cancer was investigated among workers who had been employed for at least 183 days in any of four uranium processing or fabrication plants located in Missouri (Mallinckrodt, 1942–1966), Ohio (Fernald, 1951–1989) or Tennessee (Tennessee Eastman (same facility as studied by Polednak & Frome, 1981) and Y-12 (same facility as studied by Checkoway *et al.*, 1988), USA (Dupree *et al.*, 1995). Among workers who had potentially been followed-up for at least 30 years, 787 deaths from lung cancer were identified from death certificates. One control was matched to each case on race, sex and birth and hire dates within three years. Health physicists estimated the annual doses to the lung from exposure primarily to insoluble uranium compounds for each person on the basis of data on air concentrations or, in the case of the Y-12 workers, by urine analysis and whole-body counting. External dosimetry records were available for only 54% of the years of employment. The health physicists assigned annual external radiation doses to workers for whom personal monitoring records were available. With a 10-year lag, the cumulative doses to the lung ranged from 0 to 1.4 Gy (internal and external radiation) for cases and from 0 to 0.8 Gy for controls. Archivists collected information on smoking from occupational medical records for 48% of the cases (91% of whom were smokers) and 39% of the controls (75% of whom were smokers). The odds ratios for death from lung cancer for seven groupings of the cumulative internal dose to the lung showed no increase in risk with increasing dose. There was a suggestion of an effect of exposure for workers who had been hired at the age of 45 years or older. Further analyses with the cumulative external doses of thorium, radium and radon did not reveal a clear association between exposure and increased risk, nor did categorization of the workers by facility. In a re-analysis of workers employed at Fernald, Ritz (1999) found no significant association between risk for lung cancer and internal dose of α-particles ≥ 200 mSv, lagged by 15 years (RR, 1.92; 95% CI, 0.53–6.96).

A number of other studies have been carried out of uranium workers (Archer *et al.*, 1973; Waxweiler *et al.*, 1983; Teta & Ott, 1988; Loomis & Wolf, 1996; Frome *et al.*, 1997), but they do not provide information explicitly on the effects of internal exposure.

Some studies of workers in uranium processing plants thus showed an elevated rate of mortality from lung cancer, but the finding was not consistent in all studies. The doses to the lung were relatively low. The rates of death from cancers at other sites were increased in some studies, but the small number of cases and lack of consistency between the findings reduce their significance. [The Working Group noted that the studies of exposure to uranium are hampered by limitations in measurements of

radiation dose, potential concomitant exposure to other chemicals, possible modification of health effects with age at exposure and confounding by smoking.]

2.6 Polonium

Polonium occurs in nature as a radioactive decay product of uranium, thorium and actinium and also in tobacco smoke. The commonest natural isotope of polonium, ^{210}Po, has a half-life of 138.4 days and has an effective biological half-time of 46 days. It is a pure α-particle emitter with an α-particle energy of 5.3 MeV. It has limited industrial application. Small encapsulated sources have been used to eliminate static electricity generated in such processes as paper rolling, the manufacture of sheet plastics and the spinning of synthetic fibres. It is also used on brushes for removing dust from photographic film and in nuclear physics as a source of α-particles. Mixtures of polonium with beryllium and other light elements are used as sources of neutrons, and the greatest risk of exposure to polonium occurs during production of these sources. Roasting of phosphate ores in the manufacture of some fertilizers volatilizes the natural polonium found in these ores into an aerosol waste.

A few epidemiological studies have been conducted of workers in the United Kingdom and the USA. Beral *et al.* (1988) studied 22 552 workers who had been employed by the Atomic Weapons Establishment between 1951 and 1982. Among 9389 workers who had a record of exposure to radiation, only 638 (17%) were monitored for possible internal exposure to polonium. The incidence of cancer of the kidney (three cases) among those monitored for polonium was statistically significantly elevated ($p < 0.05$), with a SMR of 5.8 [95% CI not given]. Many workers were monitored for more than one radionuclide, and no internal doses were available to assist in interpreting this finding.

Wiggs *et al.* (1991) studied a cohort of 4402 white men employed at the Mound Facility (Dayton, Ohio, USA) during the period 1944–72, when ^{210}Po was processed and Po–Be neutron sources were manufactured. Mortality rates were evaluated by two analytical methods: SMRs with external comparison populations and a dose–response analysis with internal comparisons. The death rates of white men in the country as a whole and of white men in Ohio were used to calculate the SMRs. When the rates for all white males in the USA were used, the SMR for death from any cause among 2181 ^{210}Po-monitored workers was 0.92 (90% CI, 0.85–0.98), and that for death from any cancer was 1.01 (90% CI, 0.87–1.17). The SMRs for specific cancers were not significantly increased. That for kidney cancer ($n = 2$) was 0.63 (90% CI, 0.11–1.98), and that for all genitourinary disease was not significantly increased (SMR, 1.30; 90% CI, 0.73–2.16). The SMRs based on rates for white males in Ohio were similar. Dose–response analyses were carried out on data for men monitored for polonium by analysis of urinary excretion, according to the model recommended by the ICRP (1968). Four categories of polonium dose were used: < 10 mSv, 10–99.9 mSv, 100–999.9 mSv and ≥ 1000 mSv. In order to assess potential confounding from exposure to external

radiation, the cumulative doses of external radiation of persons in the four dose categories were assessed; no significant differences were observed. The mean external doses of radiation in the four categories ranged from 26.5 mSv to 36.1 mSv. Therefore, external ionizing radiation is not important in interpreting the results of the polonium dose–response analyses. The dose–response analyses were limited to the 2181 monitored persons for whom estimates of ^{210}Po dose were available. For two- and five-year latent periods, Mantel-Haenszel relative risks and ungrouped trend statistics were calculated for all causes, all cancers and lymphatic and haematopoietic cancers combined. No significant positive dose–response trends were observed. When a 10-year latency was used, all the cancer-specific trends were negative, except that for cancer of the pancreas, but none of the trends was statistically significant. The results of this study do not support an association between dose of ^{210}Po and mortality from any cancer or any specific cancer. [The Working Group noted that a limitation of this analysis is that measured annual doses of polonium were not available. Annual doses were assigned by evenly partitioning the cumulative dose of an individual between the dates of the individual's first and last monitoring assay, which probably resulted in misclassification of doses across person–years. The dosimetry was complex and subject to substantial uncertainty.]

2.7 Iodine

The only radionuclides that are actively absorbed in the thyroid gland are the radioiodines. The euthyroid thyroid gland absorbs 20–30% of ingested ^{131}I, but a patient with hyperthyroidism could absorb as much as 60%, and none might be absorbed after administration of stable iodine. ^{131}I is essentially a β-particle emitter, contributing 85% of the absorbed tissue dose, while the contribution of γ-radiation is 15%. This fact is used in medical practice, where radioiodines have been administered for the last 50 years in the treatment of hyperthyroidism and thyroid cancer. Radioiodines not only locally irradiate the thyroid gland but are also incorporated into thyroid hormones, thus influencing other organs of the body.

Thyroid cancers can be classified into differentiated thyroid cancers (papillary, follicular and medullary) and non-differentiated tumours (anaplastic carcinoma). Papillary carcinoma is the thyroid cancer known to be caused by ionizing radiation, as shown among the atomic bomb survivors (Wood *et al.*, 1969) and recently in the Chernobyl area. In a study of 577 Ukrainian patients < 19 years of age with a diagnosis of thyroid cancer (Tronko *et al.*, 1999), 290 cases of thyroid carcinomas were evaluated histopathologically and 93% were found to be papillary carcinomas. Similar frequencies were seen in a study of 4296 patients in the USA previously irradiated for benign disorders in the head-and-neck area before the age of 16 years. Forty-one thyroid cancers were found in children who were < 20 years when the cancer developed, and 95% of these were papillary carcinomas (Viswanathan *et al.*, 1994). Thyroid nodules have also been related to exposure to radioiodine (Schneider *et al.*, 1993; Hall *et al.*, 1996a).

2.7.1 *Iatrogenic exposure*

The effects of exposure to radioiodine have been reviewed extensively (UNSCEAR, 1994), and information is also available from several large follow-up studies, the major ones being listed in Table 60. ^{131}I is used for diagnostic and therapeutic purposes (at higher doses).

In reviewing what is known of the carcinogenic effect of medical use of radioiodines in humans, the effects are divided into risks for thyroid cancer, leukaemia and other cancers. Since age at the time of exposure has a strong effect on the risk for radiation-induced cancer, special emphasis is placed on evaluating this modifier of risk.

(*a*) *Thyroid cancer*

Thyroid carcinomas vary in histology, clinical presentation, response to treatment and prognosis. The carcinogenic effect of ^{131}I is less well understood than that of external photon radiation. Before the Chernobyl accident, the effects of radioiodine in children had not been studied to any extent, since children are rarely examined medically or treated. The childhood thyroid gland, red bone marrow and premenopausal female breast are the most radiosensitive organs in the body. Although thyroid carcinomas are known to be more aggressive in children (Viswanathan *et al*., 1994), their prognosis is better than that of adults. Several risk factors have been suggested for thyroid cancers, including a history of benign nodules, miscarriages, iodine deficiency or excess and an elevated level of thyroid-stimulating hormone, but only ionizing radiation has been found to have a causative effect (La Vecchia *et al*., 1999; Negri *et al*., 1999).

Among survivors of the atomic bombings, the most pronounced risk for thyroid cancer was found among those with a dose to the thyroid of > 1 Sv before the age of 10 years, and the highest risk was seen 15–29 years after exposure; the risk subsequently began to decline, but it was still elevated 40 years after exposure (Thompson *et al*., 1994; Ron *et al.*, 1995). In a pooled analyses of seven cohorts of individuals exposed to ionizing radiation, Ron *et al*. (1995) found an ERR at 1 Gy of 7.7 (95% CI, 2.1–28.7) for persons exposed in childhood. They also reported that the ERR decreased by a factor of about 2 for each successive five-year interval of age at exposure over the range 0–14 years of age.

The National Council on Radiation Protection and Measurements (1985) estimated that the RBE of the thyroid dose from ingested or inhaled ^{131}I compared with X-rays was 0.1–1.0, on the basis of experimental studies. The report recommended that 0.3 was the highest credible value for radiation protection purposes. The report also stated that the RBE of ^{131}I relative to X-rays may be lower at high doses and dose rates, and higher (nearer to that of X-rays) at low doses and dose rates. Walinder (1972), in his experiment in mice (see section 4), obtained an RBE of 0.18 with ^{131}I doses to the thyroid in the range 22–160 Gy, whereas Lee *et al.* (1982), in their experiment in rats, found near equivalence after injecting doses giving 0.8, 3.3 and 8.5 Gy to the thyroid. Laird (1987)

Table 60. Major cohorts of patients exposed to radioiodine

Reference	Study	Type of study	Characteristics	Follow-up (years, mean), person–years of observation	Site, number of cancer cases, SIR or SMR (95% CI)
Hall *et al.* (1996b)	Diagnostic (Sweden)	Incidence	34 104; 80% women; age, 1–75	5–39 (24), 653 093	Thyroid: 67, 1.35 (1.05–1.71) diagnosed > 5 years after exposure
Hall *et al.* (1992a); Holm *et al.* (1991)	Hyperthyroid patients (Sweden)	Incidence/ mortality	10 552; 82% women; age, 13–74	1–33 (15), 139 018	*Incidence (Holm* et al.*, 1991)* Stomach: 92, 1.05 (0.85–1.28) Kidney: 66, 1.39 (1.07–1.76) Brain: 48, 1.30 (0.96–1.72) Thyroid: 18, 1.29 (0.76–2.03) *Mortality (Hall* et al.*, 1992a)* Stomach: 54, 1.41 (1.06–1.85) Kidney: 15, 0.90 (0.51–1.49) Thyroid: 12, 1.95 (1.01–3.41)
Ron *et al.* (1998)	Hyperthyroid patients (USA)	Mortality	20 949 iodine-exposed; 8054 only iodine-exposed; 10 874 unexposed; 79% women; age, < 80	1–44 (21), 385 468 (iodine-exposed) 141 543 (only iodine-exposed)	*Iodine-exposed* Thyroid: 24, 3.94 (2.52–5.86) Lung: 295, 1.06 (NG) Breast: 248, 1.10 (NG) *Only iodine-exposed* Thyroid: 11, 4.91 (2.45–3.41)
Franklyn *et al.* (1999)	Hyperthyroid patients (United Kingdom)	Incidence/ mortality	7417; 83% women; age, 49–≥ 70	1–≥ 20, 72 073	Thyroid: Incidence: 9, 3.25 (1.69–6.25) Mortality: 5, 2.78 (1.16–6.67) Small bowel: Incidence: 6, 4.81 (2.16–10.7) Mortality: 6, 7.03 (3.16–15.7)

Table 60 (contd)

Reference	Study	Type of study	Characteristics of the cohort	Follow-up (years, mean), person–years of observation	Site, number of cancer cases, SIR or SMR (95% CI)
Hall *et al.* (1991)	Thyroid cancer patients (Sweden)	Incidence	834 exposed[a], 1121 unexposed; 75% women; age, 5–75	2–34 (14), 10 073 in the ^{131}I treated group; 15 757 in the untreated group	Exposed: Salivary glands: 3, 15.0 (3.09–43.8) Kidney: 7, 3.00 (1.21–6.19) Unexposed: Salivary glands: 0, 0 (0.00–12.7) Kidney: 5, 1.48 (0.48–3.45)
de Vathaire *et al*. (1997)	Thyroid cancer patients (France)	Incidence	1771 patients: 846 received ^{131}I for therapy, 651 received ^{131}I for diagnosis; 274 unexposed; 79% women; age, 5–89	2–37 (10), 14 615	Colorectal, 1771 patients 0–0.19 GBq[b]: 6, 1.0 (reference category) > 0.19–3.7 GBq: 1, 1.4 (0.2–6.8)[c] > 3.7–7.5 GBq: 4, 4.0 (1.3–12.2) [c] > 7.5 GBq: 2, 4.9 (1.2–18.5) [c]

SIR, standardized incidence ratio; SMR, standardized mortality ratio; CI, confidence interval

[a] Individual doses based on iodine administered, 24-h uptake

[b] Cumulative activity of ^{131}I (GBq) [10^9 Bq] administered 5 years or more before diagnosis of colorectal cancer

[c] 90% CI

conducted parallel and combined analyses of six cohorts of children exposed to external radiation or ^{131}I and one cohort of adult survivors of the atomic bombings, and re-evaluated data from the large experimental study of Lee *et al*. (1982) that was specifically designed to investigate the RBE of ^{131}I. By combining the evidence from the epidemiological and experimental studies, Laird (1987) estimated a risk ratio of 0.66 (95% CI, 0.14–3.15). The RBE value at low doses remains a contentious issue (see section 4).

A Swedish study of 34 104 patients who had received ^{131}I for diagnostic purposes, whose doses were quantified on the basis of the administered dose of iodine and 24-h uptake, did not show an increased risk for thyroid cancer (Hall *et al*., 1996b; see Table 60). The size of the gland was known for half of the patients, but addition of this information did not alter the results. It should be emphasized that only 7% (n = 2408) of the patients were < 20 years of age at time of exposure and that three cases of thyroid cancer were found in this group, giving a non-significant SIR of 1.69 (95% CI, 0.35–4.93) with a mean dose of 1.5 Gy to the thyroid.

Several studies of the carcinogenic effect of radioiodine involved patients treated for hyperthyroidism, of whom nearly all were adults (Holm *et al.*, 1991; Hall *et al*., 1992a, 1993; Ron *et al*., 1998; Franklyn *et al*., 1999; see Table 60). In the two most recent studies, elevated risks were found for death from thyroid cancer (Ron *et al*., 1998; Franklyn *et al.*, 1999) and for the incidence of this cancer (Franklyn *et al*., 1999) after treatment of adults with ^{131}I for hyperthyroidism; this result contrasts with those of previous studies of hyperthyroid patients (Holm *et al.*, 1991; Hall *et al*., 1992a, 1993) and of patients examined with ^{131}I (Hall *et al*., 1996b). The reason for referral, i.e. the underlying thyroid disorder, could have influenced the risk, since the highest risk was seen < 5 years after exposure. The risk was seen primarily among patients with toxic nodular goitre, which has been identified as a risk factor for thyroid cancer; and the authors of the study in the USA suggested that some of the patients might have had an undiagnosed thyroid cancer at the time of treatment with ^{131}I (Ron *et al.*, 1998). In the British study (Franklyn *et al*., 1999), no dose–response relationship was found, again indicating that the underlying disease could have influenced the results.

The dose to the thyroid (60–100 Gy) received by most hyperthyroid patients has been considered to induce cell killing rather than a carcinogenic effect (Hall *et al.*, 1992a), but the dose to abnormal thyroid glands is difficult to measure. Non-uniform distribution of radioiodine and, thus, of the dose delivered, results in very high doses to some parts, while other areas are probably exposed to comparatively low doses.

At present, there is no direct evidence that medical use of ^{131}I induces thyroid cancers in humans, regardless of the reason for exposure. This result is not surprising, however, because few children were studied. There is also little evidence that the risk is increased by exposure of adults to γ-radiation or X-rays. For example, in the studies of atomic bomb survivors, no evidence was found of an increased risk for individuals exposed after the age of 20 (Thompson *et al*., 1994).

(*b*) *Leukaemia*

The incidence of leukaemia was studied in 46 988 persons (80% males) exposed to ^{131}I for diagnostic purposes (dose to the bone marrow, 0.01–4.44 mGy) or for treatment of hyperthyroidism (1–810 mGy) or thyroid cancer (22–2226 mGy). A total of 130 leukaemias was found, excluding chronic lymphocytic leukaemia (SIR, 1.09; 95% CI, 0.91–1.29), and the mean absorbed dose to the bone marrow was 14 mGy, which might partly explain the absence of an increased risk or, more correctly, the lack of statistical power in the study (Hall *et al*., 1992b). Ron *et al*. (1998) studied the risk for leukaemia other than chronic lymphocytic leukaemia in patients treated for hyperthyroidism after a mean absorbed bone-marrow dose of 42 mGy and found a SMR of 1.22 (not significant; 53 cases) with ^{131}I treatment in any combination with thyroid surgery or antithyroid drugs, and a SMR of 1.12 (not significant; 18 cases) for persons treated with ^{131}I only. By comparison, no excess risk for leukaemia was seen among about 23 300 atomic bomb survivors who received doses to the bone marrow of 0.01–0.99 Gy [mean, 38 mGy] (Preston *et al*., 1994).

Edmonds and Smith (1986) found three cases of leukaemia, with 0.25 expected ($p = 0.02$); Hall *et al.* (1991) found four cases of leukaemia, with 1.6 expected (SIR, 2.44; 95% CI, 0.66–6.25) and Brincker *et al.* (1973) found two cases, with 0.097 expected ($p < 0.05$), in thyroid cancer patients treated with relatively high doses of ^{131}I. Nevertheless, the available data on patients exposed to low-LET radiation do not on balance indicate an increased risk associated with radioiodine, even though the precision of these studies was low, owing to the low absorbed doses to the bone marrow.

(*c*) *Cancers at other sites*

The only tissues that receive doses of radioiodine that could have a measurable carcinogenic effect, other than thyroid and bone marrow, are the gastrointestinal and urinary tracts. Breast cancer is also discussed, since an increased risk has been found in patients treated for thyroid cancer or hyperthyroidism.

(i) *Gastrointestinal tract*

In a study of 10 552 patients treated with ^{131}I for hyperthyroidism, an increased rate of death from stomach cancer was seen when compared with national rates (SMR, 1.41; 95% CI, 1.06–1.85) (Hall *et al*., 1992a). A non-significant increasing risk with increasing dose of iodine administered was seen. Individual doses were not available. It is possible that the underlying disorder, e.g. Graves disease, is associated with atrophic gastritis, which in turn is related to gastric cancer.

Franklyn *et al*. (1999) studied 72 073 person–years of follow-up after ^{131}I treatment for hyperthyroidism and found significantly increased incidence and mortality rates for cancer of the small bowel (SIR, 4.81; 95% CI, 2.16–10.7; six observed cancers; SMR, 7.03; 95% CI, 3.16–15.7; six fatal cancers). de Vathaire *et al*. (1997) studied 1771 patients who had been treated for thyroid cancer, of whom 846 had received ^{131}I for therapy, 651 had received ^{131}I for diagnosis and 274 had not received ^{131}I. The mean

cumulative activity administered was 7.2 GBq for therapy and 0.6 GBq for diagnosis. Eighty patients developed a second solid malignancy, of which 13 were colorectal cancers, and the risk for this cancer in 11 cases was significantly related to the cumulative dose of ^{131}I administered ≥ 5 years previously (ERR, 0.5/GBq; $p = 0.02$).

Increased risks for cancers of the gastrointestinal tract are probably difficult to identify since the doses received are low, e.g. the dose to the colon is approximately 50 mGy (Hall *et al*., 1992a).

(ii) *Urinary tract*

The urinary bladder concentrates iodine, and the dose of radioiodine to the bladder wall is highly dependent on the uptake of radioiodine by the thyroid (Smith & Edmonds, 1984; Edmonds & Smith, 1986): the higher the thyroid uptake, the lower the urinary bladder dose, since radioiodine is incorporated into thyroid hormones. At the low uptakes in thyroid cancer patients, the dose to the urinary bladder has been estimated to be 2 Gy (Hall *et al*., 1991). In one study, the incidence of and mortality from urinary bladder cancer were increased among thyroid cancer patients treated with ^{131}I (Edmonds & Smith, 1986), but this result contrasted with the findings of others (Hall *et al*., 1991; de Vathaire *et al*., 1997). The dose to the urinary bladder in patients treated with radioiodine for hyperthyroidism is probably one-tenth of that received by thyroid cancer patients (Ron *et al.*, 1998), and no increase in risk has been found in hyperthyroid patients treated with ^{131}I (Hall *et al*., 1992a; Ron *et al*., 1998; Franklyn *et al*., 1999).

(iii) *Breast*

In a study in the USA, a nonsignificantly increased risk for breast cancer was seen among hyperthyroid patients receiving ^{131}I when compared with those treated by other means (standardized rate ratio [SRR], 1.9; 95% CI, 0.9–4.1) (Goldman *et al*., 1988), but no relation with dose was seen. When this cohort was included in a larger study, no significant excess of breast cancer was observed (SMR, 1.10; Ron *et al*., 1998). In a Swedish study of hyperthyroid patients treated with ^{131}I, the mean absorbed dose to the breast was 50 mGy; no increased risk was noted (SMR, 0.86; Hall *et al*., 1992a).

2.7.2 *Accidents in or discharges from nuclear facilities*

During accidents at nuclear installations, radioiodines and other radionuclides may be released into the environment. Table 61 summarizes the main accidents and releases from nuclear facilities and shows the amount of activity released, the populations exposed and the dose distributions.

The releases from the accident at the Three Mile Island reactor in Pennsylvania, USA, in 1979 were relatively small and were largely minimized by the containment building. The releases from the fire at the Windscale reactor in the United Kingdom in 1957 and particularly those from the Hanford site in Washington State, USA, over the period 1944–47 were larger and covered a wider geographical area. The releases

Table 61. Characteristics of the main large-scale accidental or non-routine releases of ^{131}I

Location (reference)	Cause	Approximate quantity released	Date	Number of exposed persons	Estimated doses
Hanford, WA, USA (UNSCEAR, 2000)	Release of radioactive iodine	^{131}I: 20–25 × 10^{15} Bq [PBq] into the atmosphere	1944–57	270 000 3193 children born in 7 counties between 1940 and 1946	Thyroid: 95%, < 0.3 Gy range, 0–2.84 Gy median, 0.1 Gy mean, 0.186 Gy
Windscale, United Kingdom (UNSCEAR, 1993; Cardis, 1996)	Fire in reactor	^{131}I: 7 × 10^{14} Bq (over South Lancashire and Yorkshire)	1957	Not reported	Thyroid: 100–2500 μSv Children, 100 mGy Adults, 10 mGy
Three Mile Island, PA, USA (UNSCEAR, 1993)	Human error in power reactor	^{131}I: 550 × 10^{9} Bq [GBq] into the atmosphere	1979	Population within 80 km	External γ-radiation average, 15 μSv maximum, 850 μSv
Chernobyl, Ukraine (Ilyin *et al.*, 1990; UNSCEAR, 2000)	Destruction of reactor core	^{137}Cs: 85 × 10^{15} Bq ^{131}I: 1760 × 10^{15} Bq	1986	135 000 evacuees from 30-km zone (new estimate, 116 000); 270 000 in strict control zones	Whole-body γ-radiation: range, 30–≥ 500 mSv average, 120 mSv Thyroid, ^{131}I, children average, 0.3 Gy range, 0.1–> 2.5 Gy Committed effective dose equivalent from γ-radiation: average, 60 mSv 4%, > 100 mSv 800 persons, > 200 mSv Thyroid, ^{131}I, children range, 0.1–>10 Gy

from the Chernobyl reactor accident in the Ukraine in 1986, however, were much more extensive, and dispersed radionuclides were measured in northern Europe (UNSCEAR, 1988). Apart from persons in the area surrounding the reactor, however, almost all individuals received whole-body doses that were a small fraction of the annual dose from natural background radiation.

(*a*) *Windscale, United Kingdom*

The fire at the Windscale works of the Atomic Energy Authority at Sellafield in October 1957 (see section 1.1.2(*c*)(i)) resulted in the release of an unknown quantity of ^{131}I into the environment. Approximately 8×10^{14} Bq [800 TBq] of ^{131}I present in a cloud of radioactive material passed over south Lancashire and Yorkshire (Crabtree, 1995). Maximum depositions of ^{131}I were found in the Seascale-Drigg area, 3–6 km from Windscale (Chamberlain & Dunster, 1958). The doses to the thyroid were estimated to be small: < 0.67 μSv/year of ^{129}I on the basis of analyses at autopsy and a similar dose from ^{131}I. The rates of registration of thyroid cancer in Cumbria during 1969–86 were positively correlated with decreasing distance from Sellafield (Bowlt & Tiplady, 1989).

(*b*) *Hanford, Washington, USA*

At the Hanford nuclear weapons site in the USA, major releases of ^{131}I into the atmosphere were made between 1944 and 1957. The total activity released is estimated to have been of the order of $20–25 \times 10^{15}$ Bq (UNSCEAR, 2000), while 18×10^{15} Bq were released between 1944 and 1946 (UNSCEAR, 1993). Individual doses to the thyroid were reconstructed for 3193 persons who had been exposed as children at the time of these releases, by the fact of having been born in one of seven counties of Washington State between 1940 and 1946. The mean and median doses were estimated to have been 186 mGy and 100 mGy respectively, with a skewed distribution (range, 0–2840 mGy) (UNSCEAR, 2000). The preliminary results of an epidemiological study of thyroid cancer in this population have been published (UNSCEAR, 2000): no association was observed between thyroid cancer risk and estimated thyroid dose. [The Working Group recognized the difficulties of reconstructing doses after several decades on the basis of dietary recall and past information on radionuclide releases.]

(*c*) *Three Mile Island, Pennsylvania, USA*

During the accident at Three Mile Island in 1979 (see section 1.1.2(*c*)(ii)), 550×10^9 Bq of ^{131}I were released into the environment (UNSCEAR, 1993). Surveillance of the mortality rates among 32 135 persons who were living near the plant on the date of the accident does not provide consistent evidence that the radioactivity released during the accident had a significant effect (Talbott *et al.*, 2000).

(*d*) *Chernobyl, Ukraine*

This section describes the Chernobyl accident and specific investigations on cancers occurring in the populations in surrounding areas. The effects of external exposure of the 600 000–800 000 'clean-up' workers (UNSCEAR, 2000) and of the general population are summarized in the first monograph on ionizing radiation (IARC, 2000). See also section 1.1.2(*a*).

The accident at the Chernobyl reactor occurred on 26 April 1986 during an experimental test of the electrical control system while the reactor was shut down for routine maintenance. A sudden power surge caused a steam explosion that ruptured the reactor vessel. An intense graphite fire burned for 10 days, and large amounts of radioactive materials were released. As discussed in section 1, the main radionuclides released from the reactor to which persons were exposed internally were ^{131}I, ^{134}Cs and ^{137}Cs. ^{131}I has a short radioactive half-life (eight days) but can be absorbed relatively rapidly from air, milk and leafy vegetables. It is then localized in the thyroid gland. Because of the dietary patterns of infants and children, the size of their thyroid glands and their metabolism, they usually receive higher doses of radiation than adults. However, the doses received are difficult to estimate unless the concentrations of ^{131}I in foods or in the thyroid gland were measured within days of the accident (UNSCEAR, 2000).

The isotopes of caesium have relatively longer half-lives (^{134}Cs, two years; ^{137}Cs, 30 years), and exposure after ingestion or from their deposition on the ground is usually longer.

The Chernobyl accident resulted in widespread radioactive contamination of areas of Belarus, the Russian Federation and the Ukraine, which were inhabited by several million people. Currently, about 7 million people live permanently in areas where the ^{137}Cs deposition density is > 37 kBq/m^2, covering about 131 000 km^2 (Balonov *et al.*, 1996; Cardis *et al.*, 1996; revised to 146 000 km^2 by UNSCEAR, 2000). The doses received by these persons resulted from external exposure to the passing cloud, from radionuclides deposited on the ground and other surfaces and from internal exposure by inhalation of material from the passing cloud in the first days and ingestion of radionuclides in foods subsequently. The estimated collective doses in various population groups are shown in Table 62. The average whole-body doses of the general population living in contaminated areas were 10–60 mSv.

Much larger doses to the thyroid (up to several Gy) were received by persons (particularly children) living in the most heavily contaminated regions in the first few days after the accident. Although the thyroid was exposed both externally and internally, most of the dose in contaminated regions was from isotopes of iodine (UNSCEAR, 2000).

Persons who participated in the clean-up of the Chernobyl accident, the so-called 'liquidators', may have received substantial doses of radiation. As shown in Table 62, the average dose of those who worked in 1986–87 was 100 mSv, mainly from external radiation. Studies of the cancer risk of Chernobyl liquidators are therefore not

Table 62. Estimates of collective equivalent doses of populations in contaminated areas of Belarus, Russian Federation and the Ukraine after the Chernobyl accident

Population	Average dose received (mSv)	Effective number	Collective dose (person–Sv)
Evacuees	11–17	135 000	1600
Liquidators (1986–87)	100	200 000	20 000
Persons living in contaminated areas[a]:			
Deposition density of ^{137}Cs > 555 kBq/m^2	50–60	270 000	10 000–20 000
Deposition density of ^{137}Cs 37–555 kBq/m^2	6–20	6 800 000	35 000–100 000

From Cardis *et al.* (1996)

[a] Doses for 1986–95; over 1996–2056, the collective dose will increase by approximately 50%.

reviewed here, except for those on thyroid cancer, as substantial doses to the thyroid from iodine isotopes may have been received by some of the liquidators who arrived on the site shortly after the accident. As discussed in section 1, the doses of populations exposed outside the European part of the former USSR were also mainly from external radiation. Therefore, this section is restricted to studies conducted in Belarus, the Russian Federation and the Ukraine.

Although a number of studies have addressed the association between exposure from radionuclides released in the Chernobyl accident and late health effects, it is still too early to evaluate the risks for most types of cancer, as only 14 years have passed. Moreover, the level of adequacy of the dosimetric data for external and internal exposures is still questionable. Most of the publications to date have focused on the increased incidences of thyroid cancer and leukaemia, sites for which the latency is shorter than those for cancers at other sites.

(i) *Thyroid cancer in young people*

Most of the studies completed to date are of the descriptive type, in which average population exposures are correlated with average rates of cancer incidence during specific periods. When no individual dosimetry is performed, it is difficult to evaluate whether the effects are radiation-related, and it is impossible to make reliable quanttative estimates. Reconstruction of individual doses is a key element of future research on radiation-associated cancers related to the Chernobyl accident (UNSCEAR, 2000).

A significant increase in the incidence of thyroid cancer in childhood has been observed in Belarus and, later, in the Russian Federation and the Ukraine since 1990. Table 63 (Stsjazhko *et al*., 1995) illustrates the time trends in the incidence of thyroid cancer in the three countries up to the end of 1994. Although reports of such increases were initially met with scepticism, there is now strong circumstantial evidence that these increases are related to the release of iodine isotopes during the Chernobyl

Table 63. Distribution of cases of thyroid cancer in children under the age of 15 years at diagnosis, in Belarus, the Russian Federation and the Ukraine

Location	1981–85		1986–90		1991–94	
	No.	Rate/10^6	No.	Rate/10^6	No.	Rate/10^6
Belarus (whole country)	3	0.3	47	4.0	286	30.6
Gomel	1	0.5	21	10.5	143	96.4
Russian Federation						
Bryansk and Kaluga regions[a]	0	0	3	1.2	20	10.0
Ukraine (whole country)	25	0.5	60	1.1	149	3.4
Five most northerly regions	1	0.1	21	2.0	97	11.5

From Stsjazhko *et al*. (1995)

[a] No data were available for the Russian Federation as a whole

accident. A total of 1420 thyroid tumours were diagnosed during 1990–97 among persons who were < 18 years of age at the time of exposure (UNSCEAR, 2000). Most of the tumours have been reviewed by international groups of pathologists and endocrinologists, with over 90% agreement (Williams, 1996). Nearly all the tumours were papillary thyroid carcinoma (solid and papillary forms), and histological studies have identified a subtype of papillary carcinoma — with a solid/follicular architecture — that is fairly prevalent in children from contaminated areas; this subtype is rarely found in adults (Williams *et al*., 1996).

Most of the tumours have been observed among subjects who were very young at the time of the accident: in Belarus, over half of the tumours occurred in people who were < 6 years old at the time of the accident (Demidchik *et al*., 1999). In a series of 472 children with thyroid cancer diagnosed up to 1995 in Belarus, only two had been conceived after the accident; nine had been exposed *in utero*, and 88% were under the age of 15 at the time of diagnosis (Pacini *et al*., 1997). In the Ukraine, over 60% of the children in whom thyroid cancer was diagnosed at the end of 1997 were under 15 years of age at the time of diagnosis (Tronko *et al*., 1999).

Like childhood tumours elsewhere, most of the tumours in children in contaminated areas had aggressive characteristics. In Belarus and the Ukraine, the tumours were generally > 10 mm in diameter and showed extrathyroidal growth (48–61% of cases), lymph node metastases (59–74%) and distant (mainly lung) metastases (7–24%) (Abelin *et al*., 1994; Nikiforov & Gnepp, 1994; UNSCEAR, 2000). Nevertheless, the prognosis of these tumours is good, and fewer than five deaths have been reported.

A number of ecological studies of thyroid cancer incidence in young people in relation to estimated dose at the settlement level have been carried out in the Ukraine (Sobolev *et al*., 1996; Goulko *et al*., 1998; Jacob *et al*., 1998), Belarus (Kenigsberg *et al*., 1996; Bleuer *et al*., 1997; Heidenreich *et al*., 1999), the Russian Federation (Parshkov *et al*., 1997) and across Belarus and the Russian Federation (Jacob *et al*.,

1999). These studies show a good correlation between the estimated dose and thyroid cancer incidence; however, because of uncertainties in estimating the dose to the thyroid and the incomplete case ascertainment in some areas and age ranges, risk estimates derived from such studies must be interpreted with caution.

A case–control study designed to test the hypothesis that the Chernobyl accident resulted in an increased incidence of thyroid cancer was carried out by Astakhova *et al*. (1998) in Belarus. The study population comprised 107 confirmed cases of thyroid carcinoma (105 papillary, two follicular) diagnosed or treated between 1987 and mid-1992 at the Aksakovtchina Clinic (a national referral centre) or the National Thyroid Surgery Centre at the Minsk State Medical Institute, where all cases of childhood (< 15 years) thyroid cancer in Belarus were seen at that time. The individual doses to the thyroid were inferred from the mean dose of adults in the settlement and the deposition density of ^{131}I or ^{137}Cs in settlements where doses to the thyroid had been 'measured'. Information on milk consumption and prophylactic intake of stable iodine was not taken into account. The contributions to the dose from external radiation, short-lived radioisotopes of iodine and other long-lived radionuclides were judged to be small in comparison with the dose from ^{131}I and were not considered. Because of uncertainties about individual doses, they were grouped into three categories, < 0.3, 0.3–0.9 and ≥ 1 Gy. Two sets of controls were matched to each case. Type I controls (107) were drawn at random from the general population of children in the 'exposure zone', matched on age, sex and urban or rural area of residence in 1986. They were chosen at random from the individual medical records of the polyclinics in each district in proportion to that district's 1986 population. Type II controls (107) were selected from among children who had had the same opportunity for diagnosis as the cases: that is, cases diagnosed in the framework of a systematic endocrinological screening programme were matched to controls who had participated in the screening. They were matched on age and sex but not on geographical location. A strong association was found between dose category and risk for thyroid cancer, with or without adjustment for age, sex, year of diagnosis, ^{131}I in soil and mode of diagnosis. The highest odd ratios were seen for children in rural areas of the Gomel region: 10.42 (95% CI, 3.46–31.25) with type I controls and 7.41 (2.5–21.7) with type II controls, for exposure to ≥ 0.3 Gy versus < 0.3 Gy. Fifteen of the 17 patients and three of the four controls who had been exposed to doses ≥ 1 Gy originated from the rural Gomel region. [The Working Group noted that the male:female ratio is close to 1, suggesting a possible screening effect, and also noted the uncertainty of the dose estimates.]

Overall, the number of thyroid cancers found among persons exposed in childhood, particularly in the severely contaminated areas of the three affected countries, is considerably greater than that expected on the basis of previous knowledge. Such a high incidence and short induction period have not been experienced in other exposed populations, and other factors have almost certainly affected the reported increase. These include screening bias, iodine deficiency and supplementation, both at the time of the accident and in following years, a possible genetic predisposition and the role of short-

lived isotopes of iodine (Cardis *et al.*, 1996; Astakhova *et al.*, 1998; Cardis *et al.*, 1999). If the current trend continues, more thyroid cancers can be expected to occur, especially among people exposed at young ages. The most recent findings indicate that the risk for thyroid cancer among people who were < 4–5 years old at the time of the accident is continuing to increase (UNSCEAR, 2000). [The Working Group noted that the time trends in age-specific incidence for people exposed at later ages are somewhat erratic and are difficult to interpret, as the treatment of adolescent and adult cases is much less centralized than that of childhood cases.]

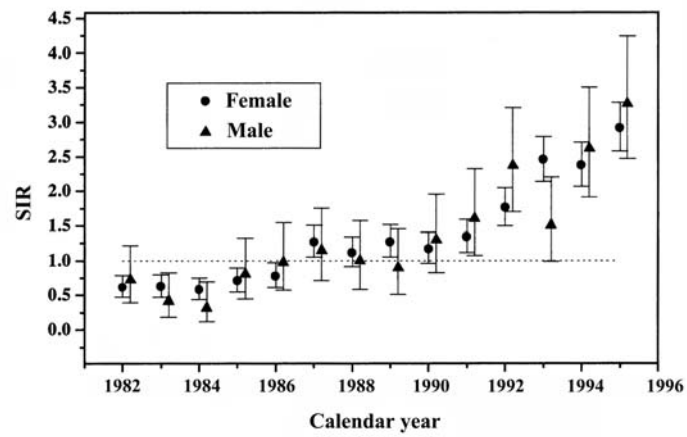
At present, it is difficult to quantify the risk of radiation-induced thyroid cancer for exposed children because (1) intense screening for thyroid cancer played some role in the detection of thyroid cancers; (2) iodine deficiency and the associated mild goitre could have contributed to the increased risk; (3) assessment of individual exposure is complex and depends on reconstructing the dietary habits of children many years in the past and estimating the radioactive iodine contents of various foods; and (4) the contribution to dose of radionuclides of iodine other than ^{131}I is not well defined, whereas these radionuclides have shorter half-lives and greater β-particle emission energies, exposing the thyroid gland more uniformly than ^{131}I and at a higher dose rate. Nevertheless, the more than 1000 thyroid cancers that have been detected among persons exposed as children are one of the clear consequences of the Chernobyl accident.

(ii) *Thyroid cancer in adults*

The incidence of thyroid cancer in the general population of children and adults in the contaminated territories of Belarus, the Russian Federation and the Ukraine and among the 'liquidators' who participated in the clean-up of the Chernobyl accident both in the 30-km area around the reactor and in contaminated regions of Belarus and the Ukraine has also been studied.

Ivanov *et al*. (1999a,b) analysed the trends in thyroid cancer incidence among persons aged 0–60 years in the four most heavily contaminated regions of the Russian Federation (Bryansk, Kaluga, Orel and Tula). The total population of these regions was 4.33 million people, and the number of children and adolescents was 1.217 million. Cases of thyroid cancer were identified from the regional oncological dispensary in each region, and 3082 cases were detected between 1982 and 1996. Of these, 2618 were among women (50 cases among girls aged 0–17), and 464 were among men (28 cases among boys aged 0–17). There were 178 cases among persons who were children or adolescents at the time of the Chernobyl accident (46 boys and 132 girls). The time trends in SIRs for thyroid cancer are shown in Figure 9 for the study regions and for the whole territory of the Russian Federation. During the period 1982–86, the SIRs in these regions were lower than those for the country as a whole. The SIR increased immediately after the accident and remained approximately constant over the period 1987–91, after which it increased substantially with time. The authors attributed the immediate increase (1987–91) to a screening effect, with the introduction of a special examination system in these regions, and the later increase to an effect of radiation from

Figure 9. Trends in the standardized incidence ratio (SIR) for thyroid cancer in Bryansk, Kaluga, Orel and Tula as compared with that in the Russian Federation as a whole



From Ivanov *et al.* (1999b). Bars are 95% confidence intervals.

the accident. [The Working Group noted that studies of external exposure indicate that the risk for radiation-induced thyroid cancer is expected to be low in persons exposed as adults.]

Ivanov *et al*. (1997a) investigated the incidence of thyroid cancer among 'liquidators' who had worked to clean up the Chernobyl catastrophe. The cohort consisted of 167 862 persons, all of whom were registered in the Russian National Medical Dosimetric Registry. A total of 43 cases of thyroid cancer were found between 1986 and 1994 among the 136 367 liquidators who had worked at Chernobyl during 1986–87. Their average age at the time they entered the 30-km area of the Chernobyl nuclear power plant was 33 years, and their mean external whole-body dose was 0.14 Gy. The expected number of thyroid cancers was 9.44. The SIR for the latent period (1986–90) was 2.6 (95% CI, 1.34–4.52) and that for the post-latent period (1991–94) was 6.45 (95% CI, 4.38–9.15); four more thyroid cancers were detected in the liquidators who worked in 1988–90. The authors found that screening had affected the detection of thyroid cancer during the first years after the accident.

Cardis *et al*. (1996) analysed the cancer incidence of liquidators who had worked in the 30-km zone around the Chernobyl plant in 1986 or 1987 and of the population living in contaminated areas of Belarus, the Russian Federation and the Ukraine. An increased incidence was seen among liquidators in all three countries, although there were relatively few cases (28 cases in 1993–94). The liquidators who worked in the 30-km zone in the first days after the accident may have received significant doses of radiation to the thyroid from short-lived iodine isotopes. The authors noted, however,

that the results must be interpreted with caution, as the liquidators are followed-up much more actively than the general population in the three countries, and, for thyroid cancer in adults, the extent of screening may influence the observed incidence. A 1.5–2-fold increase in the incidence of thyroid cancer was also seen in the general population of the contaminated regions of the three countries. Again, because of heightened awareness of the consequences of the accident and the more intensive medical follow-up of populations living in contaminated regions, these findings must be interpreted with caution, and further analyses are needed before the finding can be confirmed or refuted. This is particularly important, as no excess of thyroid cancer has been found among persons exposed when over the age of 20 in studies of populations exposed to external radiation (Thompson *et al.*, 1994) or to medical treatment with ^{131}I (see section 2.7.1).

(iii) *Other cancers*

Prisyazhniuk *et al*. (1991, 1995, 1996) analysed trends in cancer incidence in the Ukraine and in the contaminated regions of Belarus, the Russian Federation and the Ukraine. Although they observed increased incidences of all cancers and of leukaemia, they noted that the increases were consistent with pre-existing trends in the incidence of these diseases. The increases were, moreover, not related to the levels of exposure in the regions. The predominant difference from rates before the Chernobyl accident was in the rate of cancers among people in the oldest age group considered (65 years and over). The rate began to increase as early as one year after the accident, and therefore probably reflected better ascertainment of disease in this population. The increase in the incidence of leukaemia was accounted for primarily by chronic lymphocytic leukaemia, a subtype that has not been associated with exposure to radiation in other studies.

Cardis *et al*. (1996) found no increase in the incidence of all cancers in populations of contaminated regions of the Ukraine. In Belarus and the Russian Federation, a marginally statistically significant 3% increase in deaths from any cancer was noted, while no increase was observed in the incidence of leukaemia in any of the three countries. Although several authors have reported an increased incidence of leukaemia among subgroups of liquidators, these increases are not consistent. Thus, 46 cases were reported among the liquidators in the three countries during 1986–87; a non-significant twofold increase (based on nine observed cases) was observed in Belarus; in the Russian Federation, no significant difference in leukaemia incidence was found between liquidators and the general population; and in the Ukraine, a significant increase in the incidence of leukaemia was reported. Because of the more intensive medical follow-up of the populations living in contaminated regions, these findings must be interpreted with caution, and further analyses are needed before they can be confirmed or refuted.

Ivanov *et al*. (1997b) studied the cancer risk in Kaluga oblast of the Russian Federation 10 years after the Chernobyl accident in order to assess the effect of radiation on the existing rates of cancer incidence and mortality. Time trends and relative population risks were analysed. The only statistically significant effect of

radiation on cancer incidence was on thyroid cancer in women. The rates of cancer incidence and mortality in the contaminated areas generally reflected the changes in cancer incidence in the region as a whole.

In 1986, a special registry of 'haemoblastoses' was set up in the most heavily contaminated areas (^{137}Cs contamination, ≥ 550 GBq/km^2) of Bryansk region in the Russian Federation. Information on 2832 cases of haemoblastosis was accumulated in the registry up to the end of 1992. No significant difference was seen in the annual average incidence rate of specific haemoblastoses between areas with different degrees of contamination (Osechinksy *et al*., 1994).

Ivanov *et al*. (1998) analysed the incidence of leukaemia among infants in Belarus after the Chernobyl accident and compared the data with those from Germany and Greece, where increased incidences were reported in children who were *in utero* at the time of the accident. As the contamination in Belarus was far heavier than that in the other countries, it might be expected that any excess of infantile leukaemia due to prenatal exposure would continue beyond the first year after the accident. In the most heavily contaminated areas of Gomel and Mogiljev, the rate ratio for infant leukaemia incidence was increased (1.51; 95% CI, 0.63–3.61), but not significantly. Comparison of the incidence rates in Belarus, Germany and Greece in relation to the average ^{137}Cs contamination in those countries (> 60 kBq/m^2 [> 60 GBq/km^2] in Belarus and < 6 kBq/m^2 [< 6 GBq/km^2] in both Germany and Greece) led the authors to conclude that a causal relationship between the reported increases and the Chernobyl accident was difficult to accept.

2.8 Phosphorus

Use of radioactive phosphorus in the form of $^{32}PO_4$ for the treatment of polycythaemia vera was introduced in 1939 (Lawrence, 1955; Lawrence *et al.*, 1969). The incidence of this disease is two to three cases per 100 000 per year and is higher in men than in women (Berglund & Zettervall, 1992). ^{32}P has a physical half-life of 14.3 days and emits β-particles. The activities of $^{32}PO_4$ used orally or intravenously are 185–300 MBq (5–8 mCi). After parenteral administration, the skeletal uptake exceeds that of muscle, fat or skin by factors of 4–6 on the first day and 6–10 on the second. After intravenous injection to humans, 5–10% of an administered dose is excreted in the urine within the first 24 h and 20–50% within a week. Less than 2% is excreted in the faeces (Silberstein, 1993).

Few precise data on the dosimetry of phosphorus in humans are available. Spiers *et al*. (1976) measured the dose absorbed by the bone marrow in biopsy samples taken from the iliac crest and the sternum. The biological half-life of ^{32}P in the body was 39 days. The dose absorbed by the marrow in trabecular bone was 24 rad/mCi injected [0.24 Gy per 37 MBq (6.5 nGy/Bq)], and the doses from activity in trabecular bone, marrow and cortical bone were 10, 13 and 1 rad [0.1, 0.13 and 0.01 Gy], respectively. Using a compartmental approach, Seltzer *et al*. (1964) and Mays (1973) found an

average skeletal dose of 300 rad/20 mCi [0.15 Gy/37 MBq (4 nGy/Bq)] administered. ICRP (1993b) published comparable results.

2.8.1 *Haematological malignancies* (see Table 64)

It is now established that polycythaemia vera is a clonal malignancy of the pluripotent haematological stem cell (Adamson *et al.*, 1976; Berk *et al.*, 1986). An increased risk for leukaemia may therefore be a consequence of the natural course of polycythaemia vera. Alternatively, patients with this disease may be more sensitive to the leukaemogenic effects of irradiation than the general population.

As patients with polycythaemia vera must be treated as quickly as possible, it is difficult to obtain precise information on the natural course of the disease. One source of relevant information is Videbaek (1950), who presented data on 125 patients who had been followed-up in several Danish hospitals between 1920 and 1950. These patients were treated by varied protocols, most frequently with phlebotomy and X-rays, but none had been treated with ^{32}P. The median length of survival was 4–5 years for men and 8–9 years for women. The complications were haemorrhage, thrombosis and gastroduodenal ulcer. Eight patients developed fatal malignant tumours; one died from chronic myeloid leukaemia and another from stem-cell leukaemia. The treatment received by the 10 patients who died from a malignancy was not known; however, this study is useful in providing an upper limit to the risk for leukaemia in the natural course of polycythaemia vera.

A second source of information on the risk for leukaemia in the natural course of polycythaemia vera is the report of a subgroup who received no X-rays or ^{32}P in the series assembled by Modan and Lilienfeld (1965). Less than 1% of these patients developed acute leukaemia during 8–25 years of follow-up.

A third source of information on cancer risk in patients with polycythaemia vera in the absence of radiotherapy comes from the Polycythemia Vera Study Group (Berk *et al.*, 1986). This Group, which was established in 1967, conducted a randomized controlled trial with three arms: phlebotomy, chlorambucil and ^{32}P, and 431 patients were randomized to one of these treatments between 1967 and 1974. An analysis conducted in March 1983 showed 10 cases of cancer in the group of 134 patients treated with phlebotomy (two acute leukaemia and eight other cancers), which is comparable with the number expected in the age- and sex-matched general population.

Observational follow-up studies of series of patients with polycythaemia vera and treated with $^{32}PO_4$ show a clear increase in the incidence of acute leukaemia (see Table 64). Precise criteria for the diagnosis of polycythaemia vera were published in 1965 by Modan and Lilienfeld and used in their study. Series of patients in whom polycythaemia vera was diagnosed before that time or a little later (e.g. Fauvert *et al.*, 1961; Osgood, 1964; Halnan & Russell, 1965; Harman & Ledlie, 1967) may have included substantial numbers of patients who did not, in fact, have polycythaemia vera. The incidence of acute leukaemia in series of patients treated with ^{32}P is of the order of

Table 64. Incidences of acute leukaemia in patients with polycythaemia vera treated with $^{32}PO_4$ and by other means

Reference, country, date of treatment or diagnosis	No. of cases/ no. of deaths	Method of treatment, dose	Length of follow-up (years)	No. of cases
Observational studies				
Fauvert *et al*. (1961), France, 1950–1960	194 (143 followed)/ 25 deaths	> 110 MBq $^{32}PO_4$, one or several doses	10	Two acute leukaemias
Osgood (1964), USA, 1947–54	101	Average cumulative dose = 1300 MBq $^{32}PO_4$	> 10	14 acute leukaemias versus 6.5 expected (6 acute granulocytic, 8 acute monocytic)
Halnan & Russell (1965), United Kingdom, 1944–62	107 117	51 GBq $^{32}PO_4$ (total dose) plus X-rays Phlebotomy only	15	No acute leukaemia (0.2 expected); identical survival rate in the two groups
Modan & Lilienfeld (1965), Canada and USA, 1937–53	72 228 79 133	X-rays plus $^{32}PO_4$ $^{32}PO_4$ (dose not reported) X-rays No radiotherapy	8–25	12 acute leukaemias 25 acute leukaemias 7 acute leukaemias 1 acute leukaemia
Szur & Lewis (1966), United Kingdom, date not reported	169	550–2100 MBq $^{32}PO_4$ (total dose)	16	Four leukaemias (3 myelocytic, 1 chronic granulocytic) (2 had also received X-rays and one, chemotherapy)
Harman & Ledlie (1967), United Kingdom, 1948–63	132	$^{32}PO_4$ (dose not reported)	> 10	10 leukaemias (unspecified whether acute)
Tubiana *et al*. (1975), France, 1949–61	303	Average dose, ^{32}P 700 MBq (Landaw, 1976) Once or several times	12–24	50 leukaemias (mostly acute)
Najean *et al*. (1988), France, before 1976	179 64 49	> 85 MBq $^{32}PO_4$ Phlebotomy Chlorambucil or hydroxyurea	> 10	14 ANLL No acute leukaemia 3 ANLL
Randomized controlled trial				
Berk *et al.* (1986), USA, 1967–74	141 156 134	Chlorambucil $^{32}P \leq 185$ MBq per dose Phlebotomy	10–18	19 acute leukaemias 16 acute leukaemias 2 acute leukaemias

ANLL, acute non-lymphocytic leukaemia

10–20% of cases during the 10 years after administration in all the studies (for a review, see Landaw, 1976). Furthermore, in two series (Modan & Lilienfeld, 1965; Tubiana *et al*., 1975), there was a clear dose–response relationship between the frequency of acute leukaemia and the dose of ^{32}P administered. In these observational studies, patients with more severe disease may have been more likely to have been treated with radiation and higher doses.

After 10–18 years of follow-up in the trial of the Polycythemia Vera Study Group (Berk *et al.*, 1986), two cases of acute leukaemia had been reported in 134 patients treated by phlebotomy, 16 cases of acute leukaemia among 156 patients treated with ^{32}P and 19 cases of acute leukaemia plus five cases of large-cell lymphocytic lymphoma among 141 patients treated with chlorambucil (Table 64). Thus there was a clear increase in the incidence of acute leukaemia in the group treated with ^{32}P compared with that treated by phlebotomy. In spite of this, the overall survival of phlebotomy-treated and ^{32}P-treated patients was similar, owing to the complication of thrombosis that affects the former group.

2.8.2 *Other malignancies*

In the series of Modan and Lilienfeld (1965), no significant differences were found in the frequency of non-haematological malignancies between the ^{32}P-treated patients and the group receiving no radiation treatment. In the trial of the Polycythemia Vera Study Group (Berk *et al.*, 1986), an analysis conducted in 1983 suggested excess risks for skin and gastrointestinal cancers in the combined group of patients treated with ^{32}P or chlorambucil when compared with the group treated by phlebotomy. The data for patients treated with ^{32}P were not presented separately.

2.9 Mixed exposures

2.9.1 *Fall-out from atmospheric nuclear weapons testing*

The large collective doses of ionizing radiation committed to the world's population by the nuclear tests are derived mainly from internal exposure to ^{14}C, owing to the long half-life (5730 years) of this radionuclide in large populations, including future generations. The dose rates at which people are exposed to various radionuclides in fall-out are small. The cancer risk attributable to such exposures will be so small that it may not be possible to study a large enough exposed population to detect it.

The thyroid is the most frequently affected organ after exposure to radioactive fall-out close to test sites. The doses to the thyroid from radioactive iodine depend mainly on the consumption of foodstuffs contaminated with ^{131}I and other minor radionuclides deposited on the ground and, to a lesser degree, on inhalation of ^{131}I and ^{133}I. Epidemiological assessment of thyroid cancer attributable to radioactive iodines therefore requires information on individual intake of various contaminated food items and the exposure pathways leading to human intake of the radionuclides. Crude aggregate data

on environmental exposure of populations are a poor measure of internal exposure. Mean population doses can be estimated, taking into account inter-country variations in food consumption and pathways based on aggregate information. Analysis of such data still does not allow for individual variation in doses. This, together with the basic restrictions involved in ecological studies, presents some interpretative limitations.

(*a*) *Nevada test site*

After an early report of a possible increase in the incidence of thyroid cancer (Weiss *et al.*, 1967) at the Nevada test site, where testing of nuclear weapons began in 1951 (see section 1.1.1(*c*)(i)), the Public Health Service of the USA conducted a screening programme in 1965–68 for thyroid disease among several thousand pupils aged 11–18 living in southwestern Utah and adjacent Nevada, who were considered to have been exposed to fresh fission products containing ^{131}I during infancy and childhood in the early 1950s. Of those enrolled, 85–90% participated in the examination. After three years of screening, a cumulative total of 4831 children were examined; 1378 constituted a potentially 'exposed' group on the basis of residence history, and 57 were judged by the panel members to have thyroid nodularity. The prevalence of 13 cases per 1000 for boys and girls combined (14 for boys and 12 for girls) did not differ from that of 14 cases per 1000 among 'unexposed' children in Utah and Nevada (Weiss *et al.*, 1971). In further screening of 5179 children up to 1971, no differences were found in the rates of any category of thyroid disease between exposed and unexposed children (Rallison *et al.*, 1974).

More definitive evidence about thyroid cancer after exposure to fall-out comes from a further follow-up of 4819 (4831 according to Weiss *et al.*, 1971) of the schoolchildren with potential exposure to fall-out (Rallison *et al.*, 1990; Kerber *et al.*, 1993), with an expanded dose reconstruction. Of the individuals who were still living in Arizona, Nevada or Utah, 3122 were re-examined in 1985 and 1986; 2473 subjects were available for analysis. Exposure was assessed from residence history and individual food consumption data obtained by telephone interview. Models were constructed of routes of exposure, including fresh cows' and goats' milk, locally grown vegetables, inhalation and external exposure. Internal doses were estimated by analysis of ^{131}I and ^{133}I intake, taking into account consumption rate, source of milk, feeding patterns, distance from the test site and age. The rates of radionuclide deposition were obtained from the database of the 'Offsite Radiation Exposure Review Project'. The doses to the thyroid ranged from 0 to 4600 mGy (mean, 98 mGy), with a mean of 170 mGy in Utah. Approximately 73% of the exposure of the thyroid to radiation was attributable to milk consumption. During the entire period 1965–86, 56 subjects were found to have 57 thyroid nodules, comprising 11 benign neoplasms, 8 papillary carcinomas, 28 colloid adenomas and 10 non-neoplastic nodules (one subject had both a colloidal adenoma and a papillary carcinoma). The findings constitute a statistically significant excess of thyroid neoplasms (benign and malignant), with a positive dose–response trend. The dose–response relationship for thyroid carcinoma was of marginal significance, largely because of the

small number of cases (Table 65). Potential sources of bias and uncertainty were biased recall of food consumption and uniform application of parameters such as the milk transfer and dose factors to all subjects. [The Working Group noted that the methodological concerns include the fact that the interviewers were aware of the exposure status of the subjects and the apparent over-referral for physical examinations of persons known to reside in the areas with heavy fall-out.] The uncertainty in individual doses was summarized by a geometric standard deviation (a measure of uncertainty independent of dose). After adjustment for the uncertainties resulting from non-differential misclassification, the risk estimate was threefold higher than that without adjustment for uncertainties, while the *p* values remained similar.

The National Cancer Institute (1997) in the USA estimated the ^{131}I doses in counties of the USA and undertook analyses of mortality from and incidence of thyroid cancer in order to determine whether an increased risk for this cancer was related to exposure (Gilbert *et al.*, 1998a). During the period 1957–94, 4602 deaths from thyroid cancer were reported from continental counties, and 12 657 incident cases of thyroid cancer were reported in 1973–94 in selected counties where data on cancer incidence were available. Excess relative risks per Gy were estimated by relating age-, calendar year-, sex- and county-specific rates to the estimated doses to the thyroid adjusted for age at exposure. The risk for thyroid cancer associated with exposure to ^{131}I did not increase with cumulative dose or dose received at the age of 1–15 years, but associations with both mortality and incidence were suggested for individuals who had been exposed when < 1 year of age (Table 66) and with mortality for those born between 1950 and 1959. The authors noted that there was no *a priori* reason to select children under the age of one year for analysis, and the absence of an increase in risk in those aged 1–4 years was not consistent with the results of other studies of external exposure. In addition, the population of the USA is relatively mobile, especially young persons who leave home for university and employment. Thus, it is not clear whether the persons in whom thyroid cancer was diagnosed in the 1980s were living near the Nevada test site in the 1950s when exposure occurred. [The Working Group noted that the contribution to the dose of radiation from nuclear weapons tests by other countries was not taken into account.]

(*b*) *Marshall Islands*

The health of the persons living on three atolls of the Marshall Islands, Rongelap, Ailinginae and Utirik, has been followed since a nuclear explosion, known as the 'Bravo shot', in 1954 (see section 1.1.1(*c*)(ii)). The exposed population originally included 253 inhabitants (Conard *et al.*, 1974; Howard *et al.*, 1997). Since 1955, these persons have undergone a comprehensive, annual physical examination and follow-up examinations at six-month intervals. Between 1964 and 1990, all palpable thyroid nodules were surgically removed. The comparison population comprises 115 inhabitants of Rongelap, age- and sex-matched to the exposed group, who were not on the atoll at the time of the test. By 1957, attrition by emigration required the addition of other unexposed Rongelap

Table 65. Prevalence of thyroid nodules, neoplasms and carcinoma in relation to doses of radiation from fall-out from the test site in Nevada, USA, 1965–86

Dose (mGy)	All nodules			Neoplasms			Carcinoma		
	No. of cases	Rate/ 1000	Adjusted RR (95% CI)	No. of cases	Rate/ 1000	Adjusted RR (95% CI)	No. of cases	Rate/ 1000	Adjusted RR (95% CI)
0–49	29	20.5	1.0	7	4.9	1.0	5	3.5	1.0
50–249	12	18.6	0.9 (0.4–2.1)	3	4.6	0.8 (0.1–6.3)	0	0.0	0.0
250–399	8	33.3	1.9 (0.5–6.1)	5	20.8	2.8 (0.4–22.9)	2	8.3	3.8 (0.2–110.7)
≥ 400	7	41.4	2.3 (0.6–8.0)[a]	4	23.7	3.4 (0.5–26.9)[b]	1	5.9	1.7 (0.1–138.8)[c]
Total	56			19			8		

From Kerber *et al.* (1993); RR, relative risk; CI, confidence interval. RRs adjusted for age, sex and state of residence in 1965
Slope estimate for linear excess RR model (excess RR per mGy):
[a] lower bound = 0.0012 (0.00); $p = 0.16$
[b] lower bound = 0.0070 (0.00074); $p = 0.019$
[c] lower bound = 0.0079 (0.00); $p = 0.096$

Table 66. Estimated excess relative risk (ERR) per Gy of ^{131}I dose by age at exposure for persons exposed in infancy and childhood to fall-out from the test site in Nevada, USA

Age at exposure (years)	Mortality				Incidence (county-specific doses)	
	County-specific doses		State-specific doses			
	ERR/Gy (95% CI)	*p*	ERR/Gy (95% CI)	*p*	ERR/Gy (95% CI)	*p*
< 1	10.6 (–1.1, 29)	0.085	16.6 (–0.2, 43)	0.054	2.4 (–0.5, 5.6)	0.11
< 5	1.5 (< 0, 5.7)	0.35	2.7 (–1.1, 8.4)	0.19	–0.1 (–0.8, 0.8)	0.89
< 15	–0.2 (< 0, 1.6)	0.79	0.1 (–1.6, 2.3)	0.92	–0.3 (–0.8, 0.2)	0.22

From Gilbert *et al.* (1998a). ERR, excess relative risk; CI, confidence interval

inhabitants to provide an adequate number of people for the comparison group; the total comparison group eventually examined consisted of 227 individuals. The small size of the exposed population and uncertainty about the radionuclides present make it difficult to evaluate the risks for cancer and other diseases associated with fall-out in this population. However, the follow-up data are of interest, and the incidences of thyroid nodules and cancer have been reported up to 1986 (Table 67). Nine cases of papillary carcinoma of the thyroid were diagnosed among 253 exposed individuals, and two were found among 227 unexposed individuals (2.1 expected for unexposed Marshallese). With the doses estimated by Lessard *et al*. (1985), the risk coefficient for thyroid cancer was 1.5 per 10^6 persons per cGy per year. This estimate is uncertain, primarily because of the lack of precise data on the radionuclides involved. The interpretation is complicated by the possibility of hypothyroid conditions existing before exposure (which would have enhanced the uptake of radioactive iodine) and the use of thyroxine therapy to lower thyroid-stimulating hormone concentrations in the Rongelap inhabitants after exposure (Robbins & Adams, 1989).

(*c*) *Other test sites*

Few epidemiological data are available on cancers and exposure to fall-out from other nuclear test sites. Excess risks for thyroid cancers in regions adjacent to the Semipalatinsk test site in eastern Kazakhstan (see section 1.1.1(*c*)(iii)) have been suggested, but their relationship to radiation is unclear (Peterson *et al*., 1998). [The Working Group noted that the data are difficult to interpret because of potential bias in the selection of patients treated in hospitals and the lack of data on the population from which the cases came.]

The findings with regard to leukaemia among persons exposed during atomic weapons testing are described in the first monograph on ionizing radiation (IARC, 2000).

Table 67. Thyroid nodules and cancer in inhabitants of Rongelap atoll, Sifo Island (Ailinginae atoll) and Utirik atoll in the Marshall Islands through 1986

Site	Age at exposure (years)	No. of persons	Thyroid nodules		Thyroid cancer	
			No. observed	No. expected	No. observed	No. expected
Rongelap	*In utero*	3	2	0.079	0	0.026
	< 10	21	15	0.50	1	0.17
	10–18	12	3	0.92	2	0.15
	> 18	31	3	2.7	2	0.21
Sifo	*In utero*	1	0	0.026	0	0.0087
	< 10	7	2	0.18	0	0.061
	10–18	0	–	–	–	–
	> 18	11	3	0.98	0	0.075
Utirik	*In utero*	8	0	0.21	0	0.070
	< 10	56	8	1.5	1	0.49
	10–18	19	7	1.4	2	0.24
	> 18	84	8	7.5	1	0.58
All exposed		253	51	16	9	2.1
Comparison[a]		227	10		2	

From Robbins & Adams (1989). The expected numbers were based on those for unexposed Marshallese, as reported by Lessard *et al*. (1985).

[a] Age- and sex-matched unexposed Rongelap inhabitants, including additions to replace those lost to follow-up

2.9.2 *Techa River, Russian Federation*

The Techa River flows for about 240 km through the southern Ural Mountains. The history and dosimetry of exposure of the surrounding population to radionuclides from the Mayak facility is described in section 1.1.2(*b*), and the carcinogenic effects of exposure to plutonium are summarized in section 2.4.3. During 1949–56, radioactive wastes were discharged directly into the Techa River, and almost 124 000 people living on the banks of the Techa and Iset rivers received internal exposure (from ingestion of ^{89}Sr, ^{90}Sr and ^{137}Cs in contaminated water and food) and external exposure (from ^{137}Cs, ^{106}Ru, ^{95}Zr and other radionuclides) (Kossenko & Degteva, 1994; Kossenko, 1996; Yachmenyov & Isageva, 1996; Kossenko *et al*., 1997). Of the radionuclides released into the Techa River, the main contributor to internal exposure was ^{90}Sr, which accumulates in bone tissues and remains there for many years. In order to study the possible late effects of this exposure, a cohort of nearly 30 000 people was identified in 1968 from tax and medical records and evacuation lists, consisting of all persons who had been living in defined areas near the River on 1 January 1950.

A follow-up study of mortality (Kossenko *et al.*, 1997) suggested that the risks for death from leukaemia and other cancers had increased with increasing radiation dose in this population (Table 68). The dose categories were defined in terms of the estimated committed soft-tissue dose for solid tumours and the committed bone-marrow dose for leukaemia [apparently until the end of follow-up]. The excess numbers of cases were estimated as the difference between the observed number and an estimate of the number expected in the absence of exposure. The latter figure was calculated on the basis of an internal analysis of persons exposed to different doses, and appropriate external rates were not used. As significant external exposure was also received as a consequence of the release of radionuclides into the Techa River (Degteva *et al.*, 2000a,b), it is difficult to distinguish the independent effects of the internal and external exposures.

Table 68. Deaths from leukaemia and solid cancers in the Techa River cohort, 1950–89

Dose category (Sv)	Leukaemia			Solid tumours		
	Person–years	Observed	Excess	Person–years	Observed	Excess
0.005–0.1	103 031	3	–1	459 576	716	5
0.1–0.2	194 858	13	4	96 297	126	1
0.2–0.5	200 144	16	6	19 582	34	10
0.5–1	93 873	9	5	32 204	52	6
> 1	49 398	9	7	33 645	41	8
Total	641 304	50	21	641 304	969	30

Adapted from Kossenko *et al*. (1997). Person–years computed through date of death, loss to follow-up or 31 December 1989

The Techa River cohort is important because it consists of a general population (both sexes and all ages) exposed to a wide range of doses. The population living in the affected settlements includes members of two distinct ethnic groups, Russian and Tatar/Bashkir, so that ethnic differences in cancer risk might be studied. Kossenko *et al*. (1997) noted a number of limitations of their study, including difficulties in dosimetry, incomplete ascertainment of vital status and the absence of a fixed internal control group. There may also have been possible confounding from the presence of toxic chemicals in the liquid wastes released from the Mayak facility (UNSCEAR, 1994, 2000). [The Working Group noted that the adequacy of the dose estimates and the completeness of follow-up in this study are being investigated.]

2.10 Caesium

Fall-out from weapons testing in the 1950s and from the Chernobyl accident resulted in the ingestion of ^{137}Cs by Lapps who breed reindeer in the northern parts of the Nordic countries and the Russian Federation (Ahman & Ahman, 1994). In addition, small amounts of ^{241}Am and ^{241}Pu were ingested by Lapps from contaminated reindeer (Holm & Persson, 1978).

A cohort of 2034 Lapps who bred reindeer in Sweden or who were members of the households of breeders was assembled in 1960 and followed through mortality registries from 1961 through 1985. The rate of mortality from all causes was similar to that of the entire Swedish population: 428 deaths occurred, and the SMR was 0.95. A significantly lower mortality rate than expected was observed for all cancers (SMR, 0.70), and significantly decreased risks were found for cancers of the colon, respiratory organs, female breast, male genital organs and kidneys and for malignant lymphomas. The stomach was the only site for which a significantly increased risk for cancer was found (SIR, 2.25; 95% CI, 1.46–3.32) when compared with national rates. Lapps who breed reindeer have ingested fall-out products via the lichen–reindeer–man food chain since the 1950s, but no increased risk was found for cancers at the sites considered to be most sensitive to radiation (Wiklund *et al*., 1990, 1991).

2.11 Low-energy β-particle-emitting radionuclides

Several radionuclides that emit low-energy β-particles can be deposited in the body, where they act as internal emitters. Examples are ^{3}H (18.6 keV) and ^{14}C (156.5 keV) (see section 2.9.1). Both are pure β-particle emitters with stable decay products. The doses from ^{3}H are included in the dosimetry of whole-body external radiation for workers. In a case–control study of prostate cancer among workers at the Atomic Energy Authority in the United Kingdom, Rooney *et al*. (1993) found a significant association with the probable level of exposure to ^{3}H (χ^2 for trend, 5.9; $p < 0.05$; 1 degree of freedom); however, the ^{3}H-exposed workers were also exposed to external γ-radiation and a number of other radionuclides.

3. Studies of Cancer in Experimental Animals

During the past 60 years, many studies have been conducted on the biological disposition and lifetime health effects of internally deposited radionuclides in laboratory animals. These studies were conducted to (a) increase knowledge about radionuclides for which some human data are available (see section 2); (b) extend the knowledge base to other radionuclides and routes of exposure for which no human data are available; and (c) examine the underlying processes and mechanisms of the behaviour and effects of radionuclides in the body. In this section, studies of carcinogenicity of a broad range of α- and β-particle-emitting radionuclides are summarized, most of which were large and were conducted over many years in specialized facilities equipped for safe work with relatively large amounts of radioactive materials. The results of these long, expensive studies are uniquely valuable international resources.

Readers interested in obtaining more information are encouraged to consult the files of the International Radiobiology Archives of Long-term Animal Studies, described by Gerber *et al*. (1999). These archives were created by American, European and Japanese scientists to safeguard the data and make them available for use by other scientists now and in the future.

3.1 α-Particle-emitting radionuclides

3.1.1 *Pure α-particle emitters*

(*a*) *Radon-222*

^{222}Rn and its decay products were evaluated previously for carcinogenicity (IARC, 1988), and there was judged to be *sufficient evidence* for their carcinogenicity in experimental animals. After exposure by inhalation, respiratory tract tumours were induced in rats and dogs.

(*b*) *Polonium-210*

Hamster: The relative carcinogenicity of ^{210}Po was studied after intratracheal injection of a soluble form, resulting in relatively uniform distribution of radioactivity in the lung, in contrast to the non-uniform distribution of ^{210}Po adsorbed onto Fe_2O_3 carrier particles. Female Syrian golden hamsters, eight weeks of age, received multiple intratracheal instillations of ^{210}Po and/or other materials, as described below, and were observed for life. In the first study, the hamsters were divided into three

groups that received two instillations every week for seven weeks. Group 1 received separate instillations of ^{210}Po alone and Fe_2O_3 (3 mg); group 2 received an instillation of ^{210}Po plus Fe_2O_3 (3 mg) and an instillation of saline; and group 3 received the same treatment as group 2, except that the ^{210}Po was adsorbed onto 0.3 mg Fe_2O_3. The doses given to these animals were calculated from data on distribution and retention in hamsters that were killed periodically. In each group, 34–38 hamsters were examined histologically. The doses and lung tumour incidences in the three groups were: group 1, 1500 rad [15 Gy], 22/38; group 2, 2700 rad [27 Gy], 24/37; and group 3, 1700 rad [17 Gy], 15/34. The ultimate tumour incidence was not significantly different between groups 1 and 2, but the incidence in group 3 was slightly lower. These experiments at relatively high doses showed that 'hot spot' radiation is not more carcinogenic than a diffuse pattern of α-particles when the absorbed dose is taken into account. This point was examined further in an experiment with larger numbers of hamsters and lower doses. One group received ^{210}Po in saline, another received ^{210}Po on Fe_2O_3 (3 mg) particles, and the controls were either instilled with Fe_2O_3 or unexposed. The ^{210}Po was given as 15 weekly instillations of 1.25 nCi [46 Bq] each. Necropsy of 99 animals that received ^{210}Po in saline, resulting in an average dose to the lung of 55 rad [0.55 Gy], showed nine lung tumours. With the combined ^{210}Po–Fe_2O_3 treatment, the α-particle dose was 75 rad [0.75 Gy], and the lung tumour incidence was 10/82. The authors found no evidence to support the 'hot particle' hypothesis in these studies. They did note a difference in the histological features of the lung cancers in the two studies: most of the tumours found at the high dose were classified as combined epidermoid and adenocarcinomas because both histological features were often present in the same tumour, whereas all the tumours found at the low dose were combined tumours (Little *et al.*, 1978a). [The Working Group noted that these results raise an important, unexplained point: why high incidences of lung tumours were produced in hamsters by intratracheal instillation of ^{210}Po, while hamsters exposed by inhalation to aerosols of the α-particle emitter $^{239}PuO_2$ (Sanders & McDonald, 1992) or the β-particle emitter ^{144}Ce with fused aluminosilicate particles (Lundgren *et al.*, 1982) developed few lung tumours.]

The same group studied intratracheal instillation of ^{210}Po and benzo[*a*]pyrene into male Syrian golden hamsters from 11 weeks of age in order to examine the possible synergistic effects of combined exposures to these two compounds, both of which are present in tobacco smoke. Various exposure strategies were used, including simultaneous administration of the two agents and sequential administration of one agent before the other. In preliminary studies of simultaneous administration, an additive but not a synergistic lung cancer response was seen. In the study of sequential administration, 312 hamsters each received a single intratracheal instillation of 40 nCi of ^{210}Po [1480 Bq] either in saline or on Fe_2O_3 particles at 11 weeks of age. Eighteen weeks later, half of the animals were given a series of seven weekly intratracheal instillations of 0.3 mg benzo[*a*]pyrene adsorbed on 3 mg Fe_2O_3 carrier particles. No lung tumours occurred in 65 animals given ^{210}Po alone on Fe_2O_3 particles and one occurred in

74 animals given ^{210}Po in 0.9% saline. Addition of the seven instillations of benzo[*a*]-pyrene raised these numbers to 13/72 and 10/63 tumours, respectively, which the authors interpreted as a synergistic effect. Subsequent studies showed that multiple instillations of 0.9% saline alone could also significantly increase the number of ^{210}Po-induced lung tumours, even when no chemical carcinogen was present. The authors suggested that their results showed a minimal interaction between ^{210}Po and benzo[*a*]-pyrene. The effect of repeated saline injections after instillations of ^{210}Po was considered to mimic the effect of chronic lung irritation, such as might be produced by cigarette smoke acting as a potentiating factor (Little *et al.*, 1978b).

3.1.2 *Mixed α-particle emitters*

(*a*) *Radium-224*

Radium-224 is a short lived α-particle-emitting isotope (half-life, 3.6 days) which deposits most of its energy on the bone surface. It has been studied because of its medical use and to determine the relative carcinogenicity of surface- and volume-seeking isotopes.

Mouse: In a study to compare the occurrence, location and characteristics of osteogenic sarcomas induced by ^{224}Ra and by ^{226}Ra, 500 female ICR mice, 10 weeks of age, were given an intraperitoneal injection of ^{226}Ra [vehicle not specified] at a dose of 8.8 (200 mice), 24.6 (200 mice) or 70.5 μCi/kg bw (100 mice) [326, 910 and 2610 kBq/kg bw, respectively]. Radium-224 was administered by fractionated intraperitoneal injections at three- or four-day intervals for 75 weeks to another three groups of 100 mice [presumed to be female], to give total activities of 0.65, 1.8 and 5.22 μCi/mouse [24, 67 and 193 kBq/mouse]. Administration of ^{224}Ra was intended to provide a cumulative skeletal dose corresponding to that of ^{226}Ra. Skeletal tumours were identified by radiological examination and later confirmed by histological examination. The authors quantified the radiographic lesions in an attempt to differentiate tumours induced by the two nuclides. Seventy-four tumours were identified in the 500 animals exposed to ^{226}Ra and 89 tumours in the 300 animals exposed to ^{224}Ra. The authors noted that the ^{224}Ra-induced tumours tended to be diagnosed sooner than those induced by ^{226}Ra, that there appeared to be differences in their anatomical location and that the larger tumours (measured in the radiographs) were generally seen more frequently in ^{224}Ra-exposed animals (Svoboda *et al.*, 1977).

Several life-span studies on the comparative effects of single and protracted exposures to ^{224}Ra and ^{226}Ra have been conducted. In a large series of experiments, fractionated injections of short-lived bone-seeking radioisotopes were shown to cause a remarkable increase in the incidence of osteosarcomas in NMRI mice when compared with a single administration of the same skeletal dose. This effect was observed with both α- and β-particle emitters (^{224}Ra, ^{227}Th, ^{177}Lu). In addition, the latency was shortened by protracting the dose (Müller *et al*., 1983).

A study of the effect of age on osteosarcoma induction by the short-lived bone-seeking isotopes, ^{224}Ra and ^{227}Th was described. Weanling female NMRI mice, 36 days of age, and adult mice, 152–167 days of age (mean, 159 days), were given an intraperitoneal injection of 25 μCi/kg bw ^{224}Ra [925 kBq/kg bw], and the tumour incidence was compared with the spontaneous tumour incidence in 2000 control NMRI mice in the same colony. The mean skeletal dose was 750 rad [7.5 Gy]. The incidences of osteosarcoma were 17/94 (18%) in weanling rats and 21/246 (9%) in adults, after average latencies of 553 and 476 days, respectively, a statistically significant difference. The authors reported an additional five osteosarcomas of the jaw in adults, but these were considered to be a special 'feature' of rodents. [The Working Group noted that jaw necrosis is observed in humans, however; indeed 'radium jaw' was described in the 1920s.] Of animals injected with 5 μCi/kg bw ^{227}Th [185 kBq/kg bw], 21/50 (42%) weanling animals and 29/150 (19%) adult mice developed an osteosarcoma. The latencies were again significantly different, as seen with ^{224}Ra, that for the weanling animals being longer (average, 545 days) than that for adults (average, 432 days) (Luz *et al.*, 1979).

The same group later described another study with ^{224}Ra in mice. Approximately 300 female NMRI mice, four weeks of age, received a single injection of ^{224}Ra at a dose of 18.5 kBq/kg bw, corresponding to a mean skeletal dose of about 0.15 Gy. A second group of approximately 300 mice received the same total amount of ^{224}Ra in 72 injections given twice a week. Complete necropsy was carried out on all dead or moribund animals and included a radiographical examination. All diagnoses were confirmed by histopathology. A high incidence (13%) of early malignant lymphoma was observed soon after the injection period in the group given fractionated doses, and this was followed later by a 7% incidence of osteosarcomas. The group given the single injection did not develop the early lymphomas, but 5.8% developed osteosarcomas. After 800 days, no new osteosarcomas were observed in the group given the single injection, but about one-third of the osteosarcomas in the group given the protracted dose occurred after this time (Müller *et al.*, 1990).

Four groups of 400 male CBA/H mice, 12 weeks of age, were given an intraperitoneal injection of 69, 139, 280 or 550 kBq/kg bw ^{224}Ra. Another group of 400 mice was given the vehicle and served as controls. The mice were then permitted to live out their lifespan until they either died or were killed when moribund. If anaemia was detected, blood was taken and examined for leukaemia or other blood disorders. Organs and tissues were prepared for histopathology, and animals suspected of having a bone tumour were radiographed. As shown in Table 69, a dose–response relationship was apparent for both myeloid leukaemia and osteosarcomas. The authors concluded that the mice were at greater risk for myeloid leukaemia than for osteosarcomas at the doses studied (Humphreys *et al.*, 1993).

Dog: A lifetime study on the effects of ^{224}Ra in beagle dogs was started at the University of Utah but completed at the Inhalation Toxicology Research Institute (ITRI), Albuquerque, New Mexico, USA (Muggenburg *et al.*, 1995, 1996a). Two

Table 69. Leukaemia and osteosarcoma in groups of 400 male CBA/H mice injected with ^{224}Ra

^{224}Ra (kBq/kg bw)	No. of mice excluded	Median survival (days)	No. of mice with myeloid leukaemia	No. of mice with osteosarcoma
0	6	692	1	1
69	6	702	6	1
139	1	663	11	4
280	5	673	17	6
550	1	669	18	10

From Humphreys *et al.* (1993)

groups of 18 male and 18 female dogs received 10 or 50 weekly intravenous injections and a further group of 19 male and 19 female dogs received a single injection of ^{224}Ra citrate at one of four activity levels to give a mean skeletal dose to bone of approximately 0.1, 0.3, 1.0 or 3 Gy. A control group of 18 dogs of each sex was injected with citrate buffer. Skeletal tumours were detected by periodic radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected at clinical examination or at necropsy and classified by histopathology. The main late effect was the development of bone tumours, and the next most frequent was tumours of the nasal mucosa. Three dogs that received the highest single dose by injection died after 9–16 days from severe haematological dyscrasia. Eighteen dogs developed bone tumours: 15 had a single tumour, two had two tumours, and one had three tumours. Sixteen of the tumours were classified histologically as osteoblastic osteosarcomas, one as a chondroblastic osteosarcoma, one as a fibroblastic osteosarcoma, two as fibrosarcomas and one as a myxosarcoma. Kaplan-Meier methods indicated that tumours occurred sooner in the animals given protracted doses. When the number of tumours per Gy of skeletal dose was calculated and then summed across the years, there were 0.84 tumours per Gy in the dogs receiving 50 injections, 0.20 tumours per Gy in the dogs receiving 10 injections and 0.23 tumours per Gy in the dogs receiving one injection. The authors also reported (Muggenburg *et al*., 1996a) that the age-specific incidence rate for mammary tumours was increased in all three groups treated by injection and was related to dose. They concluded that the frequency of haematological dyscrasia was amplified by delivery of a relatively high dose at a high rate, whereas that of bone tumours was amplified by delivery of relatively high doses at a lower rate. Lloyd *et al.* (1997a) calculated that the ratio of toxicity of ^{224}Ra given in 50 weekly injections relative to a single injection of ^{226}Ra was 16 ± 5. This value was nearly identical to the toxicity ratio of a single injection of ^{239}Pu. Muggenburg *et al.* (1996a) estimated that the risk for developing a bone tumour was about 40 times higher in dogs than that reported in humans.

(*b*) *Radium-226*

Mouse: A large study in female CF1 mice was conducted by Mays and Finkel (1980), and the results were summarized by C.W. Mays in the discussion section of a paper by Raabe *et al*. (1983). The animals were given one intraperitoneal injection of ^{226}Ra, and the 3174 mice that lived at least 150 days were included in the analyses. The amounts injected ranged from 0 to 120 μCi/kg bw [0–4440 kBq/kg bw], and dose-related increases in the incidence of skeletal tumours were found, associated with a decrease in the average number of days after injection to the appearance of the skeletal tumours (Table 70).

Table 70. Bone sarcomas in female CF1 mice injected with ^{226}Ra

Average injected dose (μCi/kg bw)	No. of mice 150 days after injection	No. of mice with bone sarcomas	Average time from injection to appearance of bone tumour (days)	Average skeletal dose (Gy) 100 days before appearance of tumour
0	521	6	730	0
0.05	254	11	710	0.26
0.10	252	5	853	0.62
0.25	247	19	580	1.09
0.50	683	80	655	2.44
0.75	504	94	686	3.83
1.00	239	56	643	4.80
1.25	104	22	657	6.14
2.5	104	45	639	11.90
5	45	28	544	20.40
10	43	34	484	36.40
20	44	38	428	64.20
40	45	33	394	118.00
80	44	31	359	213.00
120	45	14	328	289.00

From C.W. Mays in discussion following paper by Raabe *et al*. (1983)

Five hundred female ICR mice were given an intraperitoneal injection of ^{226}Ra [carrier not reported], at 8.8 μCi/kg bw for 200 mice, 24.6 μCi/kg bw for 200 mice and 70.5 μCi/kg bw for 100 mice [326, 910 and 2610 kBq/kg bw]. An additional 300 mice were given graded doses of ^{224}Ra, and this report is described in that section (Svoboda *et al.*, 1977). While the authors did not provide a detailed report on the incidence of skeletal tumours, they reported a comparative radiological analysis of the tumours in mice exposed to ^{224}Ra and ^{226}Ra.

C57BL/Do black and C57BL/Do albino mice of each sex were given graded amounts of ^{239}Pu, ^{226}Ra, ^{241}Am, ^{239}Cf and ^{252}Cf by intraperitoneal injection in order to

determine the relative effectiveness of the nuclides, known as the 'toxicity ratio', in inducing skeletal cancers and the relative effectiveness of fission fragments (^{252}Cf) versus α-particles in inducing bone sarcoma. Groups of 12–18 mice received the nuclides at about 10 weeks of age, and 94 males and 87 females served as controls. The animals were then permitted to live out their natural life-span. The average activity of ^{226}Ra ranged from 0.057 to 9.88 μCi/kg bw [2.1–366 kBq/kg bw]. The results are summarized in Table 71 (Taylor *et al.*, 1983).

Table 71. Bone sarcomas in male and female C57BL/Do (black) mice and C57BL/Do (albino) mice injected with ^{226}Ra

Average dose injected (μCi/kg bw)	No. of mice	No. of bone sarcomas	Average time from injection to death (days)	Average skeletal dose (Gy) 140 days before death
Male, C57BL/Do (black)				
0	94	0	759	0
0.057	12	0	780	0.4
0.344	12	0	838	2.56
1.03	12	1	801	7.35
3.10	11	0	711	19.7
9.25	12	6	572	46.8
Female, C57BL/Do (black)				
0	87	1	741	0
0.057	12	0	743	0.38
0.344	12	0	761	2.32
1.03	12	0	699	6.4
3.10	12	3	675	18.6
9.25	14	4	498	39.6
Male, C57BL/Do (albino)				
0	60	0	608	0
0.058	10	0	768	0.39
0.344	15	0	758	2.33
1.08	18	0	700	6.77
3.23	14	0	635	18.1
9.88	14	1	527	45.5
Female, C57BL/Do (albino)				
0	58	0	626	0
0.058	15	0	727	0.37
0.344	12	0	752	2.31
1.08	11	0	766	7.43
3.23	14	1	752	17.6
9.88	10	4	727	56.5

From Taylor *et al*. (1983)

Rabbit: When rabbits [strain not specified] were injected with radium chloride [amount and dose is not clear], early changes were seen in lymphatic and haematopoietic tissues and cells. The authors also noted that two of the seven rabbits that survived 11–19 months developed osteogenic sarcomas (Sabin *et al.*, 1932).

Dog: Lifespan studies on the effects of ^{226}Ra given as a single injection to beagle dogs were started in 1952 in parallel with studies on ^{239}Pu, such that the results could be used to derive a 'toxicity ratio' for Pu:Ra that would serve as a basis for extrapolating data on the toxicity of Pu and other nuclides to humans.

A group of 120 young adult (17–20 months) beagle dogs equally divided by sex were given a single intravenous injection of ^{226}Ra at doses of about 0.2–440 kBq/kg bw (Lloyd *et al.*, 1991, 1993). An additional 132 animals served as unexposed controls. Skeletal tumours were detected by periodic radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology. One tumour was observed in the control group (Lloyd *et al.*, 1993). The distribution of ^{226}Ra in the bones was determined and expressed as a percentage of total activity by bone weight and percentage of total activity (Lloyd *et al.*, 1991). Fifty-seven primary skeletal malignancies were observed in 43 animals, of which 35 were found in the appendicular skeleton and 22 in the axial skeleton. The doses, average time to death, average skeletal dose to one year before death and the incidence of bone sarcomas are presented in Table 72. The authors concluded that, with few exceptions, the distribution of radium-induced skeletal malignancies follows the distribution of radium throughout the skeleton. Most tumours were observed in the tibia. The authors reported that the distribution of radium-induced skeletal cancers was similar in humans, with a preponderance of tumours in the appendicular versus the axial skeleton, and reflected skeletal mass and skeletal radium. One of the exceptions noted was a relatively greater number of tumours in the femur and pelvis of humans.

The location of selected ^{226}Ra-induced skeletal tumours was correlated with the relative amounts of cortical and trabecular bone determined by dissection and neutron activation analysis. The per cent tumour occurrence was linearly related to the corresponding percentage of cortical bone at these sites, resulting in a high correlation coefficient. A negative linear relationship between tumour location and trabecular calcium and trabecular surface was established (Jee *et al.*, 1986).

While skeletal cancers have been the predominant malignancy associated with exposure to ^{226}Ra in dogs exposed for life, the incidence of soft-tissue cancer has also been reported to be increased. Exposure to ^{226}Ra increased the incidence of eye tumours in dogs (Taylor *et al.*, 1972a; Lloyd *et al.*, 1994a; Taylor *et al.*, 2000), but tumours at this site have not been reported in humans exposed to radium. In dogs, radium is concentrated in the tapetum, a structure that is absent from the human eye.

In a detailed analysis of the soft-tissue tumours found among beagle dogs in these lifespan studies, it was suggested that the occurrence of skeletal tumours with increasing dose may have precluded the development of some soft-tissue lesions. In

Table 72. Dose–response relationship for skeletal malignancies in beagle dogs given a single intravenous injection of ^{226}Ra as young adults (17–20 months)

Dose injected (kBq/kg bw)	No. of dogs	No. of bone sarcomas	Average skeletal dose (Gy ± SD) 1 year before death	Age (years ± SD) at death with bone cancer	Age (years ± SD) at death without bone cancer
0	132	1	0	16.1	13.1 ± 2.6
0.275	10	0	0.28 ± 0.07	–	12.3 ± 1.9
0.651	25	2	0.80 ± 0.12	12.7 ± 1.7	13.4 ± 1.5
2.31	23	2	1.66 ± 0.77	10.8 ± 1.2	12.2 ± 3.5
6.13	14	2	3.57 ± 1.69	10.1 ± 1.6	10.8 ± 4.0
12.5	12	5	8.95 ± 1.98	10.3 ± 1.5	11.3 ± 4.0
39.6	12	11	19.1 ± 4.0	6.3 ± 1.1	5.8
119	12	12	43.3 ± 15.1	4.4 ± 0.5	2.4
383	9	9	101 ± 36	3.0 ± 0.5	2.4

From Lloyd *et al*. (1993)

this analysis, only the eye tumours were found to occur at a statistically significantly greater frequency in radium-exposed dogs than in the controls (Lloyd *et al.*, 1994a). In another analysis, no significant difference was found in the occurrence of the first or only mammary tumour, but a subsequent analysis indicated a significant relationship between exposure to ^{226}Ra and the number of mammary tumours and the age at which they occurred. With Cox regression statistics, an increase in risk for mammary tumours was associated with increasing dose (Bruenger *et al*., 1994).

In a lifespan study, 243 young adult beagle dogs, 435 days of age, were given eight fortnightly intravenous injections of graded doses of ^{226}Ra dissolved in a 0.1 N nitric acid–saline solution. A group of 78 control dogs was similarly injected, but the entire control group used in the comparisons included 159 animals. Skeletal tumours were detected by periodic radiographic and clinical examination and confirmed by histopathological evaluation after necropsy or amputation. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology. Several papers were published while the study was in progress. Raabe *et al*. (1981, 1983) summarized the data up to 1978 and reported that more deaths from bone tumour occurred in dogs exposed to ^{226}Ra than to ^{90}Sr (see section 3.2.1(*c*)) on the basis of average dose rate to bone. The dose–response relationship for bone cancer was represented by a log-normal curve.

A total of 155 primary bone sarcomas were identified in 131 of the 246 exposed animals (Table 73). The limbs of dogs with single skeletal tumours that were free of metastasis or other debilitating disease were amputated; after amputation, the animal was removed from the main study but was monitored separately. The authors reported that 31 additional primary bone sarcomas developed in the 44 dogs that were removed from the study after amputation. Five primary bone sarcomas were found in four of the

Table 73. Dose–response relationship for primary bone sarcoma in beagle dogs given eight fortnightly injections of ^{226}Ra at 435–540 days of age

Total dose injected (kBq/kg bw)	No. of dogs		No. of dogs with sarcomas		Skeletal dose (Gy ± SD)	Median age at death (years)
	Male	Female	Male	Female		
0	80	78	3	1	0	14.6
0.789	21	25	0	0	0.9 ± 0.2	14.5
2.37	19	19	3	1	3.0 ± 1.1	13.8
13.9	19	22	12	14	13.9 ± 3.5	10.9
41.4	20	19	19	15	31.6 ± 6.5	7.4
124	19	22	19	22	77.6 ± 22.9	5.1
370	22	19	13	12	167 ± 44	4.3

From White *et al*. (1994)

158 unexposed controls (incidence, 2.5%). The osteosarcomas in the exposed animals were relatively evenly distributed between the males and females (72:74), and the ratio of those occurring in the appendicular skeleton versus the axial skeleton was 108:38. Non-osteosarcomas predominated in the controls and the animals at the two lower doses, while osteosarcomas predominated at the higher doses. The authors reported that the incidence of osteosarcomas tended to increase with dose (White *et al.*, 1994).

To study possible age-related effects on the induction of skeletal tumours, life-span studies were conducted on beagle dogs exposed as juveniles (three months), as young adults (17–18 months) or when mature (five years). Ten juvenile dogs, 12 young adults and nine mature dogs were given a single intravenous injection of 41 kBq/kg bw ^{226}Ra in a citrate solution. Skeletal tumours were detected by periodic radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology. The incidences of dogs with bone tumours were 7/10, 11/12 and 5/9, respectively (Bruenger *et al.*, 1991a). In a final analysis, Lloyd *et al*. (1999a) reported that the dogs exposed as juveniles or when mature had fewer bone tumours per Gy of average skeletal dose than those exposed as young adults. The relative radiation sensitivities were 0.66 ± 0.12 for the juveniles, 0.53 ± 0.09 for the mature animals and 1.0 for the animals exposed as young adults. The authors noted that some of the mature dogs died prematurely and thus may not have lived long enough to develop skeletal tumours. With this caveat, the authors concluded that young adult dogs appear to be at greater risk for developing a skeletal tumour than dogs exposed to an equivalent amount of ^{226}Ra as juveniles or when mature.

Some giant breed dogs have a higher spontaneous incidence of skeletal malignancies than smaller dogs. To determine whether such differences influence sensitivity to bone-

seeking nuclides and thus present a bias for extrapolating risk to humans, a limited lifespan study was conducted to compare the radiosensitivity of beagle and St Bernard dogs. ^{226}Ra in a citrate solution was given at a dose of about 0.2 to 40 kBq/kg bw by a single intravenous injection to 91 beagle and 23 St Bernard dogs of each sex, aged 554 ± 39 days. St Bernard dogs tended to have a shorter induction time for bone tumours than beagle dogs, but there was no proportional relationship between size and the incidence of tumours. The incidence of tumours is shown in Table 81 in section 3.1.2(*e*) (Taylor *et al.*, 1997).

(*c*) *Thorium-227, thorium-228, thorium-230 and thorium-232*

Mouse: ^{227}Th is a short-lived α-particle emitter (half-life, 18.7 days). The occurrence of osteosarcoma was compared in groups of 50 female BALB/c, C57BL and NMRI mice after a single intraperitoneal injection of 5 μCi/kg bw [185 kBq/kg bw]. At day 672 after exposure, the incidence of osteosarcoma (corrected for competing risks by the Kaplan-Meier statistical method) was 51%, 41% and 50% in the three strains, respectively. While tumours tended to occur earlier in the BALB/c mice, there were no significant differences among the three strains in the incidence of osteosarcomas. No osteosarcomas were observed in any of the controls (Luz *et al.*, 1982).

A study in which Thorotrast (colloidal $^{232}ThO_2$) was compared with ^{241}Am (Taylor *et al*., 1986) is described in the section on americium.

Rat: In a study to determine whether the tumour-inducing properties of Thorotrast were due to radiation, foreign body reactions or both, 20 groups of 96 Wistar rats, 12 weeks of age, were given various volumes and doses of colloidal $^{232}ThO_2$, some of which was enriched with ^{230}Th to achieve the desired radiation dose. In the volume experiments, the animals received 60, 120 or 300 μL of colloidal suspension; in the radiation experiments, the groups were given preparations in which the total α-particle emissions varied by factors of 1, 2, 5 and 10 relative to standard Thorotrast. The animals lived 8–41 months after injection. The occurrence of liver tumours was linearly related to dose, but no association with volume was established. The liver carcinomas, intrahepatic bile-duct carcinomas and haemangiosarcomas that developed in the exposed animals had similar histopathological features to those observed in humans; in addition, some benign tumours were noted, including liver-cell adenomas and intrahepatic bile-duct adenomas (Wegener *et al.*, 1988; Wesch *et al.*, 1983).

In another experiment in Wistar rats, a colloid with properties similar to Thorotrast, called Zirconotrast (ZrO_2, non-radioactive), was made 'radioactive' by the addition of various amounts of ^{228}Th/^{230}Th during its preparation. Various volumes and doses were injected. The results again demonstrated that the frequency of hepatic or splenic tumour-bearing animals depended on the dose rate and was not correlated with the number of injected particles. The pure non-radioactive colloid did not induce primary hepatic or splenic tumours in excess (Wesch *et al.*, 1986).

The livers of female Wistar rats, 3–4 months of age, were exposed to fractionated neutron irradiation at 14-day intervals (0.2 Gy per fraction) over two years to a total

dose of 10 Gy to simulate α-particles with no foreign-body effect. Before the start of irradiation, half of the animals received non-radioactive Zirconotrast. At the end of the lifespan study, about 40% of the irradiated animals had liver tumours. In the animals treated additionally with Zirconotrast, the incidence, time of onset and overall number of liver tumours were nearly equal, indicating that fractionated neutron irradiation was the only cause of the tumours (Spiethoff *et al*., 1992).

Hamster: Colloidal $^{232}ThO_2$ or ^{239}Pu citrate was administered to Chinese hamsters in order to compare the liver carcinogenicity of uniform (^{239}Pu) and non-uniform (^{232}Th) exposure. Hamsters of each sex, aged 90–120 days, were given intravenous injections of $^{232}ThO_2$ at 0.3, 1.5 or 7.4 kBq/kg bw or monomeric ^{239}Pu citrate at 7.4 kBq/kg bw. Some animals were killed for cytogenetic analysis (see section 4.4), while others were held for lifetime observation. In a Cox proportional hazard statistical model, dose-related increases in the incidences of hepatocellular carcinomas and hyperplastic lesions in the liver were found with $^{232}ThO_2$ (Guilmette *et al*., 1989).

Dog: Groups of 4–13 beagle dogs, approximately equally divided between males and females, were given a single intravenous injection of ^{228}Th in a citrate solution at the age of 482–559 days. Twelve dogs were given an injection of the citrate carrier and served as contemporary controls (age 557 days). In later analyses, additional controls were added for statistical analyses. The injected dose ranged from 0.063 to 31.7 kBq/kg bw (see Table 74). Skeletal tumours were detected by periodic radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology. The occurrence of skeletal tumours (Table 74) showed a dose–response relationship. In a linear regression analysis, the lifetime risk for developing a bone tumour was about 39% per Gy of average skeletal dose. It was concluded that the

Table 74. Bone sarcomas in young adult beagle dogs given a single intravenous injection of ^{228}Th

Injected dose (kBq/kg bw)	Total no. of dogs	No. of bone sarcomas	Skeletal dose (Gy) 1 year before death	Age at death (days)
0	12	0	0	4763 ± 346
0.063	13	0	0.13	4770 ± 316
0.192	12	2	0.39	4309 ± 392
0.562	12	5	1.13	4006 ± 308
1.12	12	11	2.14	2943 ± 136
3.41	12	12	4.44	1708 ± 47
10.7	12	12	10.28	1353 ± 48
31.7	4	2	26.30	1259 ± 58

From Mays *et al*. (1987)

toxicity ratio for skeletal cancers in comparison with ^{226}Ra was 8.5 ± 2.3 (Mays *et al*., 1987; Lloyd *et al*., 1997a).

(*d*) *Uranium (natural)*

Mouse: In a study of the relative effectiveness of ^{239}Pu, ^{241}Am and ^{233}U in producing osteosarcomas or leukaemias, groups of 50–100 CBA/H mice, 12 weeks of age, were injected intraperitoneally with one of three activity concentrations of ^{239}Pu, ^{241}Am or ^{233}U in the citrate form; a group of 100 controls were injected with non-radioactive citrate. The three doses were selected to provide average doses to the skeleton of 0.2–0.3 Gy, 0.5–1.0 Gy and 1.3–1.6 Gy on the basis of calculations from a parallel serial sacrifice study. The mice were held for lifetime observation and were necropsied and examined histologically. A total of 42 mice developed osteosarcomas. The incidences of osteosarcoma in the three dose groups were 2, 11 and 15%, respectively, with ^{239}Pu, 0, 3 and 21% with ^{241}Am and about 2% at each of the three doses of ^{233}U. The incidence of osteosarcomas in control mice was also about 2%. The relative risks for osteosarcoma were 4.2 with ^{239}Pu, 2.3 with ^{241}Am and 1.1 with ^{233}U. The relative risks with ^{239}Pu and ^{241}Am, but not with ^{233}U, were statistically significant at the 95% confidence level. Myeloid leukaemia was found in 47 radionuclide-injected mice but in none of the controls. The incidences were 4, 6 and 9%, respectively, at the three doses of ^{239}Pu, 4, 8 and 10% with ^{241}Am and 4% at each dose of ^{233}U. The relative risks for myeloid leukaemia were 1.8 with ^{239}Pu, 2.0 with ^{241}Am and 1.5 with ^{233}U. The relative risks with ^{239}Pu and ^{241}Am, but not with ^{233}U, were statistically significant at the 95% confidence level (Ellender *et al*., 2001).

Rat: Four groups of 63 male Sprague-Dawley rats, six weeks of age, were acclimatized to the exposure process and then, at nine weeks of age, were exposed daily by inhalation in nose-only inhalation chambers to aerosols of uranium ore dust at a concentration of 0 (control), 19 or 50 mg/m^3. The ore used contained 44% elemental uranium, and about 75% of the mass of airborne uranium was in particles < 5 μm. Exposure was for 4.2 h per day on five days per week for 65 weeks. When the exposure regimen was completed, the rats were held for lifetime observation. At death, each animal was necropsied and examined grossly and histologically, and the lung burdens of U were determined radiochemically for use in calculating the total absorbed dose of α-particles. The average doses were 0.87 and 1.64 Gy. Survival data were plotted but not analysed statistically. The numbers of primary malignant lung tumours and the numbers of rats examined were: controls, 1/63; 19 mg/m^3, 22/126 and 50 mg/m^3, 20/61. The corresponding numbers of primary benign lung tumours were: controls, 1/63; 19 mg/m^3, 17/126; and 50 mg/m^3, 8/61. All but one of the benign lung tumours were bronchioloalveolar adenomas. Of the malignant lung cancers, bronchioloalveolar carcinomas were most prevalent, followed by bronchiolar carcinomas and squamous-cell carcinomas (Mitchel *et al.*, 1999).

(*e*) *Plutonium-238 and plutonium-239*

(i) *Inhalation*

Mouse: The effects of protracted and single exposures to $^{239}PuO_2$ were compared in C57BL/6J mice. [The Working Group noted that most of the ^{238}Pu and ^{239}Pu source material also contained small amounts of ^{240}Pu.] Two groups of mice were exposed once at either 84 or 460 days of age to achieve an initial lung burden of 20, 90, 460 or 2300 Bq. The groups given protracted exposure from the age of 84 days were exposed every other month for up to six exposures in 10 months in order to establish a lung burden of 20, 90 or 460 Bq. The mice were permitted to live out their lifespans and were then necropsied. The groups of mice with protracted exposure to similar cumulative doses to the lung had a 3.4–4.4 times greater incidence of pulmonary tumours (identified as adenomas and adenocarcinomas) than those exposed once. The excess number of pulmonary tumours per unit dose to the lung was also greater in the groups given protracted exposures than in those exposed once (Lundgren *et al.*, 1987).

Groups of 15 male and 15 female heterozygous $p53^{+/-}$ knock-out mice and wild-type $p53^{+/+}$ mice were exposed to 500 Bq of $^{239}PuO_2$ by inhalation. Some of the mice were killed at six months, and the remainder were permitted to live their lifespan. Four of 29 knock-out $p53^{+/-}$ mice developed lung tumours, and the latency of these tumours was significantly shorter than that of the seven lung tumours that developed in 30 of the wild-type $p53^{+/+}$ mice. The data indicate that the *p53* allele plays a role in the expression of radiation-induced cancers in mice (Finch *et al.*, 1998).

Rat: The effect of neonatal thymectomy on lung cancer induction after inhalation of $^{239}PuO_2$ was studied to examine the influence of cell-mediated immunity, which is suppressed after neonatal thymectomy. Thymectomy was carried out within the first 24 h of birth of male and female Wistar rats. At 90 days of age, the animals were exposed to $^{239}PuO_2$ by inhalation (count median aerodynamic diameter, about 2.06 μm). A total of 258 rats were used, but some were eliminated during the study for various reasons. One group underwent sham surgery and was not exposed, one group was thymectomized and not exposed, while a third group was thymectomized and exposed. The lung dosimetry indicated a broad range of doses, such that the groups were divided into four subgroups: 101–300, 301–1000, 1001–3000 and 3001–15 000 rad [1–3, 3–10, 10–30 and 30–150 Gy]. Significant numbers of lung tumours were induced in the exposed animals, but there were no differences between the intact and thymectomized groups (total, 64/122 compared with 38/70). An increase in the incidence of extrapulmonary neoplasms was attributed to the effects of thymectomy (5/122 compared with 12/70). While thymectomy had no significant effect on the frequency of lung tumours, differences were noted in the staging of the cancers that did develop, including an increase in tumour size, enhanced tumour invasion and a greater frequency of regional metastases (Nolibe *et al.*, 1981).

A series of papers have been published on a lifespan study in which female Wistar rats were exposed to ^{239}Pu aerosols. In the first paper in a series (Sanders, 1992a), the

experimental design and lung dosimetry methods and calculations were reported. The study consisted of 2105 exposed and 1052 sham-exposed rats. The body weights at the time of exposure were about 250 g. The rats were exposed by nose inhalation only to a high-fired mixture of $^{169}Yb_2O_3$–$^{239}PuO_2$ with an activity median aerodynamic diameter of 1.6 ± 0.11 μm. The average activity ratio of Yb:Pu was 0.4. Doses to the lung were calculated for the 2105 exposed rats, whereas the doses of the controls were assumed to be at background or below 0.002 Gy. The animals were permitted to live out their lifespan, and an extensive range of tissues were examined histopathologically. Survival was reduced only for rats exposed to doses > 30 Gy. Except for pulmonary tumours, no significant difference was found in tumour location or type between the controls and the exposed rats; 90% of the non-pulmonary tumours were in the pituitary gland, mammary gland, uterus and thyroid. Although twofold greater incidences of tumours of the Zymbal gland, bladder, brain and liver were observed in exposed rats, the tumour incidence in each of these organs was < 1%. Ninety-nine primary lung tumours were identified, of which 92% were classified as malignant and 80% were carcinomas. Of the malignant tumours, 49 were squamous-cell carcinomas, 23 adenocarcinomas, nine haemangiosarcomas, seven adenosquamous carcinomas and three fibrosarcomas. In the controls, one adenocarcinoma was observed. Animals exposed to < 1.5 Gy developed only four adenomas. The lowest doses at which the various types of tumours developed were 1.5 Gy for squamous-cell carcinoma, 3.1 Gy for adenocarcinoma, 4.1 Gy for haemangiosarcoma and about 9 Gy for adenosquamous carcinoma and fibrosarcoma. The incidences of all lung tumours were 0.095% in the control rats, 0.21% in the 1877 rats that received lung doses < 1 Gy and 41% in the 228 rats that received > 1 Gy. The average absolute risk for malignant lung tumours was 270 lung tumours per 10^4 rat–Gy above a dose of 1 Gy (Sanders *et al.*, 1993a,b).

Five pleural mesotheliomas were observed among the 2105 exposed rats. In a comparison of the results of this study with those of previous studies in which $^{239}PuO_2$ was given by intraperitoneal injection, the $^{239}PuO_2$ particles were found aggregated on mesothelial surfaces after injection, resulting in a higher relative incidence of these tumours (four mesotheliomas in 527 exposed rats) (Sanders, 1992b).

A total of 2272 female and 138 male Wistar rats were exposed by inhalation to $^{239}PuO_2$, and the incidence of brain tumours was compared with that in 1058 female and 60 male controls. Survival was compared by a life-table approach and the incidence of tumours by a Mantel-Haenzel statistic. In the females, six brain tumours were found in the 1058 controls and 24 brain tumours in 2134 exposed rats (survival-adjusted $p = 0.29$). In the males, two tumours were found in the 60 controls and seven tumours in the 138 exposed rats (survival-adjusted $p = 0.33$). The incidence of brain tumours in males was thus about five times greater than that in females ($p = 0.0001$), but this was not related to the exposure. The tumour types were distributed similarly among the control and exposed animals, and the mean lifespans of control and exposed rats with brain tumours were not significantly different (Sanders *et al.*, 1992).

To determine whether the strain of rat determines pulmonary carcinogenesis after exposure to ^{239}Pu, the results for Wistar rats were compared with those for Fischer 344 rats. Two hundred female Fischer 344/nTac rats were exposed at 70 days of age to an aerosol of $^{239}PuO_2$ at 0.8–1.0 Gy (lower doses) or 34–37 Gy (higher doses), and 60 rats served as sham-exposed controls. The protocol was similar to that described above for Wistar rats. The median survival times were similar in the control and low-dose groups of both strains but were significantly decreased in the high-dose groups when compared with controls. Squamous metaplasia was observed in 62–65% of the high-dose groups of both strains but not in the controls. The incidence of adenomatous metaplasia was significantly higher in the controls and low-dose groups of Fischer 344 rats than Wistar rats. The incidences of lung tumours in Fischer 344 rats were 1.7% in the controls, 20% at the low doses and 82% at the high doses, whereas the incidences of lung tumours in Wistar rats were 0.1% in the controls, 0% at the low doses and 68% at the high doses. Rats of both strains at the high doses that died with lung tumours had longer median survival times than rats at these doses that died without lung tumours. These differences were not observed at the low doses, in which the absolute risk for lung tumours was 1900 per 10^4 rat–Gy for Fischer 344 rats and 0 for Wistar rats; the absolute risk in the high-dose groups of both strains was about 210 tumours per 10^4 rat–Gy. The adenomatous tumour types predominated in Fischer 344 rats, while squamous tumours dominated in Wistar rats. The authors concluded that overall, Fischer 344 rats are more 'sensitive' than the Wistar strain (Sanders & Lundgren, 1995).

Five hundred female Fischer 344/N rats, aged 13 ± 2 weeks, were exposed to a nebulized ^{239}Pu aerosol, and the dosimetry was determined with a ^{169}Yb tracer on days 7, 14 and 21 after exposure. Six rats were killed after 7, 14, 30, 60, 120, 240 and 360 days and the tissues prepared for histological and morphometric evaluation. For determination of cytokinetics, five exposed and five control rats were each given ^{3}H-thymidine as a marker of cell proliferation, and autoradiographs were prepared. The measured retention of ^{239}Pu was calculated to commit an average dose to the lung of 16 Gy 500 days after exposure. Maximal increases in alveolar and bronchiolar epithelial cell labelling were seen 30 days after exposure and then decreased. Focal proliferative epithelial lesions had developed in the lung by 180 days and preceded the onset of lung neoplasms. Neoplasms, primarily adenocarcinomas and squamous-cell carcinomas, were initially observed at 308 days. It was concluded that Pu-induced pulmonary neoplasms develop through a sequence of focal proliferative lesions that represent developmental preneoplastic lesions (Herbert *et al.*, 1993).

In another study in Fischer 344 rats, the measured retention of inhaled ^{239}Pu was calculated to result in an average dose to the lung of 16 Gy 500 days after exposure. Immunohistochemical, histological and ultrastructural methods were used to study each histological type of lesion. The epithelial cells of the proliferative lesions and neoplasms had ultrastructural features consistent with type II pneumocytes, and the authors concluded that most ^{239}Pu- induced proliferative lesions and neoplasms in rats originate from alveolar type II pneumocytes (Herbert *et al.*, 1994).

The long-term effects of single and repeated exposure to $^{239}PuO_2$ was studied in 84-day-old Fischer 344/Crl rats. For repeated exposure, rats were exposed by inhalation to aerosols of $^{239}PuO_2$ seven times at two-month intervals: 123 rats were exposed 130 ± 52 Bq, 71 rats to 410 ± 140 Bq and 105 rats to 1500 ± 590 Bq; 98 rats were sham-exposed and held for lifetime observation. The single exposures consisted of 146 rats at 11 ± 7 Bq, 119 rats at 140 ± 81 Bq, 101 rats at 370 ± 210 Bq and 40 rats at 1400 ± 560 Bq; 82 sham-exposed rats were held for lifetime observation. Animals that died or were killed when moribund were necropsied and examined for tumours by histopathology. The incidences of lung tumours were not significantly different in the groups of rats with similar lifetime mean doses to the lungs of 0.9 ± 0.39 to 4.4 ± 1.8 Gy, whether exposed once or repeatedly. Rats that received a mean dose of 12 ± 2.4 Gy in a single exposure had a significantly higher crude incidence of lung tumours than animals that received 10 ± 2.1 Gy to the lung by repeated exposure. The crude incidence rates of benign and malignant tumours in rats that inhaled a single or repeated doses of $^{239}PuO_2$ as a function of dose to the lung could be described by a curve from a single-parameter Weibull model. The results for lung tumours in young adult rats that inhaled an insoluble form of ^{144}Ce, $^{144}CeO_2$, once or at repeated doses (see section 3.2.2(*c*)) might also be represented by this type of curve. The two curves of the crude incidence of lung tumours versus dose to lung for $^{239}PuO_2$ and $^{144}CeO_2$ were separated along the dose axis by a factor of about 21, reflecting the greater effectiveness of α-irradiation from $^{239}PuO_2$ than the β-irradiation from $^{144}CeO_2$ (Lundgren *et al.*, 1995).

The incidence of ^{239}Pu-induced pulmonary tumours was studied in rats with bleomycin-induced pulmonary fibrosis in order to identify possible modifying factors for radiation-induced carcinogenesis. Equal numbers of male and female Fischer 344/Cr1 rats, 14–16 weeks of age, received bleomycin by intratracheal instillation at a dose of 8.5 IU/kg bw to induce pulmonary fibrosis; 45–49 days later, the animals were exposed to an aerosol of ^{239}Pu at an initial lung burden of 85 or 850 Bq with a ^{169}Yb tracer for dosimetry. A group without induced fibrosis was included. Retention of ^{239}Pu in the lungs was studied in rats killed 2 h and 8, 16, 32, 64, 128, 192, 359 and 541 days after exposure. A cross-sectional study of lung function was conducted in 4–11 females in each exposed group (control, low and high dose) and in the two groups with and without bleomycin. Clearance of ^{239}Pu from the lungs was significantly decreased and the incidence of non-neoplastic lung lesions was significantly increased in the rats with fibrosis than in controls. Groups of rats that received similar doses of α-particles showed no significant effects of pre-existing pulmonary fibrosis on the incidence of neoplastic lesions in the lung, time to death of rats with lung neoplasms or the risk for lung tumours per unit dose of α-particles (Lundgren *et al.*, 1991).

A total of 310 female Wistar rats, eight weeks of age, were exposed once by inhalation to an aerosol of $^{239}PuO_2$ and then classified into one of seven groups on the basis of the mean initial lung deposition and cumulative lung dose, ranging from 0.71 to 8.5 Gy. An unexposed group of 130 controls was available. The study design and

results are shown in Table 75. At death, the animals were necropsied, their tissues were assessed by routine histopathology, and sections from all epithelial tumours were stained immunocytochemically for intranuclear *p53* protein. Primary lung tumours were found in 2.3% of the unexposed controls, in about 44% of those at a mean lung dose of 0.71 Gy and in 97% at 5.4 Gy. The dose-related appearance differed by histological type of tumour: the maximum incidence of adenomas was seen at 0.71 Gy, adenocarcinomas at 2.9 Gy and adenosquamous and squamous-cell carcinomas at 5.4–8.5 Gy (Oghiso *et al.*, 1994a, 1998).

Table 75. Primary lung tumours in female Wistar rats exposed to an aerosol of $^{239}PuO_2$

Initial lung deposition (Bq)	Number of animals	Lung dose (Gy)	Length of survival (days)	No. of primary lung tumours	Crude incidence (%)
0	130	0	790 ± 144	3	2.3
97 ± 27	43	0.71 ± 0.19	871 ± 105	19	44.2
225 ± 48	75	1.52 ± 0.28	712 ± 162	45	60.0
461 ± 118	60	2.88 ± 0.51	631 ± 158	46	76.7
787 ± 79	40	4.67 ± 118	675 ± 98	37	92.5
948 ± 76	31	5.43 ± 0.29	622 ± 105	30	96.7
1147 ± 114	31	6.61 ± 0.28	550 ± 82	29	93.5
1672 ± 261	30	8.52 ± 0.67	458 ± 95	27	90.0

[a] From Oghiso *et al.* (1998)

In studies of the possible synergistic effect of $^{239}PuO_2$ with the environmental chemical carcinogen benzo[*a*]pyrene, eight groups of male Wistar rats, two months of age, received $^{239}PuO_2$ at various doses with or without benzo[*a*]pyrene given as two intratracheal instillations of 5 mg/animal. The results are shown in Table 76. Survival decreased with increasing dose of plutonium and exposure to benzo[*a*]pyrene. Some of the data fit a multiplicative relative risk model. The incidence of malignant lung tumours, adjusted for differences in survival, increased in a dose-related manner with dose of $^{239}PuO_2$ and was further increased in the presence of benzo[*a*]pyrene (Métivier *et al.*, 1984).

Hamster: Plutonium microspheres injected intravenously into Syrian hamsters were reported to lodge in the lung capillaries and to produce a low incidence of lung tumours (Anderson *et al.*, 1975). In a study to determine whether this response is unique to the hamster or whether a dose delivered by inhalation rather than injection would cause tumours in these animals, 10 groups of 14–34 hamsters of each sex were given microspheres of ^{239}Pu- or ^{238}Pu-laden ZrO_2 ceramic particles about 10 μm in diameter by intravenous administration. These particles were large enough to lodge in the capillaries of

Table 76. Lung tumours in Wistar rats given ^{239}Pu and benzo[*a*]pyrene

Initial lung deposition (Bq)	Benzo[*a*]-pyrene (mg)	No. of animals	Median survival (days)	Median life-time dose (Gy)	No. of pulmonary malignancies
0	0	89	864	0	0
220	0	89	820	3.3	17
630	0	30	798	9.4	14
6300	0	19	345	76.3	6
0	2 × 5	38	675	0	10[a]
220	2 × 5	29	444	2.9	17[b]
630	2 × 5	22	480	8.5	16
6300	2 × 5	19	330	75.4	19

From Métivier *et al*. (1984)
[a] Also two fatal benign tumours
[b] Also 10 fatal benign tumours

the lung. One week later, six groups were additionally exposed by inhalation to the same plutonium-laden ZrO_2 particles, which were generally spheroidal and had an activity median aerodynamic diameter of approximately 1.5–2.0 μm. An untreated control group was available. The mean initial lung burdens were 8–143 nCi [296–5291 Bq] of ^{239}Pu in three groups and ^{238}Pu in the other three groups. The particles were tagged with a ^{57}Co tracer to permit whole-body counting. The animals were permitted to live out their life-spans, and moribund animals were killed. All animals were necropsied, and pathological diagnoses were confirmed by histopathology. Males in both control and treated groups lived longer than females. A plot of the survival data showed that animals that received the highest burden by inhalation had shorter lifespans than the controls, but this was not seen at lower doses. The results suggested a decreased induction time and an increased total incidence of lung tumours with increasing lung burden, particularly with ^{238}Pu. Lung tumours developed in 5–50% of animals exposed by inhalation. Inhalation of plutonium particles was also associated with lung fibrosis. Concomitant intravenous administration of particles with plutonium had little effect on the incidence of respiratory and non-neoplastic, degenerative changes in the respiratory tract. No pulmonary tumours were seen in animals treated only by intravenous injection (Thomas & Smith, 1979).

Groups of 25 female hamsters, four months of age, were exposed to a high-fired $^{239}PuO_2$ with an activity median aerodynamic diameter of 1.64 ± 0.13 μm. The initial lung burden 10 days after exposure was 2.4 ± 1.7 kBq, and, in animals killed 5–14 months after inhalation, the lung burdens were calculated to be 0.1–0.5 kBq. The dose to the lung one year after exposure was estimated to be about 12 Gy. Groups exposed to benzo[*a*]pyrene (positive control) and saline (negative control) were included. At scheduled necropsy 5–14 months after exposure, the lungs were dissected and the 10

most 'suspicious' 1-mm^3 areas were removed. Half of each sample was prepared for histology, and the other was transplanted into hamster cheek pouches for one month and then removed for histopathological evaluation. None of the lung transplants from the hamsters exposed to $^{239}PuO_2$ or the negative controls grew in the recipient cheek pouches, but 14% of the pulmonary lesions from the benzo[*a*]pyrene-exposed positive controls grew when transplanted (Sanders & McDonald, 1992). [The Working Group noted that these and other authors found that the hamster does not appear to be particularly sensitive to the development of plutonium-induced lung tumours when compared with other species].

Dog: Lifespan studies of beagle dogs have been conducted at several laboratories. The results have been reported both independently and combined for statistical strength. Studies in which dogs were given a single exposure to $^{238}PuO_2$ with a count median diameter of 0.1 μm were started in 1967 at the Pacific Northwest Laboratories in the USA, and in 1972 a study was begun with a single exposure to $^{238}PuO_2$ with an activity median aerodynamic diameter of 1.8 μm. At the Inhalation Toxicology Research Institute (ITRI), also in the USA, a study in which $^{238}PuO_2$ with an activity median aerodynamic diameter of 3.0 μm was given was started in 1973 and a study with $^{238}PuO_2$ with an activity median aerodynamic diameter of 1.5 μm was started in 1974.

The studies conducted at the Pacific Northwest Laboratories involved 136 beagle dogs in groups of 13–22 animals each, approximately equally divided by sex. A total of 116 dogs were exposed once to $^{238}PuO_2$ aerosols, resulting in lung depositions of 0 (controls), 0.13, 0.68, 3.1, 13, 52 and 210 kBq, and were observed for life. Interim reports were published as the study progressed, the early reports presenting clinical findings that had appeared at the higher doses. Some dogs developed respiratory insufficiency due to plutonium-induced pneumonitis within three years of exposure (Park *et al*., 1976). Nine of the first 11 dogs that were killed 4–6 years after exposure had developed osteosarcomas, and 30–55% of the terminal plutonium body burden was in the skeleton. Park *et al*. (1997) summarized the completed study. In the tissues of the 30 dogs that survived the longest (mean, about 14 years), about 1% of the final body burden was found in lung, 46% in the skeleton, 42% in the liver and 6% in the thoracic lymph nodes. Of the 116 exposed dogs, 34 (29%) developed skeletal tumours, 31 (27%) developed lung tumours and eight (7%) developed liver tumours. Bone tumours were the primary cause of death at the three higher doses, and the survival of these animals was significantly decreased. The total accumulated doses of radiation to the lung were higher than the average skeletal dose, but more deaths were attributed to skeletal than to lung tumours. Some of the deterministic effects observed included radiation pneumonitis, osteodystrophy, hepatic nodular hyperplasia, lymphopenia, neutropenia and sclerosing tracheobronchial lymphadenitis. Hypoadrenocorticism was also observed in a few dogs.

In the study conducted at the ITRI, 72 beagle dogs were exposed once to monodisperse aerosols of $^{238}PuO_2$ with an activity median aerodynamic diameter of 1.5 ± 1.2 μm; 72 dogs were exposed once to $^{238}PuO_2$ particles with a diameter of

3.0 ± 1.1 μm, and 24 dogs served as sham controls. Equal numbers of female and male dogs were entered into the study. The dogs were observed for life, with periodic examinations. A detailed post-mortem examination was done on all animals, and their tissues were processed for histopathology. Gillett *et al*. (1988) summarized the study to date. Significant translocation of ^{238}Pu from the lung to other tissues, especially the liver and bone, was observed. Of the 144 dogs that had been exposed, 112 had died by 4000 days after exposure. Of these dogs, 100 had developed an osteosarcoma and 28 had developed a lung cancer. Liver lesions were observed with greater frequency with increasing time after exposure. Ten primary liver cancers were diagnosed in animals that survived to 4000 days, and an additional five tumours were found in three of the nine animals that were killed after 4000 days. Most of the liver tumours were classified as fibrosarcomas and were generally not the cause of death.

Muggenburg *et al*. (1996b) summarized some of the additional findings from this study and reported that bone tumours had developed in 93 of the 144 dogs, lung tumours in 46 and liver tumours in 20. Some dogs had tumours in all three of these organs. Liver tumours occurred later than bone and lung tumours. The skeletal distribution of the bone tumours in dogs that inhaled $^{238}PuO_2$ was reported to be similar to that seen in dogs injected with ^{239}Pu citrate (Lloyd *et al*., 1994b).

A statistical analysis of the combined data from these studies involved use of age-specific risk (hazard functions) to evaluate the relationships between lung, liver and bone tumours and cumulative dose of radiation and to estimate lifetime risks. For the lung tumours, a linear–quadratic function provided an adequate fit to the data from both laboratories, and linear functions were adequate for doses < 20 Gy. Some significant differences were found between the data from the two laboratories, the estimated risk coefficients for these functions being larger when based on the data from ITRI than when based on those from the Pacific Northwest Laboratories. Furthermore, the bone tumour response functions appeared to differ between the two laboratories, but mainly at higher dose rates. The authors attributed the possible differences to 'dosimetry biases'. Both studies provided evidence of radiation-induced bone tumours at doses < 0.5 Gy. The risk for liver tumours was similar in the two laboratories, and linear functions provided an adequate fit to these data (Gilbert *et al.,* 1998b).

In dogs that inhaled $^{239}PuO_2$, significant lymphopenia was observed in 58% of the animals at the five higher doses (0.69–213.3 kBq), and lymphoid atropy, sclerosis of the thoracic lymph nodes and lymphopenia were observed at the four higher doses (> 2.5 kBq). Using a linear regression analysis, the authors found a moderate correlation between the reduction in lymphocyte values and initial lung deposition, in both magnitude and the time of appearance after exposure. No primary tumours were identified in the thoracic lymph nodes in this study, but lung tumours were found in 70% of the dogs with lymphopenia (Weller *et al.,* 1995a).

The effects on the liver of dogs exposed to $^{239}Pu(NO_3)_4$ are summarized in Table 77. At the end of the study, the liver contained $40 \pm 1\%$ of the plutonium, but this was less than the amount found in the skeleton. Autoradiographs indicated that the

Table 77. Incidences of liver tumours in dogs exposed to $^{239}Pu(NO_3)_4$ by inhalation

Initial lung burden (kBq/kg bw)	No. of animals exposed	Median survival (months) after exposure	No. of dogs with liver tumours	Liver dose (mGy)
0	20	139	1	0
0 (vehicle)	20	154	0	0
0.98 ± 0.18	20	150	3	17 ± 3
2.6 ± 0.3	20	157	3	42 ± 5
19 ± 2	20	135	3	310 ± 40
91 ± 7	20	114	5	1110 ± 70
518 ± 51	20	62	0	2960 ± 2420

From Dagle *et al*. (1996)

parenchymal cells received a higher dose rate than would have been calculated if the distribution of plutonium were considered uniform (e.g. radiochemical analysis of the whole organ). Liver tumours, primarily bile-duct epithelial tumours, occurred late and were observed at doses at which the lifespan was not shortened by lung or bone tumours (Dagle *et al.*, 1996).

The incidence of pulmonary cancers among 108 beagle dogs exposed to $^{239}PuO_2$ at the age of 12–18 months is shown in Table 78. The lung was the sole target organ for neoplasia. An increased incidence of lung carcinomas was observed in animals that received doses ≥ 2 Gy; 178 neoplasms were found, almost all of which were carcinomas (47% carcinoma, 40% adenocarcinoma, 27% bronchioloalveolar carcinoma, 12% adenosquamous carcinoma and the remainder bronchial gland carcinoma, carcinosarcoma and sarcoma) (Hahn *et al.*, 1999).

The occurrence of testicular tumours in dogs exposed to $^{238}PuO_2$, $^{239}PuO_2$ and $^{239}Pu(NO_3)_4$ in these studies was analysed separately. A statistical correlation was found between the initial lung burden and the final concentration of plutonium in the testes, the per cent of the initial lung burden in the testes ranging from 0.0001 to 0.03%, depending on the solubility of the compound. There was, however, no statistically significant difference among the three plutonium-exposed groups or the control group in the cumulative proportion of dogs with testicular tumours, the distribution of tumour types and the mean time to first tumour appearance (Weller *et al.*, 1995b).

Monkey: Twenty male cynomolgus monkeys were exposed to aerosols of $^{239}Pu(NO_3)_4$ resulting in lung burdens of about 4, 10 and 40 kBq. Six mature and six immature monkeys were exposed to 40 kBq and two mature and two immature monkeys to 10 or 4 kBq; two mature and two immature monkeys were exposed to the carrier aerosols and served as controls. The animals were killed or died 0.1, 1, 12, 40 or 99 months after exposure. The concentration of ^{239}Pu in the liver increased to a maximum, one year after exposure, but had decreased to about 10% of this value by

Table 78. Incidences of lung tumours in dogs exposed to $^{239}PuO_2$ by inhalation

Initial lung burden (kBq/kg bw)	No. of animals exposed		Median survival (days) after exposure	Incidence of lung tumours
	Males	Females		
0 (control)	18	18	4846	0
0.19	11	11	4871	7/22
0.63	17	19	4058	15/22
1.6	25	21	3080	32/36
3.7	16	16	2022	28/32
6.3	12	17	1422	19/29
14	14	13	737	4/27
30	13	11	387	0/24

From Hahn *et al*. (1999)

99 months after exposure. ^{239}Pu was efficiently cleared from the lungs, so that by 99 months < 0.05 kBq of the initial 40 kBq remained. The skeletal content of plutonium increased during the first year, but the total skeletal activity remained relatively constant for the remainder of the study; the relative fraction of ^{239}Pu in the skeleton increased during this time, however, because of clearance of ^{239}Pu from other organs. Three of the animals at the highest dose died of radiation-related pulmonary pneumonitis or fibrosis. One primary papillary adenocarcinoma of the lung was observed at the high dose at 99 months (Brooks *et al.*, 1992). [The Working Group noted the short duration of the study and the fact that it was designed to investigate toxicity and chromosomal effects (see section 4.4).]

(ii) *Injection*

Mouse: In the study of Taylor *et al*. (1983), described in section 3.1.2(*b*), groups of 11–13 mice of each sex of two strains (C57BL/Do black and C57BL/Do albino) were given an intraperitoneal injection of ^{239}Pu at 0.016–2.92 μCi/kg bw [0.6–108 kBq/kg bw] at about 10 weeks of age. The frequency of induction of skeletal cancers was about four times greater in female than in male mice of both strains, a relationship that was not observed in life-span studies in dogs (Lloyd *et al*., 1999b). When the data for both sexes and strains were combined, the relative effectiveness of ^{239}Pu in inducing skeletal cancers relative to a defined relative effectiveness of ^{226}Ra of 1, was 15.3 ± 3.9. In another study, a similar incidence of ^{239}Pu-induced bone tumours was seen in castrated male and female C57BL/Do (albino) mice (Taylor *et al*., 1981).

The effects of a single injection of monomeric ^{239}Pu-citrate were studied in adult grasshopper mice (*Onychomys leukogaster*), which are known to retain plutonium in the liver longer than strains of mice used routinely in the laboratory. The purpose of the study was to compare the responses to ^{239}Pu with those to ^{241}Am and Thorotrast.

Two groups of 10 male and 10 female mice aged 130 ± 31 days were given a single intraperitoneal injection of ^{239}Pu at a dose of 44 or 129 kBq/kg bw and permitted to live for their lifespan. They were compared with 49 controls. Eighteen primary liver tumours were reported, which included adenomas, carcinomas and sarcomas. The lowest average dose to the liver among the mice given ^{239}Pu was about 9 Gy. The risk coefficient was similar to that observed with similar doses in other strains of mice (Taylor *et al.*, 1993).

Groups of 100 female ICR mice, 10 weeks of age, were given an intravenous injection of ^{239}Pu at a dose of 0 (control), 3.0, 6.0 or 12.3 kBq/kg bw. The animals were killed when moribund or when found dead, and complete necropsies were performed. ^{239}Pu retention was measured in a separate experiment. The survival rates and the incidences of haematopoietic tumours and osteosarcomas are shown in Table 79. The increased incidence of osteosarcomas was dose-related, and the length of survival was significantly shorter for mice that died of ^{239}Pu-induced myeloid and lymphocytic neoplasms. The haematopoietic tumours were categorized into myeloid leukaemia, lymphocytic leukaemia, lymphosarcoma and reticulum-cell sarcomas. When the haematopoietic tumours were taken together, their occurrence was independent of the dose of radiation, but the frequencies of myeloid and lymphocytic leukaemia and lymphosarcoma were associated moderately strongly with exposure (Svoboda & Bubeníková, 1990). Studies on the occurrence of myloid leukaemias and osteosarcomas in mice after exposure to ^{239}Pu had been reported previously by this group (Svoboda *et al.*, 1981), and some morphological aspects of ^{239}Pu-induced granulocytic leukaemias were discussed in another paper (Svoboda *et al.*, 1982).

Female C3H mice, which have low spontaneous incidence of skeletal tumours and myeloid leukaemias, received ^{239}Pu citrate by injection at doses of 10–11 600 Bq/animal. A total of 260 exposed and 100 control animals were entered into the experiment. The survival time was significantly reduced at mean skeletal doses > 2.9 Gy, due to the appearance of bone and lymphoid tumours. The incidence of osteosarcomas was dose-dependent, reaching a maximum of 70% in animals that received a mean skeletal dose

Table 79. Incidences of haematopoietic and bone tumours in groups of 100 mice injected with ^{239}Pu

Dose injected (kBq/kg bw)	Mean survival (days ± SE)	No. of haematopoietic tumours	No. of osteosarcomas
0 (control)	617 ± 15	43	0
3.0 ± 0.1	599 ± 16	45	2
6.0 ± 0.1	569 ± 16	44	3
12.3 ± 0.1	590 ± 10	43	10

From Svoboda & Bubeníková (1990). SE, standard error

< 10 Gy; no osteosarcomas were observed in the controls. An increased incidence of non-thymic, mostly pre-B cell-type leukaemic lymphomas occurred early after ^{239}Pu exposure, whereas thymic, lymphocytic or histocytic lymphomas occurred in the controls only later. Myeloid leukaemias and myelogenous neoplasms were not observed in exposed or control animals (Oghiso *et al.*, 1994b, 1997).

These results differ from those of an earlier study in groups of 36–45 female CBA mice, 12 weeks of age, which were given ^{239}Pu in either a single injection or in 16 injections at 3–5-day intervals at doses of 1.85–18.5 kBq/kg bw. A significant, dose-related increase in the incidence of osteosarcomas was seen with both single and repeated injections. Myeloid leukaemias were found in five animals given multiple injections, whereas none had been observed in 900 controls in that laboratory (Humphreys *et al.*, 1987).

A short communication summarized the occurrence of skeletal and lymphoid cancers induced by ^{239}Pu given by intraperitoneal injection to C3H, C57BL/6 and hybrid $BC3F_1$ mice. Similar dose–response relationships were seen for both bone and lymphoid tumours in the three strains of mice, but the frequency of various types of lymphoid tumour appeared to differ. The incidence of bone tumours was significantly increased at skeletal doses from about 0.6–0.7 Gy. Pre-B-cell leukaemic lymphomas were induced preferentially soon after ^{239}Pu exposure, whereas myeloid leukaemias and other myelogenous neoplasms were either rare or not observed, depending on the strain. The authors concluded that the ^{239}Pu-induced tumours were different from those observed in studies after exposure to external low-LET radiation (Oghiso & Yamada, 1999).

Hamster: A total of 145 male and female Chinese hamsters, 100–130 days of age, were injected in five groups with ^{239}Pu citrate at activity levels of 0.074–740 kBq/kg bw, and 190 animals in six groups were injected with $^{239}PuO_2$ particles. Three groups were given a dose of 0.74, 7.4 or 74 kBq/kg bw in a particle size of 0.24 μm; one group was given 74 kBq/kg bw in a particle size of 0.84 μm, one group was given 74 kBq/kg bw in a particle size of 0.60 μm, and one group was given 74 kBq/kg in a particle size of 0.17 μm. A control group consisted of 38 animals injected with either the sodium citrate or sodium chloride solvents, and an additional 55 colony controls were not injected. ^{239}Pu citrate was distributed relatively uniformly in the liver, whereas the $^{239}PuO_2$ particles were localized primarily in the Kupffer cells, as determined by autoradiography. The animals were permitted to live for their lifespans or were killed when moribund. Histopathological results were not obtained for animals that were autolysed. The cumulative liver tumour incidence in animals that received 14 Gy to the liver from ^{239}Pu citrate was 39%, and the bone tumour incidence was 26%; the incidences of liver tumours at 2.7, 0.3 and 0.04 Gy were 32, 5 and 0, respectively. Animals that were injected with 0.24-μm $^{239}PuO_2$ particles received doses to the liver of 0.8, 7.2 and 42 Gy and had tumour incidences of 5, 26 and 34%, respectively. The histological distribution of liver tumour types was 30 hepatocellular carcinomas, 28 bile-duct adenomas, nine hepatocellular carcinomas, five haemangiosarcomas and one

classified as 'other'. The time to 50% survival of the animals injected with 740, 74, 7.4, 0.74 and 0.074 kBq/kg bw ^{239}Pu citrate was 180, 530, 1000, 860 and 1060 days, respectively. The time to 50% survival of the animals injected with 74 kBq/kg bw ^{239}Pu oxide in particle sizes of 0.17, 0.60, 0.84 and 0.24 μm was 810, 580, 980 and 680 days, respectively. The animals given 74, 7.4 or 0.74 kBq/kg bw in a particle size of 0.24 μm had 50% survival times of 680, 1030 and 950 days, respectively; the corresponding 50% survival time in the controls was 1060 days. The authors concluded that the more uniform irradiation from ^{239}Pu citrate was more effective in causing liver cancer than the non-uniform irradiation from $^{239}PuO_2$ particles. They also concluded that the local distribution of radiation dose was less important in altering tumour incidence than injected activity or average dose (Brooks *et al.*, 1983).

Dog: Lifespan studies on the effects of monomeric ^{239}Pu given as a single injection to beagle dogs were started in 1952 in parallel with studies on ^{226}Ra, such that the results could be used to derive a 'toxicity ratio' for Pu:Ra that would serve as a basis for extrapolating data on the toxicity of Pu to humans.

A group of 234 young adult beagle dogs, about 18 months of age, were given a single intravenous injection of monomeric ^{239}Pu citrate at doses of about 0.02–106 kBq/kg bw. An additional 132 dogs were given the citrate buffer and served as unexposed controls (see Table 80). Skeletal tumours were detected by periodic radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology. There were 84 radiographically identified bone tumours in 76 ^{239}Pu-injected dogs and one tumour in the control group (Lloyd *et al*., 1993). No significant difference in sensitivity to bone tumour induction was found between males and females (Lloyd *et al*., 1999b). The relationship between the percentage of dogs with tumours at any dose and the average skeletal dose calculated at one year before death (the assumed time of tumour initiation) was approximately linear below an average skeletal dose of about 1.3 Gy (Lloyd *et al*., 1993; Taylor *et al*., 1997). When these data were compared with those for ^{226}Ra (see section 3.1.2(*b*)), the relative effectiveness of bone cancer induction by ^{239}Pu was about 16 ± 5 (Lloyd *et al.*, 1993).

The skeletal tumours in plutonium-treated animals consisted of seven chondrosarcomas, one liposarcoma and one plasma-cell tumour, the remainder being osteosarcomas. The distribution of the skeletal tumours generally followed the distribution of skeletal mass and skeletal ^{239}Pu content (Lloyd *et al.*, 1994b). The tumours were approximately equally distributed between the axial and appendicular skeleton, but there was some correlation between the site of tumour occurrence and the presence of red (haematopoietic) bone marrow, indicative of greater vascularization, and increased bone turnover, indicative of greater bone surface cell activity (Lloyd *et al.*, 1997b). Similar relationships were described for other bone surface-seeking radionuclides, including ^{241}Am, ^{228}Th, ^{249,252}Cf and ^{224}Ra, but not for the bone volume-seeking nuclide ^{226}Ra.

The occurrence of soft-tissue tumours in young adult beagle dogs given a single injection of monomeric ^{239}Pu was also reported. A significant correlation was found

Table 80. Dose–response relationships for bone cancer induction in beagle dogs given a single intravenous injection of ^{239}Pu citrate as young adults

Dose injected (kBq/kg bw)	Total no. of dogs	No. of bone sarcomas	Average. skeletal dose (Gy ± SD) 1 year before death	Age (years ± SD) at death with bone cancer	Age (years ± SD) at death without bone cancer
0 (control)	132	1	0	16.1	13.1 ± 2.6
0.026	28	1	0.02 ± 0.01	13.6	12.3 ± 2.3
0.067	46	2	0.05 ± 0.01	11.8 ± 1.0	12.8 ± 2.4
0.201	38	4	0.15 ± 0.03	12.5 ± 0.9	12.3 ± 2.6
0.382	38	8	0.29 ± 0.06	12.8 ± 1.2	12.7 ± 2.6
0.576	26	10	0.42 ± 0.09	12.2 ± 2.3	12.6 ± 2.6
1.77	14	10	0.99 ± 0.31	10.6 ± 1.7	8.4 ± 3.5
3.52	12	10	1.70 ± 0.32	7.8 ± 2.4	6.5 ± 0.8
11.0	12	12	4.26 ± 0.73	5.9 ± 0.6	–
33.6	12	12	10.3 ± 1.9	5.1 ± 0.5	–
106	8	7	38.4 ± 11.8	5.7 ± 1.3	3.7

From Lloyd *et al.* (1993)

between liver tumours and increasing dose of radiation, and a significant difference was seen in the relative numbers of malignant liver tumours (22 observed, 3.2 expected) and benign liver tumours (66 observed, 18.1 expected). No other soft-tissue or haematopoietic malignancies were found in significantly increased incidence as a result of exposure to ^{239}Pu (Taylor *et al.*, 1991; Lloyd *et al.*, 1995).

To determine whether differences in the spontaneous incidence of skeletal cancers among canine species might affect their sensitivity to bone-seeking nuclides, and thus present a bias for extrapolating risk to humans, a limited lifespan study was conducted to compare the radiosensitivity of beagle and St Bernard dogs, which have a higher spontaneous incidence of skeletal cancer than beagles. Twenty-six St Bernard dogs, aged 554 ± 39 days and weighing 48.5 ± 6.3 kg, were given an intravenous injection of ^{239}Pu at doses of 0.025–11.0 kBq/kg bw, and 30 animals were given one injection of ^{226}Ra at doses of about 0.7–40 kBq/kg bw. Animals of each sex were used, but the relative numbers were not indicated. Young adult beagle dogs were treated similarly. St Bernard dogs tended to have a shorter latency for radiation-induced bone tumours (see Table 81). No radiation-induced bone tumours were observed in the distal radius, which is the site of the highest incidence of naturally occurring tumours. When these results were compared with those obtained in the group of St Bernards exposed to ^{226}Ra, the toxicity ratio for the St Bernard dogs was approximately equal to that of the beagle dogs (Taylor *et al.*, 1997).

In lifespan studies, 12 beagle dogs were exposed as juveniles (three months) and 10 when mature (60 months) to ^{239}Pu by injection of 11 kBq/kg bw and were observed for life. A group of young adult dogs that had received a similar amount of ^{239}Pu at about 18 months of age was also included. Skeletal tumours were detected by periodic

Table 81. Incidences of bone tumours in St Bernard dogs given a single intravenous injection of ^{226}Ra or ^{239}Pu

Dose injected (kBq/kg bw)	Total no. of dogs	No. of bone sarcomas	Time between injection and death (days ± SD)	Average skeletal dose (Gy ± SD) 1 year before death
Radium-226				
0 (control)	8	0	1803 ± 776[a]	0
0.71 ± 0.007	5	0	3301 ± 41	0.75 ± 0.06
2.23 ± 0.093	5	0	2371 ± 816	1.54 ± 0.35
12.54 ± 0.15	3	3	1639 ± 77	6.86 ± 1.24
39.96 ± 1.48	2	1	739 ± 305	9.30 ± 7.12
Plutonium-239				
0 (control)	8	0	1803 ± 776[a]	0
0.025 ± 0.004	3	0	2841 ± 797	0.01 ± 0.01
0.063 ± 0.007	3	1	3597 ± 187	0.04 ± 0.01
0.19 ± 0.004	6	0	3052 ± 317	0.11 ± 0.01
0.58 ± 0.015	4	2	3026 ± 433	0.33 ± 0.04
4.33 ± 1.26	3	3	1456 ± 212	1.24 ± 0.16
11.04 ± 0.52	3	3	891 ± 97	1.91 ± 0.25

From Taylor *et al*. (1997)
[a] Five dogs were killed at 2424 ± 496 days of age.

radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology (Bruenger *et al.*, 1991a). Dogs exposed as juveniles or when mature had fewer bone tumours per Gy of average skeletal dose than did those exposed as young adults. The relative radiation sensitivities were 0.27 ± 0.09 for the juveniles, 0.41 ± 0.13 for the mature animals and 1.0 for the animals exposed as young adults. When the average skeletal dose rate was considered, the juvenile and mature animals appeared to be about 0.2 times as sensitive to the induction of skeletal malignancies as young adults (Lloyd *et al*., 1999a).

(*f*) *Neptunium-237*

Rat: Groups of 40 female albino Sprague-Dawley rats, 10–12 weeks old, were given ^{237}Np at a dose of 5.2 or 26 kBq/kg bw, and 77 control rats received unspecified treatment without the radionuclide. Lifetime observations were made on 28 rats in each exposed group and the 77 controls. At death, all rats were necropsied and examined histologically. The median survival times were: controls, 800 days; 5.2 kBq/kg bw, 754 days; and 26 kBq/kg bw, 644 days. Control rats developed mainly mammary tumours (56/77) and pituitary tumours (40/77). In the treated rats, mammary tumours were removed surgically to increase the opportunity of observing radiation-induced effects,

which occurred significantly in the skeleton as osteosarcomas: controls, 1/77; 5.2 kBq/kg bw, 1/28; and 28 kBq/kg bw, 10/28. These results reflect the preferential distribution and retention of ^{237}Np on bone surfaces (Sontag *et al.*, 1997).

A group of 106 male Sprague-Dawley rats, eight weeks of age, received a single, nose-only exposure to an aerosol of $^{237}NpO_2$ (activity median aerodynamic diameter, 2.6 μm; geometric standard deviation, 2.17). The initial lung burdens of ^{237}Np in individual rats ranged from 0.1 to about 7 kBq. The exposed rats and 785 controls [treatment unspecified] were held for lifetime observation. Animals were necropsied at death, and the tissues were examined histologically. When the ^{237}Np-exposed rats were divided into four groups on the basis of mean initial lung burdens of 0.2, 0.5, 2 and 4 kBq, the mean length of survival of rats at the highest dose, 653 days, was significantly shorter than that of the unexposed controls (828 days). For the analysis of lung tumours, the exposed rats were divided into six groups on the basis of doses ranging from 0.6 ± 0.1 Gy (SD) to 26 ± 7 Gy. The numbers of rats with malignant lung tumours in these six groups, ranked from lowest to highest dose, were 2/19, 2/20, 5/18, 11/20, 11/14 and 14/15. The tumours were primarily adenocarcinomas and squamous-cell carcinomas. The incidence of adenocarcinomas versus dose fitted a linear–quadratic relationship, with a threshold for the quadratic component at doses < 2 Gy. No squamous-cell carcinomas were seen at doses < 2 Gy, and no adenosquamous carcinomas at doses < 8 Gy (Dudoignon *et al.*, 1999).

(*g*) *Americium-241*

Mouse: A total of 314 male CBA mice were given an intraperitoneal injection of ^{241}Am at 0.04, 0.2, 0.4, 8 or 16 μCi/kg bw [1.48, 7.4, 14.8, 296 or 592 kBq/kg bw]; 50 animals served as controls. Skeletal tumours were identified from radiographs, and many soft tissues were examined histologically. Higher doses were almost always associated with severe effects on the haematopoietic and lymphatic systems and osteolysis and osteonecrosis. The highest frequencies of ^{241}Am-induced tumours of the skeleton (45%) and lymphoreticular system (10%) were found among 100 animals injected with 8 μCi/kg bw. In a comparison with ^{90}Sr, ^{241}Am was considered to be more carcinogenic (Nilsson & Broomé-Karlsson, 1976).

In the study of Taylor *et al.* (1983), described in the section on ^{226}Ra (section 3.1.2(b)), the relative effectiveness of ^{241}Am at doses of 0.02–3.48 μCi/kg bw [0.74–129 kBq/kg bw] in inducing skeletal cancers was 4.9 ± 1.4 in comparison with ^{226}Ra.

The toxicity of ^{241}Am was compared with that of ^{226}Ra in male C57BL mice in order to define a 'toxicity ratio'. ^{241}Am in citrate buffer was given by intraperitoneal injection to groups of 57–107 mice aged 11–14 weeks at a dose of 0 (control), 22, 58, 190, 373 or 1197 kBq/kg bw. An additional group was given 937 kBq/kg bw ^{226}Ra. At the end of the study, histopathology was completed for 49–97 mice in each group. A dose-related decrease in mean survival time was seen: 593, 594, 475, 245, 168 and 135 days in the six groups, respectively. The early deaths at the higher doses may have

been associated with lesions of the haematopoietic and immune systems. Increased incidences of liver carcinomas, lymphomas and lymphoreticulosarcomas were associated with increasing doses of ^{241}Am. In a comparison of the regression coefficients in a proportional hazards model, the rate of death from a bone tumour was 12.9 ± 5.2 times higher with ^{241}Am than with ^{226}Ra when the regression covariate was the average skeletal dose and 3.5 ± 1.7 when the covariate was the amount of injected radioactivity. The overall mortality rate with ^{241}Am was 20.4 ± 3.6 times higher than that with ^{226}Ra when the covariate was average skeletal dose (Schoeters *et al.*, 1991).

Four groups of 15–62 adult female BALB/c mice were given ^{241}Am at 0, 0.8, 1.6 or 3.8 kBq/mouse, and two groups of males were given 0 or 2.5 kBq/mouse by intravenous injection; all animals were followed for their lifespan. Exposure significantly decreased the length of survival and increased the incidence of osteosarcomas. Female mice were more susceptible to the induction of osteosarcoma (0, 44, 43 and 39%) than males (0 and 8.6%) (Van den Heuvel *et al.*, 1995).

The effects of ^{241}Am were compared with those of Thorotrast in producing liver cancer in deer mice (*Peromyscus maniculatus*) and grasshopper mice (*Onychomys leucogaster*), which retain americium in the liver longer than conventional strains of laboratory mice. ^{241}Am citrate was given as a single intraperitoneal injection at a dose of 0–3.9 μCi/kg bw [0–144 kBq/kg bw] to 87 deer mice and 83 grasshopper mice. Thorotrast was administered by intravenous injection at doses resulting in a dose range of 0–4 Gy to the liver. Survival decreased with increasing dose of ^{241}Am in both strains. The numbers of liver cancers were increased in exposed animals of both strains, beginning at the lowest dose used (0.1 μCi/kg bw [3.7 kBq/kg bw]) for both ^{241}Am and Thorotrast. The histological spectrum of tumours (bile-duct adenomas and carcinomas, fibrosarcomas and haemangiosarcomas) was similar in animals of both strains given ^{241}Am and Thorotrast (Taylor *et al.*, 1986).

Rat: The carcinogenicity of ^{241}Am, ^{239}Pu and ^{244}Cm was compared in male August/Marshall hybrid rats given the nuclides by intravenous injection of doses of 109 kBq/kg bw of ^{239}Pu, 92 or 260 kBq/kg bw of ^{241}Am and 150 kBq/kg bw of ^{244}Cm. The rats were held for life and necropsied at death, and tissues were examined histologically. The most frequently observed late effect of all three nuclides was osteosarcoma. One leukaemia of myelogenous origin was seen in each treated group. The numbers of osteosarcomas per rat necropsied were: ^{239}Pu, 17/22; ^{241}Am (92 kBq/kg bw), 4/22; ^{241}Am (260 kBq/kg bw), 15/32; and ^{244}Cm, 10/42. The risk coefficient for osteosarcoma in ^{241}Am- or ^{244}Cm-injected rats was about one-third that with ^{239}Pu (Taylor, 1986).

Dog: Young mature dogs of each sex were exposed once by inhalation to a monodisperse ^{241}Am aerosol with an activity median aerodynamic diameter of 0.75, 1.5 or 3.0 μm or a polydisperse aerosol (1.8 μm). The animals were killed serially 8, 32, 64, 128, 256, 365 and 730 days and four, six and eight years after exposure. Osteoblastic osteosarcomas developed in four of the 15 animals that were scheduled for sacrifice at times after 1000 days (Gillett *et al.*, 1985).

Studies of the effects of single injections of ^{241}Am, ^{226}Ra and ^{239}Pu in beagle dogs are described in the sections on ^{226}Ra and ^{239}Pu above. The relative toxicity of ^{241}Am for inducing bone tumour compared with ^{226}Ra was 8.5 ± 2.3 (Lloyd *et al.*, 1997b).

(*h*) *Curium-242*

Mouse: Four groups of approximately 160 female CBA/Ca mice, 10 weeks of age, received graded exposures to ^{242}Cm fused aluminosilicate particle aerosols, resulting in initial alveolar deposits of 16.5 ± 1.3 (SE), 48.7 ± 4.0, 80.9 ± 3.8 and 142 ± 7.2 Bq per group. An additional 372 control mice inhaled unlabelled fused aluminosilicate particles, and 124 were unexposed. Fifty mice were withdrawn from each group for radiochemical analysis, and the remainder were held for lifetime observation. The overall median survival time was 910 days, with no significant differences in survival among the treated groups. At death, the animals were necropsied and examined both grossly and histologically. Bronchioalveolar adenomas were the most frequently encountered type of lung tumour, although some bronchioalveolar adenocarcinomas were observed. The numbers of mice with lung tumours were 108/372 in controls given fused aluminosilicate particles, 35/124 in untreated controls and 45/111 (low-deposit group), 49/113, 56/101 and 59/112 (high-deposit group) in the ^{242}Cm-treated mice. Four other groups of mice of the same type were exposed to the β-emitter ^{45}Ca fused aluminosilicate particles to compare the relative effectiveness of α- and β-particles in producing lung tumours. ^{242}Cm and ^{45}Ca have similar radioactive half-lives, and the common use of the fused aluminosilicate particle vector reduced possible temporal and spatial differences in comparing the effectiveness of α- and β-particles in producing tumours. Under these experimental conditions, the α-particles were approximately twice as effective as the β-particles (Kellington *et al.*, 1998). This result differs from those of others; e.g. $^{239}PuO_2$ was found to be 21 times more effective than $^{144}CeO_2$ in rats by Lundgren *et al*. (1995) (see section 3.1.2(*e*)).

Rat: Randomly bred, female Wistar rats, 70 days of age, were exposed by inhalation once for 30 min by nose only to $^{244}CmO_2$ prepared by calcination of curium oxalate at 750 °C for 2 h. The initial alveolar burdens were 0.54 nCi for 57, 4.4 ± 1.3 nCi (± SD) for 60, 48.0 ± 36.0 nCi for 55, 450 ± 300 nCi for 44 and 1800 ± 540 nCi for 24 rats [0.02, 0.163, 1.78, 16.7 and 66.6 kBq]. The tissue distribution and data on retention in other rats were used to calculate the absorbed doses of α-particles. The mean dose to the lung in the five groups ranged from 6.6 to 2100 rad [0.066–21 Gy]; the corresponding values for the skeleton were 0.8–950 rad [0.008–9.5 Gy]. Decreased survival times were observed at 450 and 1800 nCi ($p < 0.05$). Twenty-two primary lung tumours were found, all but one of which were adenocarcinomas; the other was a squamous-cell carcinoma. There were also 12 bone tumours (osteosarcomas) and two liver tumours. The increased incidences of lung and bone tumours ($p < 0.05$) were found in groups with initial alveolar burdens of 48 and 450 nCi. A significant increase in the incidence of mammary tumours was found at 4.4, 48, and 450 nCi, most of which were benign fibrosarcomas. No lung, liver or bone tumours were found in the 188 rats used as controls (Sanders &

Mahaffey, 1978). The same group compared the dose–response relationship for lung cancers due to inhaled $^{244}CmO_2$ with similar data for tumours from $^{238}PuO_2$ and $^{239}PuO_2$ inhaled by Wistar rats. Although some differences were seen in the total doses of α-particles above several Gy, the response was similar for doses below that level (Sanders *et al.*, 1976, 1977).

Because both the spatial and the temporal distribution of dose to the lung and skeleton can influence dose–response relationships, four groups of female Wistar rats, 70 days of age, were exposed once (38 rats) or 10 times separated by about 21 days (64 rats) to $^{244}CmO_2$. The activity median aerodynamic diameters were 0.70 μm for the single exposure and 0.39 ± 0.06 μm for the repeated exposure, with geometric standard deviations of 1.9–2.0. A group of 31 rats was sham exposed, and 18 were unexposed. Ten rats from each group were used for dosimetry, and the remainder were held for lifetime observation. One lung tumour and no bone tumours were observed among 49 control rats. The rats given a single exposure received a mean dose of 1.4 ± 1.3 (SD) Gy to the lung and 0.74 ± 1.1 Gy to the bone. In this group, three rats had a lung tumour and four had a bone tumour. The doses received by the rats exposed repeatedly were not statistically significantly different from those of rats exposed once, but the numbers of rats with lung tumours increased to 12 and those with tumours of the bone to 14. Overall, 15 of the 92 exposed rats had lung tumours, comprising eight squamous-cell carcinomas, five adenocarcinomas, one haemangiosarcoma and one fibrosarcoma. The one lung tumour in a control was an adenocarcinoma. The bone tumours were osteogenic sarcomas. After translocation from the lung, the ^{244}Cm was deposited in the liver and skeleton, but the retention time was much longer in the latter, which may account for the observation of more bone tumours than liver tumours (Sanders & Mahaffey, 1990). When these results were compared with those in rats exposed repeatedly to aerosols of $^{239}PuO_2$, the authors concluded that protraction of the inhaled dose of α-emitting radionuclides did not significantly influence the incidence of either lung or bone tumours in rats (Sanders & Mahaffey, 1981).

Seven groups of 84-day-old Fischer 344/CRl rats (totals of 637 males and 645 females) were exposed once to $^{244}Cm_2O_3$ or were sham-exposed to filtered air. The sizes of the groups exposed to $^{244}Cm_2O_3$ ranged from 70 to 211 rats, and the group mean initial lung burdens ranged from 0.50 to 240 kBq/kg bw; there were 157 control rats. The median survival times of male and female rats with mean initial lung burdens ≥ 27 kBq/kg bw were significantly shorter than those of the sham-exposed rats. There was a general increase in the prevalence of benign and malignant lung neoplasms with increasing initial lung burden, except at the highest exposure where survival was much shorter. The results are shown in Table 82 with data for liver and skeletal tumours. Most of the tumours were adenocarcinomas, and the next most frequent were squamous-cell carcinomas and adenosquamous carcinomas, the latter two types occurring more frequently at higher exposure. The incidence of liver tumours did not increase with dose, but a dose-related increase in the incidence of bone neoplasms was observed at 26 and 98 kBq/kg bw (Fisher's exact test, $p < 0.05$). The doses of α-particles to the bone in these

Table 82. Incidences of primary lung, liver and skeletal neoplasms in rats given aerosols of $^{244}Cm_2O_3$ by inhalation

Initial lung burden (kBq/kg bw ± SD)	Mean survival time (days)	No. of rats examined	Lung neoplasms (%)			Liver neoplasms (%)	Bone neoplasms (%)
			Benign	Malignant	Both combined		
Sham	805	157	0.64	1.9	2.5	0	0.6
0.50 ± 0.18	819	168	1.2	4.1	5.3	1.8	0.6
1.2 ± 0.32	802	210	2.9	3.3	6.2	2.9*	1.0
2.7 ± 0.82	798	130	1.5	6.9*	8.5*	1.5	1.5
9.1 ± 2.4	762	114	4.4*	18*	22*	0	1.8
26 ± 6.4	707	116	1.7	44*	46*	1.7	12*
98 ± 18	539	66	1.5	32*	33*	3.0	23*
240 ± 77	63	122	0	4.9	4.9	0	3.3

From Lundgren *et al.* (1997)
*Incidence greater than in sham-exposed rats (Fisher's exact test, two-tailed; $p < 0.05$)

two groups were 0.83 ± 0.30 and 2.3 ± 1.0 Gy, respectively. When the results for lung cancer were expressed as excess numbers of rats with lung tumours per 10^4 Gy and compared with similar values for Fischer 344 rats that inhaled $^{239}PuO_2$ aerosols (Lundgren *et al.*, 1995), $^{239}PuO_2$ was found to produce about twice as many lung tumours at a given dose. This finding is contrary to the 'hot particle' hypothesis, in which higher local doses around particles of high specific activity such as $^{244}Cm_2O_3$ should result in a higher incidence of lung cancer than particles of lower specific activity such as $^{239}PuO_2$ (Lundgren *et al.*, 1997).

(i) *Californium-249 and californium-252*

The patterns of retention, disposition and distribution of californium are similar to those of americium. ^{252}Cf is unique in that it decays by emission of an α-particle and a fission fragment, the latter accounting for about half its total decay energy. ^{249}Cf decays by emission of α-particles, with some accompanying γ-radiation. Thus, the decay of ^{252}Cf has about twice as much energy per disintegration as that of ^{249}Cf.

Mouse: In the study of Taylor *et al.* (1983) described in section 3.1.2(*b*), ^{249}Cf and ^{252}Cf were given to groups of 10–12 mice of each strain (C57BL/Do black and albino) and each sex at doses ranging from 0.013 to 3.30 μCi/kg bw [0.48–122 KBq/kg bw], starting at about 10 weeks of age. The original hypothesis had been that the more energetic decay of ^{252}Cf would induce more tumours than ^{249}Cf, but this was not the case: 26 bone sarcomas were observed in the ^{252}Cf-exposed animals and 33 in mice exposed to ^{249}Cf. The effectiveness of ^{249}Cf and ^{252}Cf in inducing bone cancers relative to ^{226}Ra was 5.0 ± 1.4 for ^{249}Cf and 2.6 ± 0.8 for ^{252}Cf. The calculated relative effectiveness of fission fragment irradiation from ^{252}Cf in inducing cancer in comparison with α-radiation was 0.02 ± 0.28.

Dog: Five or six young adult beagle dogs received intravenous injections of graded doses of ^{249}Cf or ^{252}Cf. All six animals given 10.7 kBq/kg bw ^{249}Cf and five of six given 3.42 kBq/kg bw ^{249}Cf developed an osteosarcoma. The risk coefficient for bone sarcoma was 0.28 per Gy, and the toxicity ratio relative to ^{226}Ra was 6. All six dogs given ^{252}Cf at 10.7 kBq/kg bw also developed a bone sarcoma. The authors concluded that the effectiveness of ^{252}Cf fission fragments for bone sarcoma induction was essentially negligible compared with the α-radiation from ^{249}Cf. The risk coefficient for bone sarcomas from ^{252}Cf was 0.21 per Gy, and the toxicity ratio relative to ^{226}Ra was 4 ± 2 (Lloyd *et al.*, 1994c).

3.2 β-Particle-emitting radionuclides

3.2.1 *Pure β-particle emitters*

(*a*) *Hydrogen-3*

When tritium (^{3}H) is administered as ^3H_2O, it is distributed relatively uniformly throughout the body, resulting in whole-body exposure to low-energy β-particles similar to whole-body exposure from external X- or γ-radiation (see section 4.1).

Mouse: A common theme of the lifetime studies has been to compare the biological effects of long-term β-irradiation with ^{3}H with acute or chronic irradiation from external X- or γ-rays. In a lifetime study, seven groups of about 765 male CBE/H mice, about 99 days of age, received a dose of 1, 2 or 3 Gy from injected ^{3}H or whole-body X-rays. The three ^{3}H-exposed groups received a single intraperitoneal injection of 0.9, 1.8 or 2.7×10^8 Bq per mouse, resulting in mean total absorbed doses of β-particles of 0.85, 1.86 and 3.04 Gy. Three other groups received a single exposure to 200 kVp or 150 kVp [X-ray generator maximum applied voltage; see IARC, 2000] of X-rays, resulting in average whole-body doses of 1.06, 1.98 and 2.64 Gy. The average age at death in the six groups exposed to radiation was 714–737 days, while that in controls was 767 days. During the study, 11–36 mice in the various groups were lost to follow-up, resulting in final group sizes of 732–754 mice. At death, the animals were necropsied and their tissues examined histologically. The numbers of myeloid leukaemias were 33, 47 and 45 in the three X-ray-exposed groups and 43, 48 and 60 in the three ^{3}H-exposed groups, with one case in controls. The calculated effectiveness (± SD) of β-particles from ^{3}H for inducing myeloid leukaemia relative to X-rays ranged from 1.0 ± 0.5 to 1.3 ± 0.3 with a best estimate of 1.2 ± 0.3 (Johnson *et al.*, 1995).

A series of studies was carried out in female mice given ^3H_2O throughout their lifetime. In all studies, 10-week-old female (C57BL/6N × CH3/He)F_1 mice were placed in closed exposure chambers divided into compartments to separate the dose groups. At death, each mouse was necropsied and examined histologically (Yamamoto *et al.*, 1990, 1995, 1998).

In the first study, the dose of ^{3}H in the drinking-water ranged from 3.7×10^9 to 5.92×10^{11} Bq/L. Mice that received ^3H_2O at 1.48×10^{11} to 5.92×10^{11} Bq/L died within two weeks from haematopoietic failure. This information was used to design the subsequent studies, which were conducted at lower doses. In the second study, the mice were provided with drinking-water containing one of five concentrations of ^{3}H, resulting in the mean cumulative organ doses and survival times shown in Table 83. The mean survival time increased with decreasing ^{3}H concentration. The type of tumours differed with dose: at the two highest doses (0.24 and 0.096 Gy/day), the main cause of death was thymic lymphoma, with incidences of 29/45 and 22/38; at a dose rate of 0.048 Gy/day, the incidence of thymic lymphomas decreased sharply (15/60), and the tumours observed were more diverse. At the two lower doses, more reticular-cell

Table 83. Experimental design of studies of liftime ingestion of ^{3}H by female mice

No. of mice	$^{3}H_2O$ concentration in drinking-water (Bq/L)	Estimated dose rate (Gy/day)	Mean dose ± SD (Gy)	Median survival time (days ± SD)
67	0	0	0	811 ± 134
53	3.70×10^8	0.010	5.9 ± 1.1	622 ± 121
60	9.25×10^8	0.024	11.5 ± 2.7	481 ± 112
60	1.85×10^9	0.048	19.7 ± 3.1	414 ± 66
38	3.70×10^9	0.096	24.6 ± 4.9	259 ± 52
45	9.25×10^9	0.24	38.8 ± 8.5	165 ± 36

From Yamamoto *et al.* (1995)

neoplasms, ovarian tumours, fibrosarcomas and lung tumours were seen. The third series of mice were exposed to ^{3}H in the drinking-water at a dose of 1.39×10^8, 3.48×10^7 or 8.69×10^6 Bq/L, with associated dose rates of β-particles of 3.6, 0.9 and 0.2 mGy/day and cumulative doses of 2.62 ± 0.41 Gy, 0.71 ± 0.13 Gy and 0.17 ± 0.03 Gy, respectively. The numbers of mice used were 120 at 3.6 mGy/day, 58 at 0.9 mGy/day, 55 at 0.2 mGy/day and 51 controls. The survival of mice exposed to 3.6 mGy/day was shortened, but that of mice at 0.9 or 0.2 mGy/day was indistinguishable from that of controls. The frequency of thymic lymphomas was 5% at 3.6 mGy/day and 0% at the two lower dose rates and in controls.

Rat: The relative effectiveness of β-particles from ^{3}H and 200-kVp X-rays was studied in 11 groups of about 129 female Sprague-Dawley rats aged 45–59 days. Four groups were exposed continuously to X-rays over 10 days, resulting in a total dose of 0.29, 0.57, 1.10 or 2.00 Gy. Two groups received a single exposure for about 1 h, resulting in doses of 0.57 and 1.78 Gy. The four ^{3}H-exposed groups received a single intraperitoneal injection of $^{3}H_2O$ in normal saline at a dose of 440, 890, 1780 or 3700 MBq/kg bw. Analyses of tissue and excreta indicated that the total doses of β-particles to the mammary glands were 0.46, 0.92, 1.63 and 3.85 Gy, respectively. The relative effectiveness was estimated on the basis of various criteria, including the mammary tumour incidence per Gy 450 days after irradiation and the time required to induce mammary tumours in 50% of the animals at risk. The authors calculated that β-particle irradiation from ^{3}H was 1.1–1.3 times more effective than 200-kVp X-rays (Gragtmans *et al.*, 1984).

(*b*) *Phosphorus-32*

Mouse: Thirty-six adult female BALB mice, 3–5 months of age, were given a single intraperitoneal injection of ^{32}P as Na_3PO_4: 15 mice received 40 μCi [1480 kBq], seven received 60 μCi [2220 kBq], eight received 90 μCi [3330 kBq], and six received 120 μCi [4440 kBq]. Eighty control mice received unspecified treatment without ^{32}P. All

mice were held for lifetime observation, necropsied at death and examined histologically. The authors used the term 'leukaemia' in the broad sense to include malignancies, such as lymphosarcomas and reticulum-cell sarcomas. Leukaemias were seen at all doses and in the controls, as follows: 40 μCi, 6/15; 60 μCi, 3/7; 90 μCi, 3/8; 120 μCi, 3/6; controls, 13/80. The occurrence of leukaemia in the four ^{32}P-injected groups ranged from 38 to 50%, whereas the control incidence was 16%. The authors calculated that the overall incidence of leukaemia in the ^{32}P-injected mice (42%) was significantly higher (χ^2, 7.42; $p < 0.01$) than that in controls (16%) (Holmberg *et al.*, 1964).

Rat: Adult male Wistar rats [age not specified] received one or repeated injections of ^{32}P in an unspecified form. Those injected once were the survivors of an LD_{50} dose of ^{32}P of 4.5 mCi/kg bw [167 MBq/kg bw]; the repeated injections consisted of 1.5 mCi/kg bw [55 MBq/kg bw] given every three weeks for a total of 9 or 12 mCi/kg bw [333 or 444 MBq/kg bw]. Of the 19 rats injected once, 16 were killed between six months and one year after injection, and the other three died. Five of these animals had osteogenic sarcomas and three had squamous-cell carcinomas in the soft tissues of the face. Fifteen rats received repeated injections, but seven died before they received all eight injections. Four osteogenic sarcomas were observed, three in the eight rats that survived the eight-injection regimen and one in the rat that died after six injections (Koletsky *et al.*, 1950).

(*c*) *Strontium-90*

Mouse: A series of experiments was reported on the effects of intraperitoneally injected $^{90}Sr(NO_3)_2$ in CBA mice (Nilsson, 1970, 1971; Nilsson *et al*., 1980). Groups of 120–122 male CBA mice, 75 days of age, were injected intraperitoneally with a dose of 0.2, 0.4, 0.8 or 1.6 mCi/kg bw [7.4, 14.8, 29.6 or 59.2 MBq/kg bw]. A group of 95 controls was available. Five mice per group were killed at one, two, three and four weeks and at monthly intervals thereafter until all the mice had either died or been killed. Tumours of the bone, mucous membranes of the head and haematopoietic system were found. The numbers of osteosarcomas were 0, 8, 90, 292 and 219 in controls and at the four doses, and the numbers of carcinomas of the hard palate, jaw, nose or sebaceous ear ducts were 0, 0, 3, 23 and 74, respectively. A total of 75 lymphatic or thymic lymphomas were reported in treated mice, the highest incidence occurring in mice injected with 0.4 mCi/kg bw [14.8 MBq/kg bw] (Nilsson, 1970, 1971). In a study of the effects of age and dose on the carcinogenicity of ^{90}Sr, groups of 47–51 female CBA mice were injected intraperitoneally with $^{90}Sr(NO_3)_2$ at a dose of 0.2, 0.4 or 0.8 mCi/kg bw [7.4, 14.8 or 29.6 MBq/kg bw] at 25, 75, 150 or 300 days of age. Higher incidences of osteosarcomas were seen in mice injected at 75 days of age, but no age-related effect was seen in the incidence of lymphatic tumours, which occurred more frequently at the low dose (Nilsson *et al*., 1980).

Dog: The design of a lifetime study on the effects of ^{90}Sr given intravenously to beagle dogs and early results were described by Dougherty *et al.* (1962). Groups of

12–14 pure-bred beagle dogs received a single intravenous injection of ^{90}Sr in a citric acid–sodium citrate buffer solution, and 13 control dogs received the buffer solution only. The doses and survival rates are shown in Table 84. The average dose to the skeleton was calculated from measurements made throughout the study of whole-body retention and skeletal content in dogs that died (Boecker *et al.*, 1994). Twenty-four primary bone tumours occurred in 18 dogs: 18 were osteosarcomas, five were haemangiosarcomas, and one was of undetermined histological phenotype. These tumours all occurred at a median absorbed dose of β-particles of 94 Gy (range, 18–164 Gy); none was seen in dogs that received doses to the skeleton of 0.7–18 Gy. In spite of substantial irradiation of the bone marrow, no myeloproliferative disease was observed (Gillett *et al.*, 1992).

Table 84. Experimental design of a study of beagle dogs injected with ^{90}Sr citrate at ~ 17 months of age (mean and range)

No. of dogs	Dose of ^{90}Sr injected (kBq/kg bw)	Average survival after injection (days)	Dose to skeleton (Gy)
13	0	4198 (708–5755)	0
12	21 (19–26)	4723 (2705–5902)	1.1 (0.78–2.2)
13	64 (60–75)	4129 (1973–5624)	3.5 (1.64–5.7)
12	128 (118–153)	3941 (2467–5193)	6.3 (4.6–8.5)
12	400 (370–429)	4481 (2898–5667)	23 (9.5–33)
12	1200 (1130–1500)	3645 (2093–4942)	63 (33–79)
12	2350 (2250–2380)	2125 (993–3030)	80 (51–110)
14	3620 (3430–3890)	1243 (35–2256)	94 (5.2–164)

From Boecker *et al*. (1994)

In response to concern about the possible long-term biological effects of ^{90}Sr in fall-out from atmospheric nuclear weapons tests, a second lifespan study was conducted in the USA, in which beagle dogs were exposed to ^{90}Sr *in utero* and up to 540 days of age. A detailed description of the experimental design and lifetime biological effects has been published (White *et al*., 1993) and is shown in Table 85. A total of 403 pure-bred beagle dogs (approximately equal numbers of males and females) were divided into seven groups receiving logarithmically spaced doses. The animals were derived from 125 dams fed ^{90}Sr from 40 days after breeding to 42 days after parturition when they weaned their pups. The pups received ^{90}Sr in the same ^{90}Sr:calcium ratio as the dams daily until they were 540 days of age. Eighty control dogs were fed stable strontium. Another 82 unexposed control dogs from a parallel lifetime study of ^{226}Ra were also included in the analyses when it was shown that there were no significant differences between their survival and those of the ^{90}Sr study controls. Whole-body counting and radiochemical analyses of tissue samples from the dogs at death were used to calculate the skeletal

Table 85. Experimental design of lifetime study of the toxicity of ^{90}Sr in beagles treated in the diet, from mid-gestation until 540 days of age

Dose group	No. of dogs		kBq ^{90}Sr/g dietary calcium	Ingested kBq/day	Total ingested (kBq)	Median survival age (years)	Skeletal dose (Gy) (mean ± SD)
	Males	Females					
Controls	81	81	0	0	0	14.5	0
1	38	40	0.259	0.74	370	14.2	0.4 ± 0.2
2	21	19	0.777	2.59	1 480	13.5	1.2 ± 0.3
3	33	32	4.55	16.3	8 880	14.4	6.7 ± 2.0
4[a]	38	34	13.7	48.1	25 900	14.1	22.5 ± 5.7
5[a]	30	35	41.1	148.0	81 400	12.0	50.4 ± 18.0
6[a]	32	32	123.0	444.0	241 000	5.2	80.2 ± 35.2
7[b]	12	7	370.0	1332.0	718 000	2.2	107.0 ± 32.0

Modified from White *et al*. (1993)

[a] Data include 15 dogs fed throughout life: seven in group 4, four in group 5 and four in group 6.

[b] Not in original experimental design (1961); added in 1967

doses received by individual dogs. The median survival times at the four lower doses ranged from 13.5 to 14.4 years, while that for the 162 pooled controls was 14.4 years, and those at the three higher doses were 2.2–12 years. At death, each dog was necropsied, and its organs and tissues were examined histologically. Primary sarcomas of bone were classified as osteosarcoma, chondrosarcoma, fibrosarcoma, haemangiosarcoma and undifferentiated sarcoma. In all, 66 primary bone sarcomas were found in 47 dogs, including four controls, multiple sarcomas being found in one female control, four males at the highest dose and 10 females at the two higher doses. All the bone sarcomas occurred at the four higher doses (Table 86), and 74% of these tumours were osteosarcomas; the remainder was made up of other sarcoma types. The ratio of bone sarcomas of the appendicular skeleton to those of the axial skeleton was 38:23.

Table 86. Frequency distribution by dose of bone sarcomas in beagles fed ^{90}Sr and in controls

Dose group	Incidence of sarcomas			Age at onset (days) (mean ± SD)	Skeletal dose (Gy) (mean ± SD)	Average dose-rate (mGy/day) (mean ± SD)
	Males	Females	%			
Controls	3/81	1/81	3.8	5634 ± 641	0	0
1	0/38	0/40				0.08 ± 0.03
2	0/21	0/19				0.25 ± 0.05
3	0/33	0/32				1.46 ± 0.27
4	4/38	0/34	5.6	4894 ± 898	31 ± 2	4.75 ± 1.03
5	5/30	5/35	15.4	4032 ± 875	48 ± 12	13.4 ± 2.9
6	6/32	13/32	29.7	2864 ± 466	112 ± 19	42.3 ± 8.8
7	7/12	3/7	52.6	839 ± 165	116 ± 27	133 ± 25

From White *et al*. (1993)

In a third lifetime study of the biological effects of ^{90}Sr in dogs, 33 young adult (12–14 months) male and 33 female pure-bred beagle dogs were exposed once, briefly, to an aerosol of $^{90}SrCl_2$ in a caesium chloride vector aerosol, with activity median aerodynamic diameters of 1.4–2.7 μm. The initial body burdens of ^{90}Sr were achieved by adjusting the air concentration of ^{90}Sr and the length of exposure (from 2 to 22 min). An additional 22 unexposed dogs served as controls. The dogs were housed individually in metabolism cages for the first 60 days after exposure and then transferred to the kennel facilities where they were housed, two per run, for the remainder of their lives. Whole-body counting, parallel studies of inhalation of ^{85}Sr and radiochemical analyses of the organ burden of ^{90}Sr at death were used to calculate the retained burden of ^{90}Sr in each dog and the resulting total doses received by the skeleton and other organs (Table 87). Six dogs with retained burdens of 1.7–4.1 MBq/kg bw died 18–31 days after exposure from bone-marrow hypoplasia. Bone tumours were the main biological finding, 45 tumours occurring in 31 dogs, of which 24 were osteosarcomas,

Table 87. Experimental design of lifespan study in dogs that inhaled $^{90}SrCl_2$

Group[a]	No. of dogs	Retained burden (MBq ^{90}Sr/kg bw) (range)	Median survival (days) (range)	Median skeletal dose to death (Gy) (range)	Cause of death
1	22	0	4555 (2615–5505)	0	Varied
2	12	0.067 (0.036–0.12)	4725 (2247–5948)	5.9 (4.2–13)	Varied
3	12	0.29 (0.21–0.36)	4624 (2436–5678)	32 (21–49)	Varied
4	15	1.0 (0.56–1.4)	2633 (585–4222)	100 (40–140)	Bone tumours, other
5	14	1.8 (1.4–2.5)	1386 (927–3122)	130 (76–180)	Bone tumours
6	7	3.7 (2.6–4.4)	886 (585–1142)	170 (99–220)	Bone tumours
7	6	3.7 (1.7–4.1)	18–31	8.3 (6.0–13)	Bone-marrow hypoplasia

Adapted from Gillett *et al*. (1987a,b)

[a] Groups 1–6 represent the retained burden of ^{90}Sr; group 7 consisted of six dogs that died 18–31 days after exposure.

14 were haemangiosarcomas, three were fibrosarcomas and one was a myxosarcoma. Four carcinomas of soft tissues near the bone in the nasal cavity and skull were found. Two cases of myelomonocytic leukaemia were observed in dogs, with retained burdens of 1.0 and 0.35 MBq/kg bw. Three ^{90}Sr-related tumour deaths (one bone tumour, one nasal cavity tumour and one case of myelomonocytic leukaemia) were found in 24 dogs with retained burdens of < 0.5 MBq/kg bw (Gillett *et al.*, 1987a,b).

Because of the soluble nature of the ^{90}Sr used in these three studies, the distribution and retention patterns of ^{90}Sr after inhalation can be compared with those after intravenous injection. Minor differences were found. After injection, there was rapid deposition in the skeleton, which decreased with time due to biological processes, whereas exposure by ingestion led to continuous deposition of ^{90}Sr in the skeleton up to 540 days of age and a more uniform distribution within the bones (Gillett *et al.*, 1992).

In order to compare the dosimetric and the biological results obtained in these three studies, tissue sections from all bone tumours were re-examined by one of two pathologists to ensure consistency. Table 88 shows the doses and responses in the three studies. The range of doses over which bone tumours were seen was similar after inhalation, injection and ingestion. Bone tumours appeared later in life after ingestion than in the other two studies. Differences were also noted in the distribution of tumours within the skeleton: after inhalation and injection, bone tumours were found predominantly in the axial skeleton, whereas the distribution between axial and appendicular locations was about equal after ingestion (Gillett *et al.*, 1992).

The haematological responses seen in dogs that were exposed once by inhalation or intravenous injection were compared with those in dogs or pigs (see below) that received ^{90}Sr from their mothers while *in utero* and subsequently in their daily feed. When inhaled or injected in a soluble form, ^{90}Sr was translocated quickly to the skeleton and produced effects on the bone marrow at the highest dose that were similar to acute radiation injury from external radiation. Subsequent occurrence of myeloproliferative disease in the long-term survivors in these studies was rare. The situation was reversed after long-term ingestion. Instead of a rapid decrease in blood parameters, gradual, persistent leukopenia developed due primarily to depression of neutrophils. Myeloproliferative disease was a more frequent health effect in dogs and pigs that survived for a long time than after a high single exposure. These results emphasize that differences in the patterns of dose accumulation can substantially change the types of biological effects seen (Gillett *et al.*, 1987b).

Pig: About 800 Pitman-Moore miniature pigs [sex not specified] representing three generations were fed ^{90}Sr at doses ranging from 0.037 to 115 MBq/day. Animals in the first generation were exposed from nine months of age, and those of the second and third generations were exposed *in utero*, during lactation and in their feed after weaning at a dose that was initially one-fourth that of the sow and was increased by six months to the same as that of the sow. The tumours that occurred in females in the F_1 and F_2 generations are shown in Table 89. Bone sarcomas were observed only at the

Table 88. Primary bone tumours identified in dogs exposed to ^{90}Sr by various routes and observed for lifespan

Route of exposure	No. of dogs exposed	No. of primary bone tumours	No. of dogs with tumours	Median cumulative absorbed dose to bone at time of death (Gy) (range)		Median survival (days) after exposure of dogs with bone tumours
				All exposed dogs	Dogs with bone tumours	
Inhalation	66	45	31	76 (4–220)	130 (28–220)	1702 (759–3472)[a]
Injection	83	24	18	18 (0.7–164)	94 (18–164)	1740 (960–4664)[a]
Ingestion	385	46[b]	41	9 (0.1–193)	123 (26–193)	3058 (576–5697)[c]

From Gillett *et al*. (1992)

[a] To approximate the age at death for dogs that inhaled ^{90}Sr, add 395 days (2097 [1150–3870]), and to approximate that for dogs injected with ^{90}Sr, add 550 days (2290 [1510–5210]).

[b] An additional eight tumours were documented histologically after random sampling of bone lesions identified radiographically. These tumours were not visible grossly, nor did they produce clinical signs. These eight macro-osteosarcomas were excluded from the comparison of the three studies to achieve greater uniformity in sampling. Furthermore, the slides are still in review and other tumours may be identified.

[c] Values shown are the same as the dogs' ages.

Table 89. Tumours in female miniature swine ingesting ^{90}Sr daily (combined F_1 and F_2 generations)

Dose (MBq/day)	No. of animals	Mean lifespan (years)	Cumulative skeletal dose (Gy)	Tumour site (number)					
				Bone sarcoma	Myeloid tumour	Lymphoid tumour	Liver tumour	Ovarian tumour	Uterine tumour
0	74	11	0	0	4	1	8	1 (malignant)	38
0.037	52	11	3	0	0	6	8	0	54 (4 malignant)
0.185	29	11	15	0	3	7	17	0	48 (7 malignant)
0.925	47	10	50	0	9	9	23 (2 malignant)	9 (malignant)	32 (4 malignant)
4.62	40	3.5	140	10	38	15	0	0	5
23.1	24	0.25	11[a]	8[a]	8[a]	0	0	0	0

From National Council on Radiation Protection and Measurements (1991)

[a] Two animals removed from ^{90}Sr feeding at three months of age developed bone tumours and leukaemia at three and four years of age; the remaining animals, not removed from ^{90}Sr, died at about three months of age from bone-marrow aplasia.

two higher doses. Most of the tumours occurred in the skull, including the mandible and maxilla. An increased incidence of hepatic neoplasia was seen at moderate doses, but only two of these tumours were malignant. Haematopoietic effects of irradiation of the bone marrow, including neutropenia, lymphopenia, thrombocytopenia and myeloproliferative disorders and histiocytic infiltration of organs such as the kidney, heart, testis and lung were observed among animals at the higher doses but not in controls or pigs at lower doses and rates (National Council on Radiation Protection and Measurements, 1991).

(*d*) *Yttrium-90 and yttrium-91*

Dog: A group of 46 pure-bred beagle dogs (approximately equal numbers of males and females), 12–14 months of age, received a single, brief (3–30 min) exposure by inhalation to an aerosol of relatively soluble $^{91}YCl_3$ in a non-radioactive caesium chloride vector (activity median aerodynamic diameter, 1.7 μm (1.2–2.5 μm); geometric standard deviation, 2.1 (1.5–2.4)). Another group of 12 young adult beagles served as unexposed controls, and information on control dogs in the three studies of dogs exposed to soluble forms of ^{137}Cs, ^{90}Sr and ^{144}Ce, described elsewhere in this section, was also used in analysing the results. As in the studies of inhaled $^{90}SrCl_2$ and $^{144}CeCl_3$, the exposure was expressed as the burden that remained in the body after the first, rapid clearance phase was completed soon after exposure. Whole-body counting and radiochemical analyses of tissues from a parallel dosimetric study and from dogs that died early in this study were used in dosimetry modelling and calculations. Because yttrium has metabolic characteristics of a rare-earth element, the lung, liver and skeleton were considered to be the primary target organs in this study. The experimental design and dosimetry are shown in Table 90. As in the studies with ^{90}Sr, ^{137}Cs and ^{144}Ce, several dogs at the higher doses died after 12–33 days from haematological dyscrasia. The blood-cell counts in 28 dogs that had haematological dyscrasia but survived returned to normal, and their median survival time was 4328 days, similar to that of the other seven dogs which had no early haematological dyscrasia (4392 days). None of the dogs with haematological dyscrasia that survived more than 33 days died from diseases of the bone marrow or blood-forming organs. Malignant neoplasms occurred in bone-associated nasal mucosa (three squamous-cell carcinomas), bone-associated oral mucosa (one squamous-cell carcinoma, one malignant melanoma), liver (one hepatocellular carcinoma, one lymphosarcoma) and lung (three papillary adenocarcinomas, two bronchioloalveolar carcinomas) in the exposed dogs. Five malignant lung neoplasms occurred in the 61 pooled control dogs (three papillary adenocarcinomas, two bronchioloalveolar carcinomas). Only one of these tumours occurred less than 10 years after exposure (Muggenburg *et al.*, 1998). Lung cancers occurred more frequently in aged control dogs, especially those over 10 years of age (Hahn *et al.*, 1995). [The Working Group noted that the late occurrence of lung tumours in ^{91}Y-exposed dogs may have been related to ageing.]

Table 90. Experimental design, dosimetry and survival times for dogs that inhaled $^{91}YCl_3$

No. of dogs		Retained body burden (MBq/kg bw)	Median organ dose (Gy) (range)			Survival after exposure (days) (range)
Males	Females		Lung	Liver	Skeleton	
6	6	1.5 (0.48–1.8)	6.5 (2.1–7.8)	2.0 (0.64–2.4)	5.8 (1.8–6.9)	4563 (2663–5752)
5	7	2.5 (1.9–3.6)	11 (8.0–16)	3.3 (2.5–4.8)	9.5 (7.1–14)	4563 (364–5398)
7	5	5.9 (4.0–7.6)	21 (17–31)	6.4 (2.3–9.5)	18 (5.6–27)	3125 (22–4955)
5	5	8.6 (7.7–1.9)	25 (21–38)	3.1 (2.5–11)	7.6 (6.1–32)	22 (15–4563)
6[a]	6[a]	0	0	0	0	4591 (2241–5455)
26[b]	23[b]	0	0	0	0	4738 (647–6016)

Adapted from Muggenburg *et al*. (1998)
[a] Concurrent controls
[b] Other controls

As part of a larger investigation of the carcinogenic response of the lung to chronic β-irradiation, equal numbers of young adult (12–14 months of age) male and female beagle dogs received a single, nose-only exposure by inhalation to graded activity levels of ^{90}Y or ^{91}Y in fused aluminosilicate particles and were observed for life. Use of the same insoluble vector and yttrium isotopes with different radioactive half-lives (^{90}Y, 2.7 days; ^{91}Y, 59 days) allowed a comparison of the effect of protracting the dose rate on lung carcinogenesis. The experimental design and results for lung tumours are given in Table 91. The doses were calculated from information obtained by whole-body counting, and the distribution and retention from parallel studies with serial sacrifices. All 32 dogs that inhaled ^{90}Y and had an initial lung burden ≥ 26 MBq/kg bw died within the first 500 days after exposure due to radiation pneumonitis and pulmonary fibrosis. This initial lung burden corresponded to an average absorbed dose to the lung of about 110 Gy. In the 60 dogs with lower initial lung burdens (3.0–25 MBq/kg bw

Table 91. Experimental design and incidences of lung tumours in groups of 12 young adult beagle dogs that inhaled aerosols of ^{90}Y- or ^{91}Y-fused aluminosilicate particles

Initial lung burden (MBq/kg bw)	Pulmonary injury	No. of dogs with pulmonary tumours	
		Carcinomas	Sarcomas
^{90}Y			
0	0	4	0
3.0–4.8	0	1	0
5.2–9.3	0	1	0
9.3–13	0	2	0
14–17	1	5	0
18–26	9	1	1
26–41	12	0	0
41–70	12	0	0
89–190[a]	5	0	0
^{91}Y			
0	0	0	0
0.41–0.70	0	4	0
0.85–1.3	0	5	0
1.4–2.5	1	4	0
2.6–3.3	2	10	0
3.4–4.1	4	6	0
4.1–5.5	8	4	0
5.5–7.0	12	0	0
7.0–13	12	0	0

From Boecker *et al.* (1994)
[a] Five animals

[12.7–110 Gy]), eight lung carcinomas and one lung fibrosarcoma were observed. Four carcinomas were also found in the 12 control dogs that inhaled non-radioactive fused aluminosilicate particles. In the parallel study with ^{91}Y, 96 dogs were exposed, and 12 dogs that inhaled non-radioactive fused aluminosilicate particles served as controls. All 28 dogs with an initial lung burden ≥ 4.8 MBq/kg bw (270 Gy to the lung) also died within the first 500 days from radiation pneumonitis and pulmonary fibrosis. Of the 68 dogs with lower lung burdens (0.41–4.8 MBq/kg bw with associated average absorbed doses of 23–270 Gy), 33 had lung carcinomas. No lung tumours were seen in the 12 control dogs. Comparison of the results of these two studies shows that, although lung tumours can be produced by a brief, high dose rate of ^{90}Y, the tumorigenic response is not pronounced. Increasing the lung burden only leads to early deaths from deterministic effects. In contrast, the more prolonged pattern of β-irradiation from ^{91}Y produced a substantial increase in the number of lung carcinomas at doses below those that produced early deaths from pulmonary injury (Boecker *et al.*, 1994).

(*e*) *Promethium-147*

Rat: The biological effects of ^{147}Pm inhaled in fused aluminosilicate particles were studied in 270 Fischer 344/Crl rats of each sex exposed once by inhalation to graded doses of ^{147}Pm designed to result in initial lung burdens of 0–4400 kBq. The low initial lung burdens were expected to produce early, non-stochastic pulmonary effects and pulmonary tumours. Forty rats exposed to non-radioactive fused aluminosilicate particles served as controls. The remaining 230 rats were divided into four dose groups with the following expected ranges of mortality rates one year after exposure: 60 rats, 0–2%; 80 rats, 2–25%; 50 rats, 25–95%; and 40 rats, 95–100%. All rats that died or were killed when moribund were necropsied and examined grossly and histologically. Rats at the highest doses at death (211–630 Gy) generally died during the first year from radiation pneumonitis and pulmonary fibrosis. Rats with lower lung burdens and correspondingly lower doses of β-particles lived longer, and a large proportion developed pulmonary tumours. Exposed rats developed 98 pulmonary tumours, including 43 haemangiosarcomas, 41 squamous-cell carcinomas, five lung adenocarcinomas and two lung adenomas. Only one pulmonary tumour, a carcinosarcoma, was seen in a control rat. The highest crude incidence of lung tumours (87%) was seen in rats with initial lung burdens of 2410–3280 kBq/g of lung tissue (Herbert *et al.*, 1987, 1988).

Hamster: As part of a research programme carried out at Los Alamos National Laboratory, USA, to study the lifetime biological effects of non-uniform α- and β-radiation in the lung, 10-μm ZrO_2 ceramic particles containing ^{147}Pm were injected into the right jugular vein of 241 Syrian golden hamsters such that the particles became permanently lodged in the capillary bed of the lung. Two activity levels were used, 70 and 450 pCi [2.6 and 16.7 Bq] per particle. The local and average doses to the lung were adjusted by the activity of the particle and the number of particles (total radioactivity) in the lung. Two initial dose rates to the lung were studied, 4.4–4.6 and 14–21 krad/year [44–46 and 140–210 Gy/year], with large numbers of 70-pCi particles or small numbers of 450-pCi

particles. The median survival times were not correlated with dose and were judged to be similar to those of the 528 concurrent controls. Of the controls, 192 were unexposed and the remainder injected with particles not containing ^{147}Pm. No lung tumours were seen in the controls. Of the 49 lung tumours observed in the 241 treated hamsters, 17 were adenomas, 20 were adenocarcinomas, and 12 were epidermoid carcinomas. The occurrence of death from lung tumour peaked 600 days after exposure to both the low and the high doses (Anderson *et al.*, 1979).

3.2.2 *Mixed β-particle emitters*

(*a*) *Iodine-131*

Mouse: The effects of irradiation by β-particles from injected ^{131}I were compared with single doses of X-rays in 4-month-old male CBA mice. Groups of animals were exposed to 0 (controls), 1.5, 3 or 4.5 μCi [0, 56, 111 or 167 kBq] of ^{131}I or 0, 500, 1000 or 1500 R [about 0, 5, 10 or 15 Gy] of X-rays, localized by shielding. A few moribund animals were killed at 580–680 days of age, but most were killed at 680–730 days. The pituitaries, thyroids and grossly observable tumours were sectioned and examined microscopically. Ancillary experiments were performed to evaluate cell survival and dosimetry after exposure to ^{131}I. Both treatments resulted in degenerative changes and reduced thyroid weights, but lower doses of X-rays than of β-irradiation were required to produce the same degree of weight reduction. No thyroid tumours occurred in controls, but administration of either type of radiation increased the incidence of thyroid tumours. In groups that received higher doses of radiation from ^{131}I than those from X-rays, the incidences were 4/93, 5/88 and 15/80, but similar incidences (2/96, 4/95 and 13/84) were obtained with X-rays. Dose-related increases in pituitary weight were seen and, at higher doses, pituitary tumours typical of cells with raised concentrations of thyroid-stimulating hormone (Walinder, 1972).

Rat: A total of 550 male and female Long-Evans rats, 6–12 weeks old, were injected [route unspecified] with carrier-free ^{131}I at a dose of 10, 25, 100, 200 or 400 μCi [370, 925, 3700, 7400 or 14 800 kBq]. There were 385 controls [treatment not specified]. More than half of the rats died of respiratory disease, but 156 controls and 198 treated rats survived for 18–36 months after injection. The survivors were killed, and the thyroid glands with trachea were removed and examined histologically. The thyroids of irradiated rats were smaller than those of controls, and no thyroid tissue was grossly visible in rats at the highest dose. Diffuse or nodular enlargement was observed in several irradiated thyroids. Microscopic changes, including follicular atrophy, epithelial degeneration and condensation of perifollicular stroma, were seen, and their severity increased with the dose of ^{131}I. Neoplastic lesions designated as alveolar carcinomas occurred in 59 of the 354 rats that survived; the incidence was similar in control rats and those injected with 10 or 25 μCi but was markedly lower at the high doses, and these tumours were found in only two rats at 200 μCi. The thyroid glands showed minimal evidence of radiation injury. An alveolar carcinoma was

found in the thyroid of one rat at 400 μCi that had injury comparable to that of rats at 100 μCi. Malignant thyroid epithelial lesions were seen in five exposed rats, consisting of four follicular carcinomas and one papillary adenocarcinoma in one of six survivors at 10 μCi, three of 20 at 25 μCi and one of 10 at 100 μCi. These results are important because they show that ^{131}I-induced tumours are cytologically and histologically different from naturally occurring tumours (Lindsay *et al.*, 1957).

Groups of 300 female Long-Evans rats, six weeks of age, received an intraperitoneal injection of Na^{131}I in normal saline at 0.48, 1.9 or 5.4 μCi [18, 70 or 200 kBq] to achieve mean doses to the thyroid of 80, 330 and 850 rad [0.8, 3.3 and 8.5 Gy] or local exposure of the thyroid to X-rays at a dose of 94, 410 or 1060 rad [0.94, 4.10 and 10.6 Gy]. Control rats were either injected with normal saline or sham-exposed to X-rays. The remaining two groups received localized X-irradiation at 410 rad [4.1 Gy] to the pituitary gland or the pituitary and thyroid glands. As the minimum latent period for radiogenic thyroid tumours was assumed to be six months, rats that died during the first six months were not included in the subsequent analyses. After 6–24 months, moribund animals were killed and necropsied, and the rats still alive at two years (62%) were also killed and necropsied. Two independent histological evaluations were made. The first thyroid adenoma was observed at 12 months and the first thyroid carcinoma 16 months after exposure. The numbers and types of thyroid carcinomas in rats injected with ^{131}I (36) were almost identical to those in rats exposed to X-rays (40), although more follicular adenomas were seen in the X-irradiated rats at higher doses (Lee *et al.*, 1982). No significant difference was seen in the ratio of thyroid carcinoma incidence due to X-rays and that due to ^{131}I at any dose (Table 92). The response ratios for thyroid adenomas at 0.8 and 3.3 Gy were close to unity; at 8.5 Gy, the X-rays may have been more effective in inducing adenomas, although this was not significant. X-irradiation of the pituitary alone did not increase the occurrence of thyroid tumours above the control level, and concomitant irradiation of the pituitary and thyroid did not increase the number of thyroid tumours above those seen with irradiation of the thyroid alone.

Because of the importance of these studies, an independent evaluation was made of all the histological slides. Close agreement was found with the original diagnosis of follicular-cell carcinoma, but the concordance was less close for adenomas, perhaps owing to differences in the histological categories used. These results support the overall conclusion that the proportion of rats that developed thyroid carcinoma was similar with internal ^{131}I irradiation and localized external X-rays within the range of doses used (Capen *et al.*, 1999). [The Working Group noted that no other study of this type has been conducted.]

In a recent review of studies in laboratory mice and rats in which the effects of internally deposited ^{131}I and external X-irradiation were compared, Royal (1999) noted that the effectiveness of ^{131}I relative to X-rays appeared to be 0.5–0.05, despite the use of high doses, older animals, relatively small numbers of animals and poor survival rates in the early studies.

Table 92. Response ratios of thyroid tumour induction in rats by X-rays and ^{131}I evaluated at mean thyroid doses of 0.8, 3.3 and 8.5 Gy

Type of tumour	Dose (Gy)	Response ratio	95% confidence interval
Thyroid carcinoma	0.8	1.3	0.46–2.7
	3.3	1.0	0.45–2.4
	8.5	0.9	0.31–2.6
Thyroid adenoma	0.8	1.1	0.42–2.9
	3.3	1.4	0.62–2.9
	8.5	2.1	0.52–8.5
Thyroid carcinoma or adenoma	0.8	1.1	0.32–3.7
	3.3	1.2	0.43–3.2
	8.5	1.4	0.24–7.6

From Lee *et al.* (1982)

(*b*) *Caesium-137*

Dog: Fifty-four pure-bred beagle dogs (equally divided by sex) received single intravenous injections of ^{137}CsCl in sterile isotonic saline at 12–14 months of age, six dogs receiving mean initial body burdens of ^{137}Cs of 141 MBq ^{137}Cs/kg bw and groups of 12 dogs receiving 104, 72, 52 and 36 MBq/kg bw. Twelve dogs injected at the same age with non-radioactive saline served as controls. After injection, the dogs were housed individually in cages for 60 days and then moved to a kennel facility where they lived, two per run, for lifetime clinical observations. The absorbed doses of β- and γ-radiation were determined for each ^{137}Cs-injected dog from data on its own whole-body retention and information on the tissue distribution and retention of ^{137}Cs injected in this form in parallel studies with serial sacrifices. Because ^{137}Cs is highly soluble in body fluids, it was distributed rapidly throughout the body. The γ-radiation component represented approximately two-thirds of the total dose; the β-particle component represented about one-third of the total dose, but differences were seen between organs because of differences in ^{137}Cs concentrations, i.e. skeletal muscle had higher and bones lower concentrations than the overall average. Because of the relatively short effective half-life of ^{137}Cs in these dogs, about 30 days, all dogs that lived more than one year after injection had received their full dose commitment. The total doses received in the six dose groups and the associated survival times were, in descending order by dose: 11.8 ± 2.0 Gy, 19–33 days; 16.4 ± 5.1 Gy, 24–4537 days; 14.0 ± 1.8 Gy, 77–5138 days; 11.2 ± 2.5 Gy, 2148–5298 days and 7.42 ± 1.2 Gy, 2471–5342 days; the controls survived 647–6015 days. The results for an additional 49 control dogs from contemporary studies were also used in the analyses. Eleven dogs that received ^{137}Cs at the highest dose died ≤ 81 days after injection, primarily due to haematopoietic-cell damage resulting in pancytopenia from irradiation of the

blood-forming organs. Two years after the injection, 42 ^{137}Cs-injected and 60 pooled control dogs were available for the study of late biological effects. As the whole body was exposed, the biological effects were distributed throughout the body instead of being localized in specific organs such as the skeleton. The incidence of malignant neoplasms was increased in the liver and biliary system (nine dogs) and in the nasal cavity and paranasal sinuses (four dogs). No leukaemias were found, in spite of the large radiation doses received by the blood-forming organs. When all malignant neoplasms were combined and female mammary neoplasms were excluded, a dose-related treatment response for the incidence of malignant neoplasms ($p < 0.001$) was observed in both male and female dogs (Nikula *et al.*, 1995).

A similar study was conducted by the same group in beagle dogs of various ages, with 15 juveniles (aged 142–151 days), 38 young adults (aged 388–427 days) and 10 middle-aged dogs (aged 1387–2060 days). An additional 17 dogs served as controls and lived for 2972–5680 days. The dosimetry was similar to that described by Nikula *et al.* (1995). The dogs that died soon after injection comprised three juvenile dogs exposed to 10.2–11.1 Gy, 10 young adult dogs exposed to 10.5–14.6 Gy and all 10 middle-aged dogs which were exposed to 9.4–12.9 Gy. As in the study described above, these deaths resulted from haematopoietic-cell damage that resulted in severe pancytopenia leading to fatal haemorrhage and/or septicaemia. Of the 40 dogs that died later in the study (> 2 years), five juvenile dogs that received total whole-body doses < 11.5 Gy had a median survival time of 3207 days (range, 1861–3517 days), and seven that received doses > 11.5 Gy had a median survival time of 3294 days (range, 2361–4815 days). The median survival of the young adult dogs was 3350 days (range, 2323–4690 days). Thirty-two of the 40 ^{137}Cs-injected dogs that survived > 2 years had malignant neoplasms: 11 dogs had carcinomas only, 10 had sarcomas only, and 11 had both carcinomas and sarcomas. Of the 17 control dogs, eight had carcinomas, one had a sarcoma and two had both a sarcoma and carcinoma. The most striking differences between the ^{137}Cs-injected dogs and the controls were the larger number of sarcomas with spindle-cell morphology (13 versus two in controls) and the occurrence of leukaemias and myeloproliferative disease (three in the ^{137}Cs-injected dogs and none in controls) (Nikula *et al.*, 1996). When the results of this study were contrasted with those of the study in young adult dogs described above, certain similarities and differences were seen. In both studies, the long-term effects included increased incidences of malignant, non-mammary neoplasms; however, splenic and thyroid tumours were seen in the study with dogs of various ages but not in the young adults. Conversely, the incidences of malignant mammary neoplasms and benign non-mammary neoplasms were increased in the young adults and not in the other study, and nasal cavity tumours were seen in the young adults and not in the other study. These differences may have been due, at least in part, to the relatively small numbers of dogs in both studies.

(*c*) *Cerium-144*

A large research programme was conducted at ITRI (New Mexico, USA) on the long-term biological effects of inhaled aerosols of ^{144}Ce over three decades, and the results are summarized below. The overall goals of the programme were to study the lifetime effects of inhaled α- and β-emitting radionuclides. Much of the research on β-particle emitters was focused on ^{144}Ce because of its relatively long radioactive half-life, prolonged retention in the body and emission of energetic β-particles from ^{144}Ce and its decay product, praseodymium (^{144}Pr).

Mouse: Female C57BL/6J mice, 10 weeks of age, were exposed once by inhalation to an aerosol of $^{144}CeO_2$, producing initial lung burdens of 1–12 μCi [37–444 kBq]. Of the initial 714 mice, 178 were held for lifetime observation, and 299 unexposed mice were maintained under the same conditions as the exposed mice. The high lung burdens led to a substantial shortening of survival, and no primary malignant pulmonary tumours were observed in the exposed mice (Lundgren *et al.*, 1974). A new study was therefore conducted at lower initial lung burdens in mice of various ages, and another was conducted on the lifetime effects of repeated exposure to $^{144}CeO_2$ by inhalation. The design of these studies in mice was also used in similar studies in rats, Syrian hamsters and beagle dogs, discussed below.

Female C57BL/6J mice, aged 70, 260 or 450 days, were exposed once to an aerosol of $^{144}CeO_2$ to achieve an initial lung burden of 0.2, 1.0 or 4.5 μCi [7.4, 37 or 167 kBq] in the 1178 animals. The $^{144}CeO_2$ aerosol, produced by heat treatment of airborne droplets of $^{144}CeCl_3$, had an activity mean aerodynamic diameter of 1.5–1.8 μm (geometric standard deviation, 1.5–1.7). A total of 674 control mice were either unexposed, sham-exposed or exposed once to an aerosol of stable CeO_2. A number of mice were withdrawn for dosimetric and other purposes during the study. The median survival times of the mice held for lifetime observation and exposed to the two lower doses were 93–106% of those of the respective controls. The survival times of mice at 4.5 μCi were shorter owing to early non-neoplastic radiation effects and bacterial infections. In the 918 mice (89%) available for histological evaluation, the incidence of lung adenomas (13, 4 and 9%) was significantly increased for all those with an initial lung burden of 1.0 μCi [37 kBq] after exposure at any age. Pulmonary adenocarcinomas and one squamous-cell carcinoma were also seen in mice exposed at 70 days of age. The authors concluded that 70-day-old mice are more sensitive to the development of late effects of $^{144}CeO_2$ than are 260- or 450-day-old mice (Lundgren *et al.*, 1980a).

In a study of repeated exposure, groups of 160 female C57BL/6J mice were exposed to a $^{144}CeO_2$ aerosol at 9–11 weeks of age to produce an initial lung burden of 0, 0.2, 1.0 or 4.5 μCi [0, 7.4, 37 or 167 kBq]. The mice were further exposed six more times at 60-day intervals to re-establish the lung burdens to the original levels. The reduction in median lifespan was 5% at 0.2 μCi, 37% at 1.0 μCi and 84% at 4.5 μCi. For the same total absorbed dose of β-particles to the lung, a single exposure resulted in a dose rate that was initially higher and eventually lower than that after re-established lung burdens.

In mice exposed to 0.1 or 1 μCi that had prolonged survival times, the incidence of benign and malignant lung tumours was correlated with cumulative dose and not with dose rate. The number of malignant pulmonary tumours was increased in mice exposed repeatedly: controls, 0.3%; 0.1 μCi, 6.3% and 0.2 μCi, 7.9% (Hahn *et al.*, 1980; Lundgren *et al.*, 1980b).

Rat: The biological effects of single and repeated exposures to $^{144}CeO_2$ by inhalation were studied in Fischer 344/Crl rats. Of a total of 968 animals (465 males and 503 females), 244 were used for dosimetry, leaving 453 exposed and 271 control rats that were observed for life. The study had three components: (i) a single exposure at 94 days of age to produce an initial lung burden of 1.9, 9.2, 46 or 230 kBq; (ii) repeated exposures beginning at 94 days of age and continuing every 60 days for a total of seven exposures with the goal of re-establishing the lung burden to 1.9, 9.2, 46 or 230 kBq at each exposure; and (iii) a single exposure at 500 days of age to produce an initial lung burden of 46 or 239 kBq. All exposures were to airborne, uniformly spherical particles of $^{144}CeO_2$ with activity median aerodynamic diameters of 0.9–2.2 μm (geometric standard deviation, 1.4–2.0). Control rats were either unexposed, sham-exposed or exposed to stable CeO_2, but, because no difference was observed among these types of controls, they were pooled for the analyses. Analyses of the dose to the lung of rats withdrawn at various times during the study indicated that the mean lifetime absorbed doses of β-particles to the lung were 0.26–46 Gy in rats exposed once at 94 days of age, 2.1–250 Gy in the rats exposed repeatedly and 8.5–36 Gy in rats exposed at 500 days of age. The survival rate of all groups of ^{144}Ce-exposed rats was 90–114% of that of the respective control groups, except for the group that was repeatedly exposed to re-establish a lung burden of 230 kBq, in which survival was only 70% that of the controls. The mean lifetime doses and the incidences of primary lung tumours in the various experimental groups are given in Table 93. The repeated exposure regimen to re-establish a given lung burden resulted in a lifetime dose to the lung that was about five times higher than that from a single exposure, although the initial lung burden was of the same magnitude. At the same total dose, the single exposure regimen resulted in an initially higher and eventually a lower dose rate than the re-established dose rate in the repeatedly exposed rats. The incidence of primary lung tumours was related to cumulative dose of β-particles rather than to the rate at which the dose was accumulated, especially at the higher doses. With doses to the lung > 10 Gy, there was a clear dose–response relationship for lung tumours; however, for rats with total doses to the lung of < 10 Gy, the incidences of primary lung tumours were not directly related to dose, perhaps because of the relatively smaller numbers of rats at the lower doses (Lundgren *et al.*, 1992a,b). Hahn and Lundgren (1992) described the types of lung tumours seen. Rats at the highest exposure level, with significantly shortened survival, had a high incidence of squamous-cell carcinomas of the lung and lower incidences of adenocarcinomas of the lung, haemangiosarcomas of the lung and pleural mesotheliomas. Neither the exposure mode (single or repeated) nor the sex of the animal influenced the lung tumour type or incidence. Because

Table 93. Incidences of primary lung tumours in Fischer 344 rats exposed once or repeatedly by inhalation to $^{144}CeO_2$

Desired initial or re-established lung burden (kBq)	No. of rats examined[a]	Mean lifetime dose (Gy) to lung	Incidence of primary lung tumours (%)	
			Benign	Malignant
94-day-old rats exposed once				
Controls	115[b]	0	0	0
1.9	35	0.26	0	2.8
9.2	49	1.2	0	2.0
46	39	6.8	2.6	2.6
230	57	46	3.5	26.3
94-day-old rats exposed repeatedly				
Controls	110	0	1.8	3.6
1.9	36	2.1	2.8	2.8
9.2	46	9.5	2.2	0
46	33	50	6.1	27.3
230	37	250	0	91.9
500-day-old rats exposed once				
Controls	37	0	2.7	0
46	38	8.5	0	2.6
230	62	36	1.6	8.1

From Lundgren *et al*. (1992b)

[a] Only rats held for lifespan observation and evaluated histologically

[b] Pooled controls

$^{144}CeO_2$ is relatively insoluble, most of the deposited material remained in the lung instead of translocating to the liver and skeleton as more soluble forms of cerium might do. Five osteosarcomas of the ribs were seen, perhaps due to β-radiation originating from the lung.

To examine the possible dose–response relationships for lung cancer caused by $^{144}CeO_2$ at lower doses, a study was conducted with larger numbers of rats (Lundgren *et al.*, 1996). This study was designed to be the β-emitter counterpart to the study of Sanders *et al.* (1993a,b), which involved relatively low doses to the lung from inhaled α-emitting $^{239}PuO_2$ in rats. A total of 2751 Fischer 344/N rats (1358 males and 1393 females) were used. Of these, 1059 received a single exposure to $^{144}CeO_2$ by inhalation to achieve an initial lung burden of 18 kBq (low level), 247 rats to achieve 60 kBq (medium level) and 381 rats to achieve 180 kBq (high level). Samples of the $^{144}CeO_2$ particles from the 36 exposures showed them to be uniformly spherical with an activity median aerodynamic diameter of 1.4 ± 0.1 μm (geometric standard deviation, 2.0 ± 0.2). The 1064 control rats were exposed for 25 min to an aerosol of stable CeO_2 to produce

lung burdens of cerium that were similar to those from ^{144}Ce. The organ doses were calculated from the distribution and retention of ^{144}Ce in rats that were killed periodically during the study. The total absorbed doses of β-particles to the lung from this relatively insoluble form of ^{144}Ce were 3.5 ± 1.3 Gy (SD) for the low-dose group, 12 ± 4.6 Gy for the medium-dose group and 40 ± 10 Gy for the high-dose group. The total dose to the liver was approximately 1/55 and the mean skeletal dose about 1/200 of the corresponding dose to the lung. A total of 2571 rats were held for lifetime observation, and 2538 (99%) were evaluated histologically. The median survival times of the rats at the three levels of exposure were 96–102% of those of controls. Table 94 shows the distribution of lung tumour types in the four experimental groups. These tumours were the cause of death in 71% of controls, 64% of rats at the low dose, 67% of those at the medium dose and 67% of those at the high dose. In decreasing order, the commonest malignant lung tumours were adenocarcinoma, squamous-cell carcinoma and adenosquamous carcinoma. The crude incidences of benign and malignant lung tumours combined were 0.57% in the controls, 2.04% at the low dose, 6.1% at the medium dose and 19% at the high dose. These crude incidence values were well described by a linear function with an intercept of 0.13 ± 0.12% (SD) and a slope of 0.51 ± 0.00054/Gy (correlation coefficient, $r^2 > 0.999$). Several other functions, such as the linear–quadratic, exponential linear–quadratic and Weibull functions, also described these results adequately, but a quadratic function did not.

Hamster: A lifetime study of the biological effects of single or repeated inhalation of aerosols of $^{144}CeO_2$ in Syrian hamsters was reported. Male Syrian hamsters [Sch:SYR] inhaled aerosols of $^{144}CeO_2$, and 222 controls were either unexposed or exposed to stable CeO_2. For the single exposure, 311 hamsters inhaled $^{144}CeO_2$ at 84

Table 94. Primary neoplasms in the lungs of rats exposed by inhalation to aerosols of $^{144}CeO_2$ and held for life

Lung neoplasm	Exposure level			
	Controls	Low	Medium	High
Total number/rats examined histologically	7/1049[a]	22/1025[a]	18/295	30/133[b]
Adenoma, alveolar or papillary (%)	14	23	39	11
Adenocarcinoma, alveolar, papillary or tubular (%)	58	41	39	53
Adenosquamous carcinoma (%)	0	9	11	17
Squamous-cell carcinoma (%)	14	23	11	17
Fibro- or osteosarcoma (%)	14	4	0	3

From Lundgren *et al*. (1996)

[a] One rat in each group had two lung neoplasms each.

[b] Two rats in each group had two lung neoplasms each.

days of age (0.4, 2 or 10 μCi [14.8, 74 or 370 kBq]), 220 days (2 or 10 μCi) or 360 days (2 or 10 μCi). Three groups of about 75 hamsters were exposed to $^{144}CeO_2$ to re-establish a lung burden at 0.4, 2 or 10 μCi at each exposure, and 75 of the controls received repeated exposures to stable CeO_2. The aerosols were produced by heat treatment of airborne droplets of $^{144}CeCl_3$ and stable $CeCl_3$; the resulting aerosols had activity median aerodynamic diameters of 0.9–2.2 μm (geometric standard deviation, 1.4–2.0). Electron micrographs showed that the particles were spherical with minimal aggregation. Information on whole-body and organ retention was used to calculate the doses to the lung and other organs and tissues. The mean dose to the lungs of hamsters exposed once was 10 ± 3.7 Gy (SD) for an initial lung burden of 0.4 μCi [14.8 kBq], up to 190 ± 59 Gy for an initial lung burden of 10 μCi [370 kBq]. The mean doses to the lung from repeated exposure ranged from 2800 ± 720 rad [28 ± 7.2 Gy] for lung burdens re-established at 0.4 μCi to 290 ± 72 Gy for a re-established lung burden of 10 μCi. The doses of β-particles to the liver were about 1/100 to 1/400 of that to the lung, and those to the skeleton were about 1/300 to 1/900 of that to the lung. Decreased survival was seen primarily in hamsters exposed once or repeatedly to a lung burden of 10 μCi. Hamsters exposed to 0.4 or 2 μCi had median survival times that were 98–113% that of the controls. Of 659 hamsters held for lifetime observation, 641 (97%) were evaluated histologically. No difference was seen between the two types of controls. The only neoplasms for which significantly (χ^2 test, $p < 0.05$) increased incidences occurred when compared with controls were primary lung tumours. Eleven carcinomas (four adenocarcinomas, six squamous-cell carcinomas and one undifferentiated carcinoma) and two alveolar adenomas were observed in the ^{144}Ce-exposed hamsters, whereas none was found in the controls. Repeated exposure to ^{144}Ce did not change the incidence of lung tumours or time to death with lung tumour when compared with hamsters exposed once (Lundgren *et al.*, 1982).

Dog: A lifetime study on the biological effects of an inhaled, relatively soluble form of ^{144}Ce, $^{144}CeCl_3$, was reported. This study involved 70 pure-bred beagle dogs, 55 of which (28 males and 27 females) received a single, nose-only exposure by inhalation to an aerosol of $^{144}CeCl_3$ at 12–14 months of age. Eight male and seven female animals were unexposed. The $^{144}CeCl_3$ aerosol was generated from a solution containing $^{144}CeCl_3$ (0.7–1% by weight of stable cerium and other total solids) in 0.1 or 1 M HCl. The resulting aerosol had activity median aerodynamic diameters of 1.4–2.4 μm (geometric standard deviation, 1.6–2.1). The animals were exposed for 3.6–28 min in order to obtain the desired initial body burdens. Because the first, rapidly cleared component of whole-body retention did not contribute substantially to the long-term organ burdens or doses, the tissue distribution and dosimetry were expressed as functions of the retained whole-body burden. The results of a parallel study of dogs exposed to a similar aerosol and killed in series were used to model the disposition and average organ dosimetry of ^{144}Ce inhaled in this form. The resulting total dose coefficients of β-particles (Gy/MBq retained burden of ^{144}Ce per kg bw) were: liver, 59; tracheobronchial lymph nodes, 50; bone-associated nasal mucosa, 30; lung, 24; bone, 18;

bone-associated oral mucosa, 18; bone marrow, 9; thyroid, 7.5; and kidneys, 7.5. All other organs that were examined received doses that were smaller by at least a factor of 2.5. Because of variation in the deposition and retention of ^{144}Ce among dogs in this study, the retained burdens ranged from 0.1 to 13 MBq/kg bw. In subsequent analyses of survival times, the animals were divided into five groups of exposed dogs and one group of controls. The median survival times for the five exposed groups ranged from 31 to 4382 days, and the median value for the control dogs was 5064. Nine dogs at the highest dose died within the first 2.5 years from haematological dyscrasia, three from radiation pneumonitis and three from hepatic degeneration. The neoplasms observed are summarized in Table 95. Neoplasms occurred relatively early, 2.2–6.8 years after exposure, in the liver, bone, bone marrow and oral mucosa closely associated with bone. Neoplasms occurred more than seven years after exposure in the liver, lung and nasal mucosa closely associated with bone. Although only one primary bone tumour was found, 11 tumours were found in bone-associated tissues (oral and nasal mucosa and bone marrow) (Hahn *et al.*, 1995, 1997).

In a study of ^{144}Ce embedded on fused aluminosilicate particles, 111 beagle dogs (58 males and 53 females) were exposed once at 12–14 months of age to an aerosol prepared by nebulizing a suspension of montmorillonite clay particles containing ^{144}Ce. The airborne droplets were passed through a tube furnace at 1150 °C to produce ^{144}Ce fused aluminosilicate particles with activity median aerodynamic diameters of 1.4–2.7 μm (geometric standard deviation, 1.5–2.3). Another eight males and seven females of the same age were exposed to an aerosol of stable cerium in fused aluminosilicate particles. The initial lung burdens achieved ranged from 0.093 to 7600 kBq/kg bw ^{144}Ce. The dogs were assigned to groups of 6–16 on the basis of their initial lung burdens. The median survival times ranged from 5264 days at the lowest dose to 177 days at the highest; the median survival time was 4652 days. Dogs with the highest lung burdens died of radiation pneumonitis and pulmonary fibrosis. In the 94 dogs that survived more than two years, neoplasia was the primary long-term biological effect: neoplasms occurred in the lung in 28 dogs, in the tracheobronchial lymph nodes in 23 dogs and in the heart in three dogs. Some of the insoluble particles were cleared from the lung via the lymphatic system to the tracheobronchial lymph nodes, which resulted in β-irradiation of the lymph nodes and adjacent heart tissue which also produced haemangiosarcomas in these organs. Haemangiosarcomas were also found in the lung in some surviving dogs at the highest dose. At lower doses, carcinomas of various kinds were observed in the lung. The percentage distribution of the 32 lung neoplasms by type was: adenoma, 6.2%; adenocarcinoma, 31%; carcinoma, 25%; bronchiolo-alveolar, 19%; adenosquamous, 3%; squamous-cell, 3%; carcinosarcoma, 9.4%; and sarcoma, 28% (Hahn *et al.*, 1999).

Table 95. Neoplasia in target organs of beagle dogs that inhaled $^{144}CeCl_3$ and in controls

Target organ	Exposed (41 dogs at risk: alive two years after exposure)		Unexposed controls (15 dogs at risk: alive two years after exposure)	
	Benign neoplasms	Malignant neoplasms	Benign neoplasms	Malignant neoplasms
Bone	None	Osteosarcoma-vertebra (1)	None	None
Bone marrow	Myelodysplasia (1)	Myeloid leukaemia (2)	None	None
Bone-associated oral mucosa	None	Squamous-cell carcinoma, maxilla (3)	None	None
Bone-associated nasal mucosa	None	Squamous-cell carcinoma (4) Haemangiosarcoma (1)	None	None
Liver	Biliary cystadenoma (4) Fibroma (1)	Haemangiosarcoma (7) Fibrosarcoma (1) Cholangiocarcinoma (1) Hepatocellular carcinoma (1)	Biliary cystadenoma (1) Biliary adenoma (1)	None
Lung	Bronchioalveolar adenoma (1)	Adenocarcinoma (3) (bronchioalveolar, papillary, mucocystic)	None	Adenocarcinoma (2) (papillary, bronchioalveolar)[a]
Thyroid	Follicular adenoma (3) Solid-follicular adenoma (1)	Solid-follicular adenocarcinoma (3)	Solid adenoma (1)	Solid adenocarcinoma (2) Solid follicular adenocarcinoma (2)

From Hahn *et al*. (1997). In parentheses, number of dogs with neoplasms; some dogs had more than one neoplasm.
[a] Three primary lung tumours in two dogs

(*d*) *Radium-228* (see Table 7 of General Remarks, footnote l)

Dog: Groups of 6–13 beagle dogs aged 511–550 days were given a single intravenous injection of ^{228}Ra in a citrate solution, and 13 dogs aged 584 days were given an injection of the citrate carrier and served as contemporary controls. In later statistical analyses, further controls were added. The animals were about equally divided between males and females, and the injected amounts ranged from about 0.65 to about 307 kBq/kg bw. Skeletal tumours were detected by periodic radiographic examination and confirmed by histopathological evaluation after necropsy. Soft-tissue tumours were detected by clinical examination or at necropsy and classified by histopathology. The occurrence of skeletal tumours is presented in Table 96, which shows a dose–response relationship. From a linear regression analysis, the authors concluded that the lifetime risk for the development of bone tumours was about 9% per Gy of average skeletal dose. The toxicity ratio (^{228}Ra /^{226}Ra) for skeletal cancers was 2.0 ± 0.5 (Mays *et al*., 1987; Lloyd *et al*., 1997a).

Table 96. Effects of ^{228}Ra given as a single intravenous injection to young adult beagle dogs

Dose injected (kBq/kg bw)	Total no. of dogs	No. of bone sarcomas	Skeletal dose (Gy) 1 year before death	Age at death (days)
0	13	0	0	4755 ± 348
0.65	12	0	0.93	4849 ± 201
1.84	13	1	2.39	4494 ± 261
5.66	12	10	6.32	3570 ± 142
11.2	11	8	8.36	2619 ± 224
34.8	11	11	18.21	2059 ± 63
92.5	6	5	27.88	1548 ± 74
307	6	1	52.73	1302 ± 63

From Mays *et al*. (1987)

3.3 Pre- and perinatal carcinogenesis

Only a limited number of radionuclides have been evaluated for carcinogenicity during the pre- and perinatal periods, although the internal and internal plus external exposures differ from those of adults. Radionuclides that emit α- or β-particles include some that deliver a dose to the fetus, resulting from internal deposition or from external β or photon emissions from maternal depositions. It is not always possible to differentiate between the two.

Perinatal carcinogenesis due to external radiation in human populations and experimental animals was considered in a previous monograph (IARC, 2000). Most of the major incidents in which pregnant women or experimental animals have been

exposed to ionizing radiation were acute or of relatively short duration and, at least in part, involved external sources (X-rays, γ-rays or neutrons). Such radiation passes through the abdomen and uterus, often with little attenuation. The resulting exposure of the conceptus does not involve placental transport or metabolism, and the energy deposited or the radiation dose is roughly uniform throughout the entire fetoplacental unit. This section addresses studies of tumour development associated with exposure of pregnant or neonatal animals to radionuclides. Studies on exposure of male parents before conception are summarized in section 3.4.

3.3.1 *α-Particle emitters*

(*a*) *Plutonium-238 and plutonium-239*

Several investigators (see also section 4.1) have shown that the placental transfer of plutonium and metabolically related actinides is limited. Actinides are initially deposited mainly in the liver and on bone surfaces in both adults and newborns. Their biological behaviour during the prenatal period is complex, as it is strongly influenced by maternal metabolic relationships and by patterns of deposition throughout the feto-placental unit, hepatic development and localization and redistribution in bone dependent on the stage of gestation.

A series of comparative long-term studies was carried out which included sequential measurements of tissue concentrations and dosimetry (Sikov, 1989).

In the initial study, young adult (3-month-old) and weanling (21-day-old) Wistar-derived rats were injected intravenously with 0.3, 1 or 3 mCi/kg bw [11.1, 37 or 111 MBq/kg bw] of ^{239}Pu prepared in a 100-fold excess of citrate, so that it was primarily a monomeric solution. Rats at 19 days of gestation were injected with 6, 20 or 60 mCi/kg bw [222, 740 or 2220 MBq/kg bw] of the same solution in order to expose the fetuses, and newborns were injected intracardially with 3, 10 or 30 mCi/kg bw [111, 370 or 1110 MBq/kg bw]. Other rats were injected with citrate solutions at the same concentration to serve as controls. The doses were selected to deliver similar doses of radiation to the femur (7, 23 or 70 rad [0.07, 0.23 or 0.7 Gy]) during the first 10 days after injection in all age groups, although the cumulative doses in the group exposed prenatally fell below the target dose. Because of dilution due to greater growth rates, the concentration decreased more rapidly in the newborn animals, and since the skull grew less than the remainder of the skeleton, it received a relatively greater dose. Most of the dose was received within the first few months after exposure, while adults continued to be exposed at a higher level throughout life. Groups of about 25 male and 25 female rats in each age group (adults, weanlings, newborns and fetuses) and each group of plutonium dose as well as controls were selected for long-term observation, and two additional cross-fostered groups of prenatally exposed and control newborns were used in an ancillary experiment. Survival decreased significantly with increasing dose in the three groups exposed postnatally. In this and subsequent studies of this series, moribund animals were killed, and all survivors were killed at 30 months of

age. Complete necropsies, with radiographs, were performed, and histopathology was carried out when not precluded by autolysis. The incidences of bone tumours in the adult and weanling rats increased progressively with dose (0, 10, 37 and 60% in adults and 2, 4, 23 and 39% in weanlings), but reached a plateau in the newborns (4, 15, 18 and 17%, not statistically significant). The incidence in the group exposed prenatally was slightly increased by the lowest dose (4%), became maximal at the intermediate dose (10%) but decreased at the highest dose (4%). When the offspring of some dams at the highest dose were cross-fostered with the litters of control mothers, they had a higher incidence (27%) of osteogenic sarcoma than offspring kept with their own mothers (3%). The pattern of relative sensitivity may be misleading when expressed on this basis, however, because the doses of radiation were not proportional to the administered dose in all four age groups (Sikov *et al.*, 1978).

In a second experiment, pregnant Sprague-Dawley rats were injected intravenously with ^{239}Pu citrate at a dose of 0.3, 3 or 30 mCi/kg bw [11, 111 or 1110 MBq/kg bw] on day 9, 15 or 19 of gestation. The cumulative dose rate of radiation and the doses to the embryo or fetus and offspring increased with prenatal age at injection. Exposure had dose-related effects on postnatal growth and survival that were more severe and/or more frequent among offspring from litters injected at 19 days than at 9 days of gestation, while they were of intermediate severity in those exposed at 15 days. The incidence of adenomatous hyperplasia of the liver was analysed only for the 46–75 pooled rats per dose group that survived beyond 800 days. The incidence progressed from 8/75 in controls to 29/70, 35/74 and 46/56, respectively, in the three exposed groups, and a numerical score for severity tended to be higher with increasing gestational age at exposure. The incidence of bone tumours was increased in the offspring of dams injected with the highest dose at 19 days. The incidence of 14% bone tumours at a cumulative femur dose of 40 rad [0.4 Gy] was compatible with the results of the first experiment (Sikov, 1982, 1983, 1989).

In a third experiment, the influence of foster-rearing of rats on the postnatal effects of prenatal exposure to plutonium was examined. At 19 days of gestation, pregnant Sprague Dawley-derived rats were injected intravenously with 60 mCi/kg bw ^{239}Pu citrate [2220 MBq/kg bw] or with a citrate (control) solution. A matrix of six experimental groups was formed by giving one-day-old offspring for fostering to control or exposed dams (see Table 97). Subgroups of offspring, each containing no more than two males and two females from each litter, were kept for long-term studies, and the other offspring were killed at intervals for dosimetry. The growth curves and body masses of prenatally exposed offspring reared by control dams were similar to those of control offspring reared by their own or control foster dams, but the curves for control offspring that were nursed by exposed dams were depressed. In contrast, the three groups of offspring that were exposed prenatally lived significantly less long than control groups, although a consistent effect of fostering was not detected. As shown in Table 97, the incidence of osteogenic sarcomas was significantly greater (about 15%) in the offspring of the three groups that were injected with ^{239}Pu citrate

Table 97. Incidences of osteosarcomas in the offspring of rats injected with ^{239}Pu on day 19 of gestation

Exposure		No. of offspring examined	No. of osteosarcomas			
Prenatal	Postnatal		Skull	Axial skeleton	Appendicular skeleton	All
Exposed	Not fostered[a]	75	10	1	2	13
Exposed	Exposed	80	8	2	3	13
Control	Exposed	75	0	0	0	0
Exposed	Control	81	8	2	2	12
Control	Control	88	0	0	0	0
Control	Not fostered[a]	78	0	0	1	1

From Sikov (1987)
[a] Kept with their dams.

than in controls injected with citrate (1%). The incidences of bone tumours were not influenced by exposure of rats that reared the offspring. The incidences of several histopathological lesions of soft tissues, including tumours of the liver and adrenal gland, were increased in the three groups that were exposed to plutonium prenatally, but the incidences were not influenced by fostering or by the exposure of the dams that reared the offspring. These patterns are in accord with measurements that showed that most of the lifetime ^{239}Pu burden was derived from placental transfer after prenatal exposure and that milk made little contribution (Sikov, 1985, 1987a, 1989).

The relationships between the absorbed doses of radiation to the skeleton and its components after injection of pregnant rats on day 19 of gestation and the resulting incidences of osteogenic sarcoma in the offspring in the three experiments show a consistent pattern. When the data on bone tumours were analysed together, the composite dose–response curve for tumour incidence showed a progressive increase with dose, as described by the equation: Incidence (%) = $1.6 + 0.5 \times$ Dose (cGy). This was followed by a sharp downwards inflection at a dose of 40 cGy (Sikov, 1989). The comparisons of the dose–response relationships suggested that the perinatal skeleton is more radiosensitive to oncogenesis than that of the adult. The actual pattern of sensitivity cannot be identified because, as indicated above, the dose rates and cumulative radiation doses to embryos, fetuses and offspring are affected by the age at injection, and temporal and spatial considerations are superimposed on the radiation doses. Within the useable range for each age group, however, the average dose that would produce a 10% increase in bone tumour incidence was estimated roughly to be 43 rad [0.43 Gy] to 19-day-old fetuses, 86 rad [0.86 Gy] to newborns, 110 rad [1.1 Gy] to weanlings and 275 rad [2.75 Gy] to adults (Sikov, 1983). Another consistent finding was that tumours of the head predominated in perinatally exposed rats in all three experiments; this pattern clearly differed from that in animals that were older when exposed, in which axial and

appendicular tumours predominated. The tumour distribution in adults was similar to that found by others, and the effect of age agrees well with the age-related spatial and temporal distributions of ^{239}Pu and the resulting radiation doses (Sikov, 1989).

In a summary of studies by the Ministry of Health of the former USSR on the carcinogenic effects of perinatal exposure to plutonium, pregnant or nursing Wistar rats were given the radionuclide ^{238}Pu or ^{239}Pu. Malignant tumours were found in the offspring in the organs in which the nuclides were deposited preferentially, specifically the skeleton and liver. After intraperitoneal injection of ^{238}Pu nitrate at 185 kBq/kg bw, liver tumours developed in 1/86 offspring injected on day 15 and 3/73 injected on day 19; no liver tumours were found among 78 control rats. Osteosarcomas were found in 2/86 offspring that received cumulative lifetime doses to the skeleton of 8–8.5 mGy after injection on day 15 and in two offspring injected on day 19 that received a lifetime absorbed dose of 3.4 mGy. No liver or bone tumours were found among 74 offspring of dams treated on day 4 with a cumulative dose to the skeleton of 164 mGy [this value may be incorrect]. The incidence of other tumours did not differ from that in controls (Moskalev *et al.*, 1989).

In another experiment, female Wistar rats were given ^{239}Pu citrate by intravenous injection one day *post partum* at a dose of 1600 kBq/kg bw, so that the offspring received plutonium in the milk. Three of 152 suckling rats (1.97%) that received an absorbed dose of 90 mGy to the skeleton developed osteosarcomas. There were no tumours in the controls [number and treatment unstated], but the spontaneous incidence in this strain was reported to be 0.015%. The authors stated that the quantitative results and the location of most osteosarcomas in the skeletal components that contained ^{239}Pu were in good agreement with those reported by others (Moskalev *et al*., 1989).

(*b*) *Americium-241*

When female rats were given ^{241}Am at a dose of 92.5 kBq/kg bw by intravenous administration on day 16 of gestation, four ostosarcomas were detected among the 78 female and 52 male offspring, while none was found in controls. One of the tumours was found in the head and three in the femur. The authors reported that tumours of the bone and liver occurred at cumulative doses of 3–8.5 mGy incorporated during the embryonic and fetal periods or during lactation (Moskalev *et al.*, 1989).

Pregnant BALB/c mice, 12 weeks of age, were injected intravenously with ^{241}Am at a dose of 100, 500 or 1500 kBq/kg bw on day 14 of gestation, and the offspring were reared by unexposed dams. Control mice were sham-injected, and their litters were raised by other dams. Radioanalyses for ^{241}Am in the femur were performed on litters on days 15 and 17 of gestation (one and three days after injection of their dams), at birth and four additional times in three months. The offspring were kept until death, when they were necropsied and radiographed, and the main organs and any others that appeared abnormal were examined histologically. The mean length of survival of exposed offspring was not reduced. As shown in Table 98, the incidences of osteosarcoma and all sarcomas were significantly increased, although the results of the statistical tests were

Table 98. Per cent of deaths from tumours in offspring of mice exposed to ^{241}Am during gestation

Tumour	Dose of ^{241}Am administered (kBq/kg bw)							
	Females				Males			
	0	100	500	1500	0	100	500	1500
(No. of mice evaluated histologically	46	45	41	49	81	46	55	77)
Osteosarcomas	0	4.4	2.4	4.1	0	2.2	1.8	0
Lung carcinomas	15	16	15	14	27	26	25	32
All malignant tumours	54	71	58	65	57	72	64	65
All leukaemias	35	38	27	39	18	30	31	29
All sarcomas	2.2	11	9.8	8.2	4.9	11	7.3	1.3

From Van den Heuvel *et al.* (1995)

not consistent. The incidences of all malignant tumours and leukaemias were significantly increased in male offspring (Van den Heuvel *et al*., 1995).

3.3.2 *β-Particle emitters*

(*a*) *Hydrogen-3*

The radioactive isotope of hydrogen (^{3}H) is distributed rapidly throughout the body water after ingestion of the inorganic form, usually as $^{3}H_2O$ (see section 4.1). As such, it freely crosses the placenta and shows no strongly preferential site of localization. This minimizes many of the potential dosimetric complications that pertain to other nuclides, and average tissue doses can be calculated by sequential measurements. As with other radionuclides, the distribution of ^{3}H differs when it is administered in different organic compounds. Several studies have addressed the disposition in pregnant animals of organic compounds of metabolic importance labelled with ^{3}H or radiocarbon. Most of these studies were of normal placental transfer and maternal–fetoplacental physiology, but some were conducted for radiological protection. Tritiated thymidine has been studied in particular to establish the mechanism of action of radiobiological compounds.

(i) *^{3}H-Labelled water*

Mouse: Groups of nine pregnant mice were injected with $^{3}H_2O$ at a dose of 0.067, 0.135 or 0.27 Ci/kg bw [2.5, 5 or 10 GBq/kg bw] on day 9 of gestation or kept as controls. The litter sizes and perinatal mortality were not affected, although more deaths ocurred before weaning among offspring at the highest dose. There was no effect on mortality rate in the period between weaning and 4–5 months of age, when many

offspring were killed and examined. Growth and survival were decreased at 0.27 Ci/kg bw, and tests of mating at two months of age showed that these offspring were not fertile; furthermore, females at 0.135 Ci/kg bw, but not males, showed reduced fertility. The weights and histological integrity of the gonads were reduced in both males and females at all doses, and the brain weight was reduced at higher doses (see section 4.3). A total of 21 females and 23 males at 0.27 Ci/kg bw and the 59 female and 80 male controls were held until 18 months of age. The incidence of ovarian tumours in the exposed offspring (67%) was markedly higher than that in the controls (14%), but the incidences of other tumours were not markedly altered (Török *et al.*, 1970).

Groups of 138–142 male and 109–120 female C57BL/6 mice received a single intraperitoneal injection of ^3H_2O at a dose of 1 μCi [37 kBq] after weaning; 1 μCi/mL in drinking-water after weaning and throughout life; a single intraperitoneal injection of 1 μCi to females after the birth of their litters; 1 μCi/mL in the drinking-water of females and their newborn litters throughout life; or 1 μCi/mL in the drinking-water of females identified as pregnant by a vaginal plug and of their offspring throughout life. The 577 male and 525 female control mice received ordinary drinking-water and were observed throughout life. An extensive array of tissues and tumours were taken for histological evaluation. Statistically significant increases in the incidences of tumours were found in all treated groups, the type of tumour depending on sex and exposure regimen. The incidences of reticulo-endothelial tumours were increased in the group given 1 μCi/mL in drinking-water after weaning and that treated from conception. Tumours were found in the liver, lung, intestine and other organs, in decreasing order of frequency. The incidences of lymphocytic lymphomas were significantly increased in mice of each sex in all groups, and the increase was most marked in mice exposed via maternal milk and those exposed from conception (Méwissen *et al.*, 1989).

Rat: Pregnant Sprague-Dawley rats, about 125 days of age, were injected intraperitoneally with ^3H_2O to produce a dose to body water of 0, 1, 50 or 100 μCi/mL [37, 1850 or 3700 kBq/mL]. These nominal equilibrium body water concentrations were maintained by providing ^3H_2O in drinking-water throughout gestation. There were 36 control rats and 24 rats at 1, 26 rats at 10, 23 rats at 50 and 36 rats at 100 μCi/mL of labelled body water. The corresponding cumulative whole-body doses of β-particles were calculated to be 0.6–660 rad [0.006–6.6 Gy] for the pregnant animals and their fetuses. All rats were allowed to give birth and to wean their litters, after which the dams were maintained for lifetime evaluation (Cahill *et al.*, 1975a). The offspring were held for long-term study, the results of which were described in a second paper. The dams were kept until death or were killed and necropsied for histological evaluation. For logistics, the study was initiated as six separate increments or replicates; analysis of variance showed no statistically significant effect of this design, but the age differences had to be addressed in some of the statistical analyses. The survival of exposed dams was reduced, but this was not attributable to tumours. In order to allow for deaths from other causes, the incidences of mammary tumours, which developed late in life, were evaluated on the basis of rat–days at risk. The incidence was found to be increased by treatment. The

increase in the incidence of fibroadenomas was significant at the two higher doses, and that of malignant mammary neoplasms was increased at all doses but statistically significantly so only at the highest dose. Offspring that survived to 30 days of age were defined as the study population, and the numbers were 242 control rats, 111 rats at 0.006 Gy, 187 rats at 0.06 Gy, 170 rats at 3.3 Gy and 207 rats at 6.6 Gy, approximately evenly divided by sex. Exposure to 6.6 Gy decreased the survival of offspring of each sex, and the microscopic appearance of the male and female gonads confirmed the previous report that rats exposed to 3.3 or 6.6 Gy were sterile. This finding is also consistent with the results of studies of prenatal exposure to external X- or γ-rays and other radionuclides under conditions that resulted in congenital ovarian hypoplasia. The incidence of tumours of the ovary was increased among female offspring at the two higher doses, but the differences were not statistically significant when adjustments were made for replicate and litter interactions. On the basis of rat offspring days at risk, there was no increase in the incidence of mammary fibroadenomas (Cahill *et al.*, 1975b).

(ii) *[^{3}H]Thymidine*

[^{3}H]Thymidine has been studied in relation to tumorigenesis because the ^{3}H labels a precursor of DNA. A fraction (roughly estimated at 10%) is incorporated into the DNA of proliferating cells, while the remainder is rapidly catabolized and excreted. The incorporated thymidine remains in the DNA until the cell divides, at which time it is distributed among its descendents or until the cell dies, when it can be re-used. Because of their short range, the weak β-particles selectively irradiate the nucleus. Estimates of the corresponding average radiation dose are of uncertain significance because of the non-homogeneity of the energy deposition within the cell.

Groups of about 100 C × A hybrid mice were injected subcutaneously with 1 mCi/kg bw [37 MBq/kg bw] [^{3}H]thymidine at birth or at 2, 6 or 12–14 months of age. Another group of 85 newborn mice was injected once with 0.1 mCi/kg bw [3.7 MBq/kg bw], and two groups of 85 and 113 mice received 10 mCi/kg bw [370 MBq/kg bw] either at birth or as six injections over eight days. A group of 176 offspring exposed prenatally were obtained from dams that had been injected with a dose of 250 μCi [9250 kBq] between days 15 and 17 of gestation, which resulted in an estimated ^{3}H concentration of 1 mCi/kg bw [37 MBq/kg bw] in the fetuses. The control group was composed of 464 mice that received unlabelled thymidine or water. Another group, which was initiated later, consisted of newborns that were injected with 15 mCi/kg bw [555 MBq/kg bw] ^3H_2O; these mice were kept only until 27 months of age, although the other groups were studied for life. These regimens generally reduced the survival of the newborn mice, and the effect was significant at 1 and 10 mCi/kg bw. The incidence of 'miscellaneous' tumours, which occur infrequently in this strain, was significantly increased in newborns and offspring at 1 and 10 mCi/kg bw. The induction time for lung tumours and lymphomas was decreased in newborns at 10 mCi/kg bw, and the latency for lung tumours was decreased in the offspring of dams exposed during gestation to 1 mCi/kg bw (Baserga *et al.*, 1966).

Quantitative comparisons were made of the relationships between radiation modality, dose, carcinogenesis and tumour type in irradiated and control pathogen-free C57BL mice. In one component of the study, groups of 21–56 male and 22–47 female newborn mice were given an intraperitoneal injection of 0.3, 0.4, 0.6, 0.9, or 1.5 mCi/kg bw [11–55.5 MBq/kg bw] [^{3}H]labelled thymidine. A group of 178 male and 205 female controls was available. The treated mice and controls were observed for life and evaluated histologically. The numbers of animals available for necropsy ranged from 43 to 99 in the groups exposed to ^{3}H (total, 344) and was 383 in controls. The incidence of all tumours combined was significantly higher in the ^{3}H-exposed newborn mice than in the controls, although the group sizes were insufficient for analysis by dose (see Table 99). The differences in incidence were attributable to a significantly increased incidence of lymphosarcomas. The age-specific incidence rates for reticular-tissue tumours tended to be higher in both exposed males and females than in their corresponding controls. The tumour incidences were independent of sex, and a dependence on dose was not established, perhaps because of the small group size and the relatively narrow dose range (Méwissen *et al.*, 1978).

Table 99. Differences in crude incidence rates (%) of tumours in newborn C57BL/6 mice injected with [^{3}H]thymidine in comparison with controls

Tumour	Males	Females	Significance
Lymphosarcoma	+9.4	+9.3	$p < 0.05$
Thyroid	–1.4	–0.6	
Liver	–0.1	+0.1	
Lung	+1.7	–4.0	
Other	–3.2	–1.3	
All	+4.9	+5.2	$p < 0.05$

From Méwissen *et al*. (1978)

In-dwelling subcutaneous catheters were used to infuse [^{3}H]thymidine continuously for 12 days from day 7 of gestation through term in pregnant SAS/4 mice. The amounts infused (0.6, 1.1, 1.7 or 3.3 MBq/day) resulted in four groups of 'fully ^{3}H-labelled' neonates, which had organically bound ^{3}H concentrations of about 10, 27, 50 and 130 MBq/kg bw. The calculations were based on measurements of bound ^{3}H and ^3H_2O concentrations in serially sacrificed fetuses and offspring. The corresponding intrauterine doses of radiation were estimated to range from 15 to 172 cGy. The average dose to mice at the highest concentration during the remainder of their life was about 50 cGy. The exposed offspring and a group of controls were kept until death, and complete histopathological evaluations were performed. Growth and survival were adversely affected at the higher doses, and an increased frequency of non-neoplastic symptoms was seen and referred to as general 'ill health'. As shown in Table 100, the

Table 100. Per cent tumour incidence in groups of 200–300 offspring of SAS/4 dams that received infusions of [^{3}H]thymidine from day 7 of gestation through term

Tumour	Controls		Dose infused (MBq/day)							
	Male	Female	0.6		1.1		1.7		3.3	
			Males	Females	Males	Females	Males	Females	Males	Females
Lung	37	36	35	35	38	44	41	38	48	15
Hepatoma	5	0	10	0	12	2	14	0	15	3
Reproductive tract	1	11	0	10	0	18	0	19	0	22
Leukaemia	4	21	8	25	13	28	11	28	11	30
Harderian gland	12	6	11	5	16	9	18	13	20	15

From Lambert & Phipps (1983)

incidence of neoplasia, especially of uncommon tumours, including those of the lung and liver and leukaemias, increased with increasing ^{3}H burden. The incidence of mammary tumours decreased at the highest doses, apparently in relation to the reduced lifespan (Lambert & Phipps, 1983).

(*b*) *Carbon-14*

The experiments of Baserga *et al*. (1966) on the carcinogenicity of ^{3}H, described above, also provide information on the perinatal carcinogenicity of ^{14}C. Thymidine is incorporated into DNA irrespective of the label, but ^{14}C β-particles are more energetic, so that the entire cell is irradiated, rather than just the nucleus. Four groups of newborn mice were injected with a single dose of 0.02, 0.2 or 2 mCi/kg bw [0.74, 7.4 and 74 MBq/kg bw] [^{14}C]thymidine and with six doses of the highest concentration over eight days. The overall incidences of tumours were similar in the experimental groups and in the controls. The group that received multiple exposures, however, had an increased incidence of 'miscellaneous' tumours and a decreased incidence of lymphoma. There were no significant effects on tumour latency in any group.

(*c*) *Phosphorus-32*

When ^{32}P is injected as inorganic phosphates, it readily crosses the placenta, and the average concentrations in the embryo or fetus soon reach those of the pregnant animal. Phosphorus is incorporated preferentially into proliferating tissues and bone matrix, resulting in differences in the concentration and radiation doses in tissues, depending on gestational stage.

Mouse: Pregnant BALB mice [number unspecified] were injected intraperitoneally once between days 11 and 15 of gestation with $Na_2{}^{32}PO_4$ at a dose of 2.5, 5, 10, 20, 40, 60 or 90 μCi per animal [92.5, 185, 370, 740, 1480, 2220 and 3300 kBq]. A comparison group of 36 adult female mice were injected at 3–5 months of age with a dose of 40, 60 or 90 μCi per animal. Eighty females and 20 males were used as controls. The pregnant mice were allowed to give birth, and 108 out of 149 offspring that survived until five months of age and were not autolysed were used in the analysis. All surviving mice were killed at two years of age or when moribund and were evaluated by necropsy and histological examination. The incidences of 'leukaemias', which included reticulum-cell sarcoma and lymphosarcoma, were calculated for each dose group but were pooled without regard to gestational stage. The overall incidence among the 71 exposed female offspring (20.2%) was significantly greater than that in 80 controls (16.2%). The incidences in each group ranged from 22 to 71%. In 37 prenatally exposed males, the overall incidence was 10.8%, while that in 20 control males was 10%. Latency was unaffected in animals of either sex. The incidences of leukaemia in the female offspring were similar to those in adults that had been exposed to doses of 40–90 μCi per animal (Holmberg *et al.*, 1964).

Rat: Pregnant BD rats were injected intravenously with $Na_2{}^{32}PO_4$ at a dose of 50, 100, 400 or 800 μCi [1850, 3700, 14 800 and 29 600 kBq] from day 2 of gestation. Malignant tumours developed in 17/130 offspring, which led to death at 270–800 days. Eleven of these tumours were neurogenic (three in the brain, two in the spinal cord, four in the peripheral nervous system and two in the heart) and were histologically identical to the tumours found after exposure to alkylating agents (*N*-methyl-*N*-nitrosourea and *N*-ethyl-*N*-nitrosourea). Of the other six rats with tumours, two had lung carcinomas, two had skin carcinomas, one had a liver carcinoma and one had an osteosarcoma of the jaw (Druckrey, 1973).

The effects of radioactive phosphate were evaluated after intraperitoneal injection of pregnant Sprague-Dawley rats with 1 or 3 mCi/kg bw [37 or 111 MBq/kg bw] on day 16, 18 or 20 of gestation. About 18–22 offspring in each age group received 1 mCi/kg bw, and 48–57 received 3 mCi/kg bw. A total of 128 control rats [age and treatment not stated] were studied throughout the experiment, but comparisons for evaluation of carcinogenesis were made with historical controls. Other litters were used to measure milk transfer by reciprocal cross-fostering and by analysis of stomach contents. The total dose per fetus was calculated to be approximately 10 rad [0.1 Gy], with non-uniform distribution. The offspring were evaluated throughout life, sacrifice and excision of breast tumours being conducted as needed. All animals were necropsied and examined histologically. Growth was unaffected at 1 mCi/kg bw but appeared to be reduced during the first year at 3 mCi/kg bw. The mean lifespan was not affected by 1 mCi/kg bw but was substantially reduced by 3 mCi/kg bw [statistics not presented]. The curves for 'cumulative deaths not due to tumours' of animals at 3 mCi/kg bw were shifted to the left for both males and females, as were the curves for 'cumulative mortality from tumour-associated deaths' in males. The spontaneous incidence rate of leukaemia, which is low in this strain, was not affected by exposure. The incidence of bone tumours, which were selected *a priori* as the primary end-point, was not increased among offspring of exposed dams, but showed a clear tendency to appear earlier in postnatal life among exposed offspring than in controls (Berry *et al.*, 1983).

(*d*) *Strontium-90*

Strontium and its isotopes have long physical and biological half-lives. As strontium is a homologue of calcium, it displays site-specific deposition in the perinatal skeleton. Both elements are distributed throughout the bone volume, as is radium, in contrast to other actinide elements, which are deposited on surfaces. The placental transfer, gastrointestinal absorption, dosimetry and early and delayed effects of radiolabelled strontium administered to prenatal or neonatal animals have been evaluated in numerous studies, but fewer studies have been reported of late effects, especially carcinogenesis.

Mouse: Groups of five to eight CBA mice were given an intravenous injection of ^{90}Sr as the nitrate at a dose of 46.3, 92.5, 185, 370 or 740 kBq on day 19 of gestation. Three controls were available. The female offspring (15–26 per group) were housed individually with untreated CBA males when they reached adulthood, and were bred for

seven months. The mice were killed at an average age of 10 months and the ovaries prepared for histological evaluation. The ovaries of mice at the higher doses were severely depleted of follicles and oocytes, but multiple corpora lutea were seen at lower doses. Interstitial fibrosis and cysts were the primary findings at the lower doses, and the incidence reached a maximum of about 50% at 185 kBq. Hyperplasia of interstitial cells and 'down-growth' of the germinal epithelium into the ovarian parenchyma was seen at this dose and above. Ovarian tubular adenomas were found in 1/19, 5/10 and 12/21 mice treated with 185, 370 and 740 kBq, respectively (Rönnbäck & Nilsson, 1982).

Rat: ^{90}Sr as the nitrate was injected intravenously into 12-week-old Wistar rats on day 18 of gestation. One group of 13 dams was injected with 100 μCi [3700 kBq], 11 dams with 150 μCi [5555 kBq] and another 24 dams received sterile saline. The offspring (60 males and 60 females and 53 males and 47 females in the two treated groups, and 111 male and 113 female controls) were necropsied at death or at 30 months of age and examined histologically. Strontium was selectively deposited in the ossification centres of the basioccipital bones of the skull and near the sella turcica, where the dose rates were maximal 96 h after injection. The cumulative inter-surface dose was calculated to be 60–120 rad [0.6–1.2 Gy] over the lifespan; approximately one-half of the lifetime dose was received within the first week after injection. Pituitary tumours (chromophobe adenomas) were detected at necropsy in exposed animals as young as 15 months of age, but were found in the saline-injected controls only after 22 months. Among animals killed at 30 months, the incidence of pituitary tumours in exposed male offspring (about 30%) was about 10-fold that in controls (2.7%), and the rate in females (46–50%) was about three times higher than that in controls (15.9%). A dose-related increase in the incidence of mammary hyperplasia was found in exposed female offspring, while the frequency of hyperplastic nodules or adenomas of the adrenal glands was increased in animals of each sex at the lower dose but was similar to that in controls at the higher dose. About 9% of the male controls had lymphatic tumours of the thymus; this incidence rose to 16% at 100 μCi but was the same as in controls at 150 μCi. The incidence was increased to 55% and 50% in the two exposed groups of females compared with 35% in controls. The authors indicated that 'about 30% of the thymomas were of a preponderantly epitheloid cell type, where the lymphocytes often only seemed to be dispersed within the epitheloid cell bonds' and that this special type of thymoma was usually observed with a pituitary tumour (Schmahl *et al.*, 1979; Schmahl & Kollmer, 1981). Metastatic meningeal sarcomas were detected in 11 and 10 offspring from the two exposed groups (5.8 and 7.0%) but not in the controls (Schmahl & Kollmer, 1981).

(*e*) *Cerium-144*

Rat: Groups of newborn, weanling or adult Sprague-Dawley rats [group sizes not specified] were injected intracardially or intravenously with ^{144}Ce at a dose of 0.25, 0.5 or 1.0 mCi/kg bw [9.25, 18.5 and 37 MBq/kg bw]. All animals were radiographed at intervals, and some from each treated group were killed for radioanalysis and histo-

logical examination. Routine gross and radiographic examination of the rats revealed gross lesions only 5–6 months after exposure. At that time, tumours were palpable on the legs of many of the weanlings exposed to 1.0 mCi/kg bw. The radiographs showed a 50% incidence of bone tumours, which increased to 80% by nine months. These tumours were confirmed histologically as osteogenic sarcomas. The lungs of some animals contained calcified metastatic nodules, while metastases to the spinal column were found in others. At this time, about one-half the adults that received 0.5 mCi/kg bw had bone tumours, but no tumours were detected in those exposed to 0.25 or 1.0 mCi/kg bw. None of the animals exposed as newborns developed bone tumours (Mahlum & Sikov, 1969).

(*f*) *Iodine-131*

Studies with ^{131}I illustrate the important role of stage of gestation or early postnatal life on the local tissue concentration, the associated doses of radiation and both early and late effects. Injection of pregnant animals after onset of fetal thyroid function leads to retarded neonatal growth, as also seen after neonatal exposure. The thyroid glands of offspring exposed to high doses show necrosis, fibrosis and compensatory hyperplasia (see section 4.3.3).

In an experiment with CBA mice, the effects of maternal exposure to X-rays (180 rad [1.8 Gy] to the fetus), prenatal exposure to ^{131}I β-particles or exposure to both X-rays and ^{131}I on day 18 of gestation were compared. The surviving offspring were killed and evaluated after 680–750 days. The initial group sizes and the doses of ^{131}I were not specified, but the numbers of thyroids examined histologically and the calculated range of doses to the lobe centre were reported (Table 101). A total of 488 untreated controls and 95 offspring that received X-rays only were available. One goal of the study was to compare the results with those of an experiment in adults, described in section 3.2 (Walinder, 1972). A quantitative comparison was not possible because the control thyroids weighed about twice that in the previous experiment, and the pituitary weights were also greater. The morphological changes seen in ageing control thyroids were different in this study (increased number and size of hyperplastic areas) and accounted for the weight difference. In contrast to the experiment in adults, no increase in pituitary weight with increasing thyroid dose was seen. Thyroid tumours were detected in moribund mice from 558 days of age. Some thyroid tumours occurred in the control offspring, but the incidence was not increased in those that received X-rays only. As shown in Table 101, the thyroid tumour incidence was increased at the three lower doses of β-particles, and the effect appeared to be greater in males than in females. There was no further increase in the incidence of thyroid tumours at the highest dose in males, and the incidence fell slightly in females. The quantitative effect of combined exposure to X-rays and ^{131}I was not clear; however, there was a greater incidence at the higher dose from ^{131}I, with no sex difference. The overall incidence of tumours was greater than in the experiment with adults. The effective doses were lower in prenatal animals than in adults (Walinder & Sjödén, 1972).

Table 101. Incidences of thyroid tumours in offspring of mice that received ^{131}I and/or X-rays at 18 days of gestation

^{131}I median dose to lobe centre (Gy)	X-Ray dose (Gy)	No. of animals examined	Sex	% with thyroid tumours
0	0	263	Male	4.2
		225	Female	1.2
20	0	172	Male	10.2
		160	Female	3.1
38	0	89	Male	15
		58	Female	3.5
48	0	16	Male	31
		20	Female	25
70.5	0	102	Male	34
		83	Female	18
0	1.8	48	Male	4.2
		47	Female	0
16.5	1.8	79	Male	6.3
		73	Female	6.9
28	1.8	46	Male	20
		30	Female	20

From Walinder & Sjödén (1972)

In a subsequent experiment, involving exposure of both fetuses and adults, necropsies were performed at one year of age to avoid loss of animals by death, and no thyroid tumours were found among mice exposed as adults after this relatively short interval. In contrast, an increased incidence of thyroid tumours (7/109) was detected in the offspring of dams that had received the highest dose of ^{131}I, which resulted in a dose of 78 Gy to the fetal thyroid (Walinder & Sjödén, 1973).

On the basis of their comparisons of the effects of radiation on the kinetics and regeneration of the cell cycle in the thyroid, Walinder and Rönnbäck (1984) provided additional explanations of the greater frequency of thyroid tumours and shorter latent period in offspring that had been irradiated *in utero*, relative to those irradiated as adults. At equal doses of radiation, cell killing was more frequent during adulthood than prenatally, suggesting that the primary carcinogenic event is independent of age. The greater sensitivity of the prenatal thyroid to tumour development may be associated with age-related differences in cell proliferation rates and the short life of epithelial cells.

Weanling and adult Sprague-Dawley rats were exposed to ^{131}I by gavage, newborns via maternal milk and fetuses via placental transfer and maternal milk. Carrier-free ^{131}I was administered by gavage on five successive days at four activity concentrations over ranges that were adjusted to produce similar subacute effects in rats of the four ages. The total administered amounts of ^{131}I were 1, 15 and 150 μCi [37, 555 and 5555 kBq]

to adult, newborn and pregnant rats and 0.25, 3.75 and 37.5 μCi [9.25, 139 and 1390 kBq] to weanlings. A pooled control group comprised rats representative of all four ages. To establish the dosimetry and early effects, groups of rats from each age and dose group, including pregnant dams and offspring, were killed serially. The animals for long-term observation were identified at weaning and were kept until death or 30 months of age. Selected organs were preserved at necropsy, and the thyroid and pituitary glands were examined histologically. A total of 76 controls and 20–65 animals from of each age and dose group were evaluated. All slides were examined, and the tumours were classified into C-cell and follicular-cell tumours (Sikov *et al*., 1989). The predominant thyroid neoplasm found in control rats of all ages was C-cell tumours, which correspond to the alveolar carcinomas described by Lindsay *et al*. (1957). The incidence of C-cell tumours in the pooled controls (18.4%) was similar to those at the low doses, but the incidence was markedly and significantly decreased (0–5%) in all age groups at the highest dose. A single follicular tumour was seen among the controls, but these were the most frequent thyroid tumour type in exposed groups. Their incidence was increased at the two lower doses in all age groups but was decreased in adults and weanlings exposed at the highest dose. In the groups exposed prenatally or neonatally, however, the incidence was even greater at the highest dose (12/40 in newborns and 37/61 in the prenatal group). The mammary tumour incidence was increased by postnatal exposure but was not affected by prenatal exposure.

3.4 Exposure of male parents

3.4.1 *α-Particle emitter: Plutonium-239*

Mouse: An experiment was carried out to test the hypothesis that paternal irradiation might alter susceptibility of offspring to the development of defects of the lymphatic or haematopoietic system or predispose them to disease due to various insults. Groups of 20 DBA2 and 20 CBA/H male mice, 12 weeks of age, were injected intravenously with ^{239}Pu citrate at a dose of 128 or 256 kBq/kg bw, while controls received the citrate carrier. Twelve weeks later they were mated with 12-week-old female mice of the C57BL or CBA/H strain. All of the female BDF_1 offspring were injected at 10 weeks of age with 50 mg/kg bw *N*-methyl-*N*-nitrosourea (MNU), while female CBA/H offspring were exposed to 3.3 Gy of ^{60}Co γ-rays by whole-body irradiation. The mice were killed when they showed overt signs of disease, such as weight loss, hyperventilation, languor or enlargement of the spleen or liver. The first malignancy seen in a control BDF_1 offspring was a thymic lymphoma that developed 89 days after injection of MNU. Subsequently, lymphomas and myeloid leukaemias developed, so that 50% of the MNU-treated controls were affected by 185 days. The first symptoms in the offspring of irradiated fathers were seen 28 days earlier (a significant decrease), and were expressed as thymic lymphomas, which were detected at 61 and 69 days in mice that received 128 and 256 kBq/kg bw and MNU, respectively,

while leukaemia first developed at 77 and 86 days in these groups, as compared with 92 days in the controls. Thereafter, leukaemia accumulated at approximately twice the rate of the lymphomas, so that mice in these groups had to be killed after a significantly shorter time than the controls. By 250 days, 93 and 83% of the mice at the two doses, respectively, had developed tumours, as compared with 70% in the control group. The first of the CBA/H offspring in the control group that received whole-body radiation was killed at 215 days with developing myeloid leukaemia. Pathological conditions also developed in several other tissues in all groups. A total of 69% of the irradiated mice were killed during the 635 days after exposure. Lymphatic and haematopoietic system tumours were detected in 30% of the irradiated mice and about 20% of the control group. Although the latent period for onset of lymphatic or haematopoietic disease appeared to be delayed by preconceptional paternal exposure to ^{239}Pu, the subsequent incidences were significantly increased. At 128 kBq/kg bw, the incidence of lymphoid leukaemia was more than doubled ($p < 0.001$). This increase competed with the development of myeloid leukaemia, however, so that its incidence fell (–30% compared with controls). In animals at 256 kBq/kg bw, the incidences of myeloid leukaemia and lymphoid leukaemia were increased (+ 16% and + 100%) when compared with controls (Lord *et al.*, 1998a,b).

3.4.2 *β-Particle emitter: Hydrogen-3*

Mouse: Males of a subline of inbred C57BL/6M mice, 35 days of age, received drinking-water containing ^{3}H at a concentration of 10 μCi/mL [370 kBq/mL] for 35 days. The mice were then mated with unexposed females. The offspring were separated after weaning, and the new generation of males was given ^{3}H-labelled drinking-water by the same dose regimen and then mated with their untreated female siblings. This sequence was repeated for a total of 18 generations. The number of offspring and the sex ratio were recorded. Some mice of each generation were maintained for lifetime observation, and the others were killed. The mice of the original line were maintained similarly but without ^{3}H in their water. In the 15th generation, three male and four female offspring from a litter of the exposed line were paired with mice of the opposite sex from the control line and allowed to produce further litters without restriction. The sibling pairings in the first generation (F_1) produced a second generation (F_2) of animals, which were kept for lifetime observation. This procedure was repeated through the fifth generation. Multiple adenocarcinomas of the intestine were observed in the cross between the control and ^{3}H-exposed lines. The tumours were heritable and were found in an average of 44% of the 117 males and 70% of the 88 females examined in the F_1–F_5 generations. The corresponding latent periods were 441 and 542 days, and the incidences of other tumours were 24 and 15% (Méwissen *et al.*, 1984).

On the basis of the reports of Nomura of an increased incidence of leukaemia after X-irradiation of paternal N5 mice (see IARC, 2000), the question of the carcinogenic effect of preconceptional irradiation of males was addressed in a comparison of $^{3}H_2O$

and X-irradiation. Male descendants of the same strain of mouse were exposed to internal irradiation from ^{3}H or to X-rays and mated with untreated females. $^{3}H_2O$ was given as six intraperitoneal injections at 6-day intervals to groups of 33 and 39 males at a dose of 15 or 22.5 MBq at each injection, resulting in a total dose of 1 or 1.5 Gy. Another group of 28 mice received a single exposure to X-rays at 5 Gy, and 27 control males received no exposure. The males were mated 3, 10 or 17 days after the last injection or exposure. The progeny from these groups were kept for study, but the group sizes were randomly reduced to about 300 at one month of age. Because there was an adequate number of offspring of mice given 1.5 Gy of ^{3}H, the mice at the lower dose were discarded. There were thus 305 controls, 165 mice treated with X-rays and 312 mice treated with $^{3}H_2O$. None of the offspring of mice exposed to X-rays for 17 days survived beyond one month of age. The probability of dying from leukaemia during the one-year observation period was significantly greater for offspring of X-irradiated than for those of unexposed fathers, but the difference for offspring of ^{3}H-exposed fathers was not significant ($p = 0.2$). Leukaemia occurred earlier in both the X-ray and the ^{3}H-exposed groups, and treated fathers were more likely to have more than one affected offspring than were control males. The leukaemia rate at 210 days was 8/312 in the offspring of fathers given $^{3}H_2O$ and 1/305 in controls. In the offspring of $^{3}H_2O$-treated fathers mated after 3, 10 or 17 days, the leukaemia rates were 2/100, 4/108 and 8/104, respectively. The leukaemia incidence rate was higher in female than in male offspring (Daher *et al.*, 1998).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion of radionuclides

The most important routes of intake of radionuclides are by inhalation and ingestion, for both workers and members of the public. Ingestion is a less important route for workers, but a proportion of inhaled material is escalated from the trachea and lungs and swallowed. Entry through contaminated wounds may also occur in certain industrial situations. Entry through intact skin is rare, although exposure to $^{3}H_2O$ vapour can lead to appreciable doses by this route.

Entry of radionuclides into the body by inhalation and ingestion leads to irradiation of the respiratory and gastrointestinal tracts. Entry through contaminated wounds also results in local irradiation of tissues. After intake by any route, the subsequent behaviour of the radionuclide depends on the element concerned and its chemical form during exposure. These factors determine its solubility and the extent to which it is dissolved and absorbed into the blood. On reaching the blood, the distribution to and retention in body tissues depend on the chemical nature of the element. If a radionuclide that enters the bloodstream is an isotope of an element that is normally present (e.g. sodium, potassium, chlorine), it will behave like the stable element. If it has similar chemical properties to an element normally present, it will tend to follow the metabolic pathways of that element (e.g. ^{90}Sr and ^{226}Ra behave similarly to calcium and ^{137}Cs and ^{86}Rb similarly to potassium), although the rate of transfer between the various compartments in the body may be different. For other radionuclides, the behaviour in the body depends on their affinity for biological ligands and other transport systems. Radionuclides entering the bloodstream may be distributed throughout the body (e.g. ^{3}H, ^{42}K, ^{137}Cs), be deposited selectively in a particular tissue (e.g. ^{131}I in the thyroid, ^{90}Sr in bone) or be deposited in significant quantities in a number of different tissues (e.g. ^{239}Pu, ^{241}Am, ^{144}Ce).

While dissolved radionuclides are distributed in the body directly via the blood, insoluble materials may be transported slowly as small particles through the lymphatic system, which can lead to accumulation of radionuclides in regional lymph nodes (e.g. tracheobronchial lymph nodes after transport from the lungs; axillary lymph nodes after transfer from a wound in the hand). Particles may reach the bloodstream slowly and then be removed rapidly from the circulation by phagocytic cells of the reticulo-endothelial system in the liver, spleen and bone marrow.

The ICRP has reviewed the data on the biokinetics of radionuclides in humans and animals after intake by inhalation and ingestion and has developed biokinetics and

dosimetric models for calculating organ and tissue doses (ICRP, 1979, 1980, 1981, 1986, 1989, 1993c, 1995a,b). The dose coefficients of ICRP for intake of radionuclides (dose per unit intake) have been incorporated into legislation in Europe (EURATOM, 1996) and other parts of the world.

The following sections describe the biokinetics of individual radionuclides after intake by inhalation and ingestion, including their distribution after absorption into the blood, the duration of retention in organs and tissues and the routes of excretion. Information on placental transfer is also provided. For each radionuclide, the data on humans and animals are considered together. In a final section, the use of biokinetics and dosimetric models to estimate organ and tissue doses is described, and examples are given of doses from intakes of the radionuclides considered.

4.1.1 *Hydrogen-3*

(*a*) *Inhalation*

Tritium (^3H) may be inhaled as elemental tritium gas ($^3H_2$), as ^3H-labelled water (^3H_2O), in the form of organic compounds or in particulate aerosols (reviewed by Hill & Johnson, 1993). $^3H_2$ is relatively insoluble, and < 0.1% of an inhaled dose was taken up to the blood in one study in humans. ^3H_2O vapour is rapidly absorbed from the lungs to blood. Small amounts of volatile, highly soluble organic acids may be released as effluent from tritium facilities and, because of their chemical characteristics, it is reasonable to assume that absorption to the blood will be high. Studies of the absorption of ^3H to blood after intratracheal installation of 1-μm (count median diameter) titanium tritide particles in rats indicated intermediate solubility (ICRP, 1995b).

(*b*) *Dermal intake*

Exposure to an atmosphere contaminated by ^3H_2O results in absorption through intact skin as well as from the lungs. In an adult person at rest, about 1% of the radioactivity in 1 m^3 of air was absorbed through the intact skin per minute. The ICRP (1995b) concluded that this route contributes about one-third to the total absorption of ^3H_2O to blood. An increase in physical activity results in an increase in the proportion of ^3H_2O absorbed through the lungs.

(*c*) *Ingestion*

In volunteers, ingested ^3H_2O was rapidly and virtually completely absorbed from the gastrointestinal tract. A large proportion of organically bound ^3H may be broken down in the gastrointestinal tract, producing ^3H_2O. For example, studies in rodents indicated that 80–90% of ingested [^3H]thymidine is catabolized before reaching the blood, and only a small proportion (< 5%) is incorporated into DNA in body tissues. The absorption of intact molecules of other forms of organically bound ^3H, including ^3H-labelled amino acids, and transfer to body tissues may be substantially greater. Although a proportion of

ingested organically bound ^3H may be unavailable for absorption, such as that in indigestible cellulose, it is generally assumed that absorption will be complete, either as organically bound ^3H or after catabolism to ^3H_2O (ICRP, 1979, 1989).

(*d*) *Systemic distribution, retention and excretion*

The radiobiology of tritium has been reviewed (Straume & Carsten, 1993). Studies of the urinary excretion of ^3H_2O in humans after exposure by inhalation or ingestion indicate rapid mixing of ^3H_2O with body water after absorption into the blood (see ICRP, 1979, 1989; Hill & Johnson, 1993). Since the body water is distributed fairly uniformly, it is generally assumed that all organs and tissues receive the same dose. The half-time of retention of ^3H_2O corresponds to the loss of body water, with an average value of about 10 days for adult humans. In animals, however, a small proportion of ^3H absorbed as ^3H_2O is incorporated into organic molecules and retained for longer periods (ICRP, 1979, 1989). The half-times of retention attributable to organically bound ^3H have not been characterized with precision in humans, but the range appears to be 20–80 days for the major component and 280–550 days for a smaller component (Etnier *et al*., 1984). It has been estimated that total incorporation of ^3H from ^3H_2O into organic molecules adds little (< 10%) to the total integrated activity and hence the dose (ICRP, 1979).

Comparisons in animals of the relative incorporation of ^3H into organic molecules after intake of ^3H_2O and organically bound ^3H indicated that 3–30 times more organically bound ^3H was present after intake of the radionuclide in this form (Rochalska & Szot, 1977; ICRP, 1989; Komatsu *et al*., 1990; Takeda, 1991). Takeda (1991) gave rats ^3H_2O or ^3H-labelled leucine, lysine, glucose, glucosamine, thymidine or uridine in the drinking-water for 22 days. At the end of this period, the highest concentrations of organically bound ^3H were found in rats exposed to ^3H-labelled amino acids (four to nine times higher than those in rats exposed to ^3H_2O), with intermediate concentrations after exposure to ^3H-labelled DNA/RNA precursors. Rochalska and Szot (1977) fed ^3H-labelled food or ^3H_2O to rats for five days and determined organically bound ^3H in the tissues on day 6. Incorporation, measured in dried tissues, was highest after intake of organically bound ^3H by factors ranging from three for brain tissue to 15–17 for liver and small intestine. Takeda (1991) and Komatsu *et al*. (1990) concluded that intake as organic molecules rather than ^3H_2O may increase the radiation dose by about a factor of 2. Although the distribution of organically bound ^3H between body organs and tissues has been shown to be less uniform than that of ^3H_2O in body water, greater uptake in certain organs is associated with greater metabolic activity in those organs (e.g. the liver and intestinal wall), and with shorter retention times. The doses from organically bound ^3H are therefore generally calculated on the basis of uniform distribution in the body, as for ^3H_2O (ICRP, 1979).

Because of the low energy and short range of β-particle emissions from ^3H (average energy, 5.7 keV; mean range, 0.7 μm), the doses to cell nuclei and DNA from ^3H-labelled DNA precursors have been investigated. The National Council on Radiation

Protection and Measurements (1979) compared the calculated doses to human haematopoietic and spermatogonial stem-cell nuclei after ingestion of ^3H_2O and [^{3}H]thymidine. After a single intake, [^{3}H]thymidine was estimated to give the greater dose, by a factor of about 8. In studies with mice, administration of [^{3}H]thymidine during gestation resulted in estimated doses to the offspring that were several times greater than those from administration of ^3H_2O (Saito & Ishida, 1985).

Both the loss of ^3H_2O in body water and the turnover of organically bound ^{3}H are more rapid in children than in adults. The approach adopted by ICRP (1989) for the ^3H_2O component was to relate daily water balance to energy expenditure at different ages. Similarly, shorter retention times for organically bound ^{3}H were based on estimates of body content and loss of carbon.

(*e*) *Placental transfer*

^3H_2O crosses the placenta rapidly and equilibrates between maternal and fetal tissues. The composition of the human fetus undergoes marked changes throughout gestation, with a general trend to a progressive decrease in the proportion of body water and increases in body protein, fat and minerals. The body water content is about 920 mL/kg bw in a 10-week-old fetus and declines to about 700 mL/kg bw at birth; the average value throughout the fetal period is about 800 mL/kg bw. For reference, the body water content of a nongravid female is about 500 mL/kg bw (ICRP, 1975).

The amount of non-exchangeable ^{3}H in rat dams and neonates was compared after oral administration of ^3H_2O or lyophilized ^{3}H-labelled rabbit meat from three weeks before conception to term. The ^{3}H-labelled meat was obtained by repeated intraperitoneal injection of rabbits with ^3H_2O. After administration of ^3H_2O, the specific activity of non-exchangeable ^{3}H in neonatal tissues was about 20% higher than that in maternal tissues, whereas after administration of labelled meat, no difference in specific activities was found between fetal and maternal tissues. Administration of labelled meat led to three- to fivefold greater concentrations of non-exchangeable ^{3}H in both fetal and maternal tissues (Pietrzak-Flis *et al.*, 1982). The maternal and fetal concentrations of ^{3}H were also compared 24 h after oral administration of ^3H_2O, [^{3}H]thymidine or [^{3}H]lysine to rats on day 13 or day 17 of pregnancy. After administration on day 17, transfer to the fetuses represented about 8, 9 and 19% of the administered dose, respectively, per litter. The fetal doses after administration of [^{3}H]lysine were estimated to be 1.5–3 times higher than those after ingestion of ^3H_2O or [^{3}H]thymidine (Takeda *et al.*, 1994).

4.1.2 *Carbon-14*

(*a*) *Inhalation*

Three main classes of carbon compounds may be inhaled: gases such as carbon monoxide (CO) and carbon dioxide (CO_2), organic compounds and aerosols of carbon-containing compounds such as carbonates and carbides (see ICRP, 1981, 1995b).

Extensive data are available on the retention of inhaled CO in body tissues. The gas is relatively insoluble in water and the doses are dominated by retention of CO bound to haemoglobin and, to a lesser extent, other iron–haem-containing compounds, including cytochrome oxidase. The results of a study of the formation and dissociation of carboxyhaemoglobin in individuals taking light exercise indicated that about 40% of inhaled CO was retained, with a half-time of about 200 min. Because CO is bound predominantly to circulating haemoglobin, it is reasonable to assume that doses of ^{14}C-labelled CO are delivered uniformly throughout the body (ICRP, 1981).

As CO_2 is transferred rapidly across the alveolar membrane, it is generally assumed that absorption of ^{14}C-labelled CO_2 is complete. CO_2 exists in the blood mainly as the bicarbonate. A study of the whole-body retention of ^{14}C in 13 normal persons after an intravenous injection of [^{14}C]bicarbonate showed retention of two components, about 18% with a half-time of 5 min and 82% with a half-time of 1 h. In mice, the presence of a third component was reported, with a retention half-time of 10 days or more, consistent with incorporation into organic molecules (ICRP, 1981).

Most organic compounds are not very volatile under normal circumstances and the probability of inhalation as vapours is low. In the absence of information, it seems reasonable to assume that volatile compounds are soluble when inhaled and readily absorbed into the blood.

The results of studies in which rats inhaled ^{14}C-labelled diesel exhaust particles indicated intermediate solubility (Lee *et al*., 1987; ICRP, 1995b).

(*b*) *Ingestion*

The fractional absorption of dietary carbon is usually in excess of 0.9 although some carbon compounds may be less completely absorbed, including cholesterol, fat-soluble vitamins and cellulose (ICRP, 1981).

(*c*) *Systemic distribution, retention and excretion*

The distribution and retention of ^{14}C in organs and tissues depends strongly on the chemical form in which it enters the systemic circulation. Because information is not available for the majority of these compounds, it has generally been assumed that all ^{14}C-labelled compounds are distributed rapidly and uniformly in all body organs and are retained with a half-time of 40 days. This biological half-time was derived from the average daily carbon intake (~ 0.3 kg/day) and the mass of carbon in the body of a ‘reference man’ (16 kg), according to the equation:

$$t_{½} = \ln 2 \times [\text{total body carbon/daily carbon intake}] = 0.693 \times 16/0.3 = 37 \text{ days}$$

or about 40 days (ICRP, 1975, 1981, 1989).

The retention of carbon incorporated in various metabolites in organs and tissues of the body shows wide variation. For example, studies on autopsy samples from people exposed to ^{14}C in fall-out (Stenhouse & Baxter, 1977a,b) suggest that bone collagen and bone mineral retain ^{14}C with a biological half-time that may exceed 20 years. The

retention of ^{14}C after intravenous injection of labelled glycine or acetate into patients decreased in various phases, with biological half-times between 0.1 and 17 days (ICRP, 1981). In a study with accelerator mass spectrometry of the retention of ^{14}C in three healthy men after ingestion of [^{14}C]triolein, measured as ^{14}C in exhaled CO_2, 30% of the administered ^{14}C was eliminated in the first 24 h; the remainder was retained with a half-time of at least several hundred days (Stenström *et al.*, 1996).

The rate of metabolism of ^{14}C-labelled compounds is age-dependent. For example, in rats, metabolic incorporation and release of ^{14}C from glycine or stearic acid was more rapid in younger animals (ICRP, 1989). As for organically bound ^{3}H, ICRP (1989) applied shorter retention half-times for ^{3}H and ^{14}C in organic form in children on the basis of differences in carbon balance by age.

(*d*) *Placental transfer*

CO_2 entering the blood distributes rapidly throughout the bicarbonate pool of the body water. No information on bicarbonate transfer to the embryo or fetus was found, but it may be assumed to diffuse readily through the placenta and into the fetus.

Most amino acids are actively transported across the placenta. In the human placenta, transport proteins for many amino acids are located in the microvilli and basal membranes of the syncytiotrophoblast (Moe, 1995). Few quantitative data are available, although Moe (1995) reported fetal:maternal blood concentration ratios of ~ 3 for lysine, ~ 2 for alanine and ~ 1 for glutamate and aspartate. In a study of the placental transfer of ^{11}C-labelled sugars, amino acids, adenine, adenosyl-methionine, fluorodeoxyuridine and coenzyme Q_{10} in rats, when the data allowed direct comparison of maternal and fetal tissue concentrations, the fetal values were generally similar to or lower than the corresponding maternal values, the exception being for amino acids, for which the fetus-to-placenta ratios were consistently > 1 (Ishiwata *et al.*, 1985).

4.1.3 *Phosphorus-32*

(*a*) *Inhalation*

The ICRP Task Group on Lung Dynamics (ICRP, 1966) reviewed the behaviour of materials in the lung and classified most compounds of phosphorus as soluble, assuming rapid absorption to blood. The exceptions were phosphates of zinc, tin, magnesium, iron and bismuth and the lanthanides, which were considered to be less soluble and to be retained in the pulmonary region of the lungs with a half-time of about three months.

(*b*) *Ingestion*

Dietary phosphorus is generally well absorbed, as are inorganic forms of phosphorus (see ICRP, 1979). Measurements in seven volunteers who ingested fish contaminated with ^{32}P from reactor coolant water demonstrated complete absorption of the radionuclide (Honstead & Brady, 1967). The fractional absorption of radiophosphorus of

unspecified form administered to patients was approximately 0.2–0.3, as shown by the difference in skeletal uptake of subjects after oral or intravenous administration (Castle *et al*., 1964). However, less than 5% of the phosphorus-containing compound diphosphonate etidronate was absorbed in normal subjects (Fogelman *et al*., 1986).

(*c*) *Systemic distribution, retention and excretion*

The retention of phosphorus in the body has been reviewed (Jackson & Dolphin, 1966). It was concluded that retention as phosphate in humans is well described by four terms corresponding to blood plasma, intracellular fluids, soft tissues and bone mineral. Initially, 15% of absorbed phosphorus is excreted rapidly directly from blood, with a half-time of 0.5 days, followed by loss of a further 15% from intracellular fluids with a half-time of two days. Retention in soft tissues with a half-time of 19 days was reported to account for 40%, and the remaining 30% was assumed to be permanently retained in the bone. Studies of the dietary balance and body content of phosphorus (ICRP, 1975) suggest a half-time of retention in bone of about four years. Since the radioactive half-life of ^{32}P is 14.3 days, the assumption of infinite retention in bone is appropriate for the purposes of estimating doses. Because of the short half-life of ^{32}P, ICRP (1979) calculated the doses to bone surfaces and red bone marrow, assuming that the nuclide is retained on bone surfaces. In addition, a small amount of radioactive phosphate entering the body is incorporated into cellular DNA, especially in rapidly dividing tissues such as red bone marrow and the lining of the small intestine. This fraction is larger if the radioactive phosphorus enters the blood in the form of a DNA-precursor nucleotide.

(*d*) *Placental transfer*

Studies in rats have shown that phosphate readily crosses the placenta but that the transfer of phospholipid is much slower (National Council on Radiation Protection and Measurements, 1998). Experiments in guinea-pigs, sows and rats yielded consistent results. The overall pattern is of an increase in the relative concentrations in embryos and fetuses as ^{32}P is administered at progressively later stages of gestation; the rapidity in reaching maximum activity and retention followed the same pattern.

4.1.4 *Sulfur-35*

(*a*) *Inhalation*

Information is available on the behaviour of inhaled sulfur dioxide (SO_2) gas and carbon disulfide (CS_2) vapour. In a study of volunteers, virtually all of the inhaled non-radioactive SO_2 was absorbed by the nasal mucosa (Speizer & Frank, 1966). Studies in dogs showed rapid absorption into blood after deposition of SO_2 in the respiratory tract. Studies of inhaled CS_2 have shown deposition and absorption into the blood in various animal species, including rats and humans. Deposition and

absorption were not quantified in these studies, but the absorption in rats was rapid, indicating high solubility (ICRP, 1995b).

No detailed information is available on the rate of absorption of ^{35}S after inhalation of particulate materials, but two cases of accidental exposure, one to elemental sulfur and another to an unknown form, indicate high solubility in the lungs (ICRP, 1995b).

(*b*) *Ingestion*

As reviewed by ICRP (1993c), studies of sulfur balance indicated that 68–90% of dietary sulfur is absorbed by pre-adolescent girls, apparently depending on dietary nitrogen levels. Studies in rats treated by oral or intraperitoneal administration of ^{35}S as the sulfate or as [^{35}S]L-methionine (the most abundant organic form of sulfur in the diet) indicated that the fractional absorption was 0.9 or higher. Elemental ^{35}S was less well absorbed in rats, with a value around 10%.

(*c*) *Systemic distribution, retention and excretion*

Measurements of the concentration of stable sulfur in human organs and tissues have been reported. The concentrations in most tissues, including testes, were 1–2 g/kg, although the value for cartilage was higher (5.5 g/kg) and that for bone marrow was lower (0.7 g/kg). The distribution and retention of ^{35}S in rats were compared up to 130 days after intravenous injection of [^{35}S]methionine and up to eight days after injection of [^{35}S]sodium sulfate. The distribution of ^{35}S from the organic compound between tissues was fairly uniform, all the concentrations being within a factor of 3 except for a lower concentration in bone. After administration as the sulfate, the ^{35}S concentrations varied by about a factor of 20, the highest values being found for cartilage and the lowest for muscle (ICRP, 1993c).

Approximately 70–90% of ^{35}S injected intravenously as sodium sulfate in humans was excreted in the urine within the first three days. Similar results were reported for ^{35}S as sulfate in rats, while excretion of ^{35}S administered as methionine was about 10 times slower. The data on dietary intake and whole-body content in adult humans (ICRP, 1975) are consistent with a half-time of retention for organic sulfur in the diet of about 140 days, assuming complete absorption in the blood (ICRP, 1993c).

(*d*) *Placental transfer*

Little information is available on the transfer of inorganic sulfur to the fetus, although placental transfer and fetal incorporation of ^{35}S as sulfate has been demonstrated (Hagerman & Villee, 1960). Active transport of methionine and other sulfur-containing organic molecules was shown (Ishiwata *et al.*, 1985). The placental transfer of the sulfur-containing amino acids cysteine and methionine was studied in pregnant women about to undergo abortions in weeks 16–22 of pregnancy. About 15–45 min after injection of 0.5 mmol of non-radioactive L-methionine, the fetal:maternal blood concentration ratio was ~ 2. In contrast, 45–60 min after injection of 2.5 mmol L-cystine

or L-cysteine, the fetal blood concentration of the amino acids was only about half that found in the maternal blood (Gaull *et al.*, 1973).

4.1.5 *Gallium-67*

(*a*) *Inhalation and ingestion*

On the basis of studies in rats that showed little absorption of gallium chloride from the gastrointestinal tract, ICRP (1981) used a fractional absorption value of 10^{-3} for ingested gallium. However, for most forms of inhaled gallium, intermediate absorption into blood was assumed to apply, with a half-time of up to three months.

(*b*) *Systemic distribution, retention and excretion*

^{67}Ga is usually used in carrier-free form. ^{67}Ga injected intravenously to rats was initially distributed fairly uniformly throughout all tissues and organs, but by 24 h after injection greater concentrations were found in the skeleton, liver, kidneys and spleen. Human autopsy samples and γ-ray spectroscopy showed a similar distribution, with accumulation also in the adrenal glands and in the placenta during pregnancy. Studies in animals and humans indicate a biphasic release of gallium from the body, with biological half-lives of about one day and 50 days (ICRP, 1981). In volunteers given ^{67}Ga citrate by intravenous injection, more than half of the injected dose was still present in the body after 21 days. The liver and the skeleton were the major sites of deposition after 24 h, and the principal route of excretion was via the kidneys, with about 10% excretion in the faeces. This nuclide is cleared slowly from the blood, indicating protein binding (Priest *et al.*, 1995a). Studies of whole-body retention in cancer patients indicated that 10–20% of injected ^{67}Ga (as citrate) was lost from the body with a half-time of approximately one day and the remainder with a half-time of about 26 days (Saunders *et al.*, 1973). Excretion via the urine is the major excretory pathway of ^{67}Ga in humans, about 10% of the radioactivity in the systemic circulation being excreted within the first 24 h. However, there was a wide range (3–35%) among the 29 patients studied (Zivanovic *et al.*, 1979).

4.1.6 *Strontium-89 and strontium-90*

(*a*) *Inhalation*

Measurements following accidental inhalation of strontium carbonate ($^{90}SrCO_3$) by humans showed high solubility. Similarly, experiments in animals have shown that strontium in simple ionic compounds (chloride and sulfate) is cleared rapidly from the lungs, consistent with high solubility. A study *in vitro* on strontium-containing airborne fission products released during the Three Mile Island reactor accident confirmed these results (ICRP, 1995b).

(*b*) *Ingestion*

Owing to the presence of strontium isotopes in fall-out material and its long-term retention in bone as a calcium analogue, the metabolism of strontium has been the subject of a number of studies in volunteers. Similar absorption values were obtained in studies in which inorganic forms of radiostrontium were administered orally in solution and in experiments in which known quantities of radiostrontium incorporated in food were ingested (reviewed by ICRP, 1989). The mean values were between 0.15 and 0.45. In a study of the absorption of strontium from real and simulated fall-out and after administration of $^{85}SrCl_2$, 10 volunteers ingested samples of local fall-out, largely comprising silicaceous soil constituents (40–700-μm particles). The estimated absorption rate was 3%, with a range of 0–9%, while that for simulated fall-out prepared as glass microspheres (30–40 μm) was 16% (range, 6–25%), with a value of 17% (8–34%) after administration as $^{85}SrCl_2$ (LeRoy *et al.*, 1966).

A number of factors have been found to increase the absorption of strontium, including fasting and low dietary levels of calcium, magnesium and phosphorus; milk diets and vitamin D may also increase absorption. Overnight fasting increased the fractional absorption from about 0.25 to 0.55 in one study, and an average fractional absorption of 0.55 (0.38–0.72) was seen in four volunteers after an overnight fast compared with 0.11 in a single volunteer who ingested strontium after breakfast. A decrease in the dietary intake of calcium from 30–40 to 0–10 mg/kg per day increased the fractional absorption of strontium from an average of 0.2 to 0.4. The results of animal studies are generally similar to those for volunteers (ICRP, 1989).

The results of measurements of the absorption of strontium in seven-day-old infants fed cows' milk suggested values > 73%. Similar levels of absorption have been reported for 5–15-year-old children and adults. However, studies in beagles and rats have shown that the period of increased absorption of strontium extends beyond the time of weaning. In beagles, the retention values for strontium 3–9 days after ingestion were 20%, 15% and 8% in 48-, 80- and 140-day-old animals, respectively. The absorption of strontium was estimated to be 70–90% in 35- and 75-day-old rats and 12% in 270-day-old rats (ICRP, 1989).

(*c*) *Systemic distribution, retention and excretion*

The behaviour of strontium in the body is similar to that of calcium, but there are quantitative differences that reflect discrimination against strontium and result in less effective incorporation and retention in bone and more rapid urinary excretion. Long-term retention of strontium, like that of calcium, is confined to the skeleton, and doses from ^{90}Sr absorbed into blood are delivered largely to bone surfaces and red bone marrow (see Leggett *et al.*, 1982; Leggett, 1992a; ICRP, 1993c).

A great deal of information is available on the age-specific behaviour of strontium in humans. ^{90}Sr from fall-out has been measured in bones from persons of various

ages. Biokinetics models have been developed in which the body's discrimination between calcium and strontium is taken into account (Leggett *et al*., 1982).

The fraction of activity from ^{90}Sr that leaves the plasma and goes to the urine and faeces is 0.15, the assumed ratio of cumulative urinary to faecal excretion being 3.3. Strontium that enters the skeleton is assumed to deposit initially on bone surfaces but to migrate to exchangeable bone volume within a few days. About half of the strontium leaving this compartment, with a half-time of about 80 days, binds to non-exchangeable sites in bone crystal. It is assumed that roughly 1% of total body strontium is present in soft tissues after many years of exposure (ICRP, 1993c).

Measurements in human bone of ^{90}Sr from fall-out and information on dietary intake during the appropriate exposure period (Leggett *et al*., 1982) indicate that strontium is less efficiently retained in bone than calcium, consistent with discrimination against inclusion of strontium in hydroxyapatite crystals (Leggett, 1992a).

There is considerable evidence in humans and laboratory animals that the initial uptake of strontium and calcium by the skeleton is much greater in growing than in mature individuals. The available data are consistent with changes in the rate of addition of calcium to the skeleton with age. Bone turnover is also greater at younger ages, as indicated by human histomorphometric measurements and turnover rates inferred from studies on radionuclide retention in humans (Leggett *et al*., 1982; Leggett, 1992a; ICRP, 1993c).

(*d*) *Placental transfer*

Studies of human tissues and animals in which direct comparisons have been made show that strontium is transferred to the fetus less efficiently than calcium (Rivera, 1963; Mays & Lloyd, 1966; Twardock, 1967; Kawamura *et al*., 1986; Taylor & Bligh, 1992). The available data suggest a placental discrimination factor in humans of about 0.6.

The concentrations of ^{90}Sr were measured in six stillborn fetuses and their mothers who had drunk water from the Techa River at various times before pregnancy. The skeletal concentration ratios (fetus:mother) were 0.01–0.03 when maximum intake of ^{90}Sr had occurred largely during the childhood of the mother (< 15 years) and 0.19–0.24 when maximum intake had taken place during adulthood (> 25 years) (Tolstykh *et al.*, 1998).

$^{85}SrCl_2$ was administered intraperitoneally to rats at a dose of 20 kBq/kg bw one month before conception or on day 2, 13 or 19 of gestation. Neonates retained an average 0.002%, 0.03%, 0.1% and 3% of the injected activity, respectively, corresponding to fetal:dam concentration ratios of 0.03, 0.06, 0.2 and 5 (Stather *et al.*, 1987).

4.1.7 *Technetium-99m*

(*a*) *Inhalation*

Studies of ^{99m}Tc as pertechnetate ($^{99m}TcO_4$) showed that absorption by the lung after administration to humans, dogs and rats was rapid; total absorption occurred within a few hours. [^{99m}Tc]Diethylenetriaminepentaacetic acid (DTPA), used to study the permeability of the lung, was rapidly absorbed, with a half-time of about 1 h. The use of ^{99m}Tc-labelled materials, such as albumin, erythrocytes, ferric oxide, polystyrene, resin and teflon, to study mucociliary clearance from the bronchial tree relies on the fact that relatively little is absorbed from the lungs to the blood in the first day or so after deposition (ICRP, 1995b).

(*b*) *Ingestion*

Technetium administered as [^{99m}Tc]pertechnetate is well absorbed in humans. An extensive study demonstrated that the absorption was about 0.7 in most cases, although the individual values varied from 0.03 to 1, the variation occurring between subjects and between measurements in a single subject. In rats, the fractional absorption of technetium chloride was reported to be about 0.5. Incorporation into food appeared to reduce the absorption of technetium. The uptake from soya beans and animal tissues by rats and guinea-pigs was about half that seen after administration as the pertechnetate. Similar results have been reported in rats and sheep fed technetium either as pertechnetate or incorporated into maize (ICRP, 1993c).

Hunt (1998) and Hunt *et al*. (2001) measured the absorption of ^{99}Tc from cockles and lobster from the Irish Sea in a group of six volunteers. In the first study, absorption from cockles was estimated by the relatively insensitive method of comparing the ingested activity and total faecal elimination over seven days. The results indicated a 'gut-transfer factor' of about 0.6 for four subjects, the other two showing 4.6-fold lower values. In the second study, absorption from lobster was estimated by comparing urinary excretion of ^{99}Tc over seven days with the results obtained by Beasley *et al*. (1966) for excretion after intravenous injection of [^{99m}Tc]pertechnetate. The results indicated that the absorption rate was in the range 0.02–0.1.

(*c*) *Systemic distribution, retention and excretion*

The whole-body retention of technetium in humans after intravenous administration as pertechnetate can be described by three components with half-times of 1.6 days (77%), 3.7 days (19%) and 22 days (4%). Retention appeared to be fairly uniform in various tissues, except that greater concentrations were measured in the thyroid, salivary glands, stomach wall, colon wall and liver (Beasley *et al.*, 1966).

(*d*) *Placental transfer*

Studies of the placental transfer of technetium in humans and animals have been carried out almost exclusively with radiopharmaceuticals. Roedler (1987) used the available data to estimate whole-body fetus:mother concentration ratios of 0.04–4.8 for technetium as pertechnetate, 0–0.05 for technetium DTPA, 0.002–0.11 for technetium colloids, 0.006–0.018 for technetium polyphosphate and 0.004–0.05 for technetium pyrophosphate.

4.1.8 *Iodine-123, iodine-125 and iodine-131*

(*a*) *Inhalation*

Studies of the human biokinetics of iodine inhaled as elemental iodine vapour showed almost complete absorption in the conducting airways. Inhaled methyl iodide was less well retained (average, 70%). Much of the activity, however, was swallowed and readily absorbed from the gastrointestinal tract. In animals, iodine administered as silver iodide or sodium iodide was also rapidly absorbed into the blood (ICRP, 1995b).

(*b*) *Ingestion*

The absorption of iodide from the human gastrointestinal tract is virtually complete, with reported values of 0.9 and greater (see ICRP, 1979, 1989). A rate of absorption of about 5%/min was reported in fasted individuals, with complete absorption within 2 h. The rate of absorption of iodide ingested with food was slower, but absorption was nevertheless virtually complete after about 3 h (Keating & Albert, 1949). Iodide is absorbed in both the stomach and the small intestine, although the latter predominates. Absorption of other chemical forms may not be complete, but there is little direct evidence.

(*c*) *Systemic distribution, retention and excretion*

The average normal adult thyroid gland contains about 10 mg of stable iodine with a daily turnover of about 70 μg per day, corresponding to a retention half-time in the thyroid of 80 days (see ICRP, 1989). Fractional uptake by the thyroid of iodine absorbed to blood is about 0.3 at a dietary intake of about 200 μg/day. Since dietary intake varies considerably between individuals and between population groups, fractional uptake by the thyroid also varies considerably. In areas with low iodine intake, the thyroid absorbs a greater proportion of the iodine in the blood. As a result, the gland becomes enlarged, and the concentrations of iodine and hence radioiodine do not vary substantially.

Thyroxine and tri-iodothyronine released from the thyroid gland are metabolized in body tissues, and inorganic iodide is released into the circulation, allowing recycling to the thyroid. About 20% of organically bound iodine is excreted from the liver in bile, mainly as thyroxine conjugated with glucuronic acid; the conjugated hormone is not readily reabsorbed from the intestine. The amount of organically bound iodine in the

body has been reported to be 500–1200 μg, with an average value of about 800 μg, consistent with reports in the literature of a turnover rate about 10 times that in the thyroid; that is, a half-time of about eight days. In adults, there is no net increase in the body content of iodine, and the total daily urinary and faecal excretion balances the intake. At average levels of intake, > 90% of the iodine that enters the circulation is excreted in urine, mostly in inorganic forms (ICRP, 1989).

Uptake of radioiodine by the thyroid gland is enhanced in newborns (ICRP, 1989). In one study, the uptake was about 70% (range, 46–94%) in seven newborn infants given an intramuscular injection of ^{131}I; another study showed values of 50–70% for a group of 19 newborn infants. Uptake of ^{131}I by the thyroid was highest in infants two days after birth and reached adult values or less by five days of age. After the first days or weeks of life, the uptake of iodine by the thyroid appears to vary little with age at intake. Information on age-related changes in the retention of iodine in the thyroid has been reviewed (Dunning & Schwarz, 1981; Stather & Greenhalgh, 1983). Although the available data show a wide range, they indicate that the turnover rate of iodine in the thyroid is higher at younger ages.

(*d*) *Placental transfer*

Measurements of ^{131}I activity in the fetal thyroid after diagnostic administration before therapeutic abortions or after exposure to nuclear weapons fall-out have been reported. The concentration of iodine in the fetal thyroid increases progressively during fetal life and can exceed the concentrations in the maternal thyroid by factors of about 3–10 for intakes towards the end of gestation (Book & Goldman, 1975; Berkovski, 1999).

4.1.9 *Caesium-137*

(*a*) *Inhalation*

After accidental inhalation of caesium sulfate, caesium was transferred rapidly to the blood. In animals, simple ionic compounds (chloride, nitrate) were rapidly and completely absorbed. Studies of exposure to caesium associated with irradiated fuel fragments, including particles released after the Chernobyl accident, indicate that much of the caesium was rapidly absorbed within days but a fraction was retained within the particle matrix and absorbed over a period of months. High solubility and rapid uptake were also reported in a study of caesium absorption in rats exposed to a suspension of residues from a reactor fuel-cooling pond (ICRP, 1995b).

(*b*) *Ingestion*

In volunteers who ingested various radioisotopes of caesium in soluble inorganic form, absorption was virtually complete (ICRP, 1979, 1989). For example, Rundo (1964) measured an average fractional absorption of 0.99 for 10 normal subjects after ingestion of ^{137}CsCl.

Radioactive caesium incorporated into insoluble particles may be less readily available for absorption. LeRoy *et al*. (1966) reported values of < 0.1 for the uptake of ^{134}Cs from real and simulated fall-out in a study of 102 volunteers.

Measurements of uptake by volunteers of ^{137}Cs from meat (venison, mutton, caribou) contaminated as a result of the Chernobyl accident gave values in the range 0.6–0.99 (Henrichs *et al*., 1989; Talbot *et al*., 1993).

(*c*) *Systemic distribution, retention and excretion*

The monovalent alkali metal caesium behaves similarly to potassium after absorption to blood and is accumulated in all cells. Higher concentrations of caesium have been reported in muscle than in other tissues, but the differences are small. It is generally assumed that caesium is distributed uniformly between and within body organs and tissues (see ICRP, 1989).

There is a large body of data on the retention of ^{137}Cs in humans (ICRP, 1989). After entering the blood, it is cleared rapidly and deposited more or less uniformly in the tissues. Muscle contains the largest fraction of the total body burden of caesium, and slightly higher concentrations have been reported in muscle in comparison with other tissues. Studies of the whole-body retention of ^{137}Cs in several hundred persons across the world established that retention in adults can be expressed adequately by a two-component exponential function, with a fast component, amounting to ~ 10% of the total systemic burden, being cleared with a half-time of approximately two days and the remainder being lost with a half-time of the order of 100 days. It is now well established that the rate of clearance is faster in women than in men and that clearance may be further accelerated during pregnancy (Schwartz & Dunning, 1982; Rundo & Turner, 1992; Melo *et al*., 1997; Thornberg & Mattsson, 2000). The mean equivalent biological half-time of caesium ranges from about 47 to 152 days in men and from about 30 to 141 days in women. The rate of clearance of caesium is faster in children. The major excretory pathway is via the kidneys and urine (ICRP, 1989).

(*d*) *Placental transfer*

The transfer of caesium isotopes to the fetus has been followed in both humans and animals. The concentrations of ^{137}Cs arising from exposure to fall-out from nuclear weapons were measured in nine newborn children within three days of birth and in their mothers. The concentrations were similar (Wilson & Spiers, 1967). After an accident in Brazil in which a woman in her fourth month of pregnancy was contaminated with ^{137}Cs, both the mother and her newborn child were monitored one week after birth. The concentration of ^{137}Cs in the mother (0.91 kBq/kg bw) was similar to that in her newborn child (0.97 kBq/kg bw), and the concentration in the placenta was the same as that in the whole maternal body and the fetus (Bertelli *et al.*, 1992).

4.1.10 *Cerium-141 and cerium-144*

(*a*) *Inhalation and ingestion*

In a case of accidental human exposure to a ^{144}Ce–praseodymium-contaminated atmosphere, measurement of lung clearance showed intermediate solubility (see ICRP, 1995b). Studies in animals have also indicated intermediate levels of solubility in the lung for a number of forms of cerium, including ^{144}Ce chloride in dogs, ^{144}Ce hydroxide in rats, ^{144}Ce oxide in rats and hamsters and ^{144}Ce in irradiated fuel fragments in rats (ICRP, 1989).

The fractional absorption of ingested cerium was reported to be $< 1 \times 10^{-3}$ in humans (after accidental intake), and a similar value was found in rats, pigs, goats and other species (ICRP, 1979).

(*b*) *Systemic distribution, retention and excretion*

In adult rats and dogs, about 50% of cerium entering the blood is deposited in the liver, 30% in the skeleton and 20% in other tissues. The half-times of retention in liver and bone in dogs were both about 10 years. In animals, deposition in the skeleton is greater at younger ages, and liver uptake increases with age (ICRP, 1989).

(*c*) *Placental transfer*

In mice given ^{144}Ce citrate by intraperitoneal injection at 3 μCi (111 kBq) two or one months before mating or just before mating, placental transfer resulted in maximum retention in the litters (average of 10 individuals per litter) of 0.65, 0.67 and 1.4%, respectively, of the mother's body burden (Naharin *et al.*, 1969).

When ^{144}Ce chloride was administered intravenously to rats on day 15 or 19 of gestation, the ^{144}Ce concentration in the fetus one day later was about 0.02% of the administered dose per gram of tissue at both times. A considerably higher concentration was measured in the placenta and in the fetal membranes, indicating that ^{144}Ce does not freely pass from the maternal circulation to the fetus (Mahlum & Sikov, 1968). ^{141}Ce chloride was given to rats by intravenous injection before conception or at various stages during gestation and to guinea-pigs in late gestation. The retention in rat fetuses measured three days after administration was 4×10^{-5}% of the injected activity per fetus on day 13, increasing to 0.01% shortly before birth, the fetus:dam concentration ratios increasing from 0.004 to 0.02. Retention in guinea-pigs seven days after administration was about 0.05% of the injected activity per fetus, corresponding to a fetus:dam concentration ratio of about 0.01 (Levack *et al.*, 1994).

4.1.11 *Rhenium-186 and rhenium-188*

Limited data are available on the systemic distribution of rhenium in rats, but they suggest that its behaviour is similar to that of technetium. In the absence of more extensive data, ICRP (1980) assumed that the absorption of inhaled or ingested rhenium

and its systemic kinetics are similar to those for technetium. For all rhenium compounds, an absorbed fraction of 0.8 is assumed for uptake from the gastrointestinal tract.

4.1.12 *Bismuth-212*

(*a*) *Inhalation and ingestion*

Data from dietary balance studies (ICRP, 1975) suggest that the fractional absorption of bismuth is about 0.08. In the absence of relevant data, bismuth compounds were assumed to be of high or intermediate solubility in the lungs (ICRP, 1980).

(*b*) *Systemic distribution, retention and excretion*

The short-lived radioisotopes of bismuth, ^{212}Bi and ^{210}Bi, arise as products of the decay of ^{232}Th and ^{238}U. They have limited use in research, but use of ^{212}Bi-labelled antibodies for tumour treatment has been suggested (Hassfjell *et al.*, 1997). After entry of inorganic bismuth into the systemic circulation, about 40% becomes deposited in the kidneys, another 30% becomes more or less uniformly deposited in the other tissues, and about 30% is excreted rapidly. The rate of loss of bismuth from all tissues appears to be quite rapid, 60% being eliminated with a half-time of about 14 h and the remainder with a half-time of approximately six days (ICRP, 1980).

4.1.13 *Polonium-210*

(*a*) *Inhalation*

Studies of the absorption of polonium in humans after inhalation of a ^{210}Po source, which probably comprised small oxide particles, and after inhalation of ^{210}Po in tobacco smoke, indicated intermediate solubility. Studies in rats have also shown intermediate solubility after intratracheal instillation of ^{210}Po chloride in a sodium chloride aerosol. Similar treatment of rabbits with a ^{210}Po hydroxide colloid confirmed these results (ICRP, 1995b).

(*b*) *Ingestion*

ICRP (1993c) reviewed the studies in humans, including a measurement of polonium uptake in a patient being treated for chronic myelogenous leukaemia. The blood concentrations and urinary excretion after oral administration of ^{210}Po chloride suggested a fractional absorption of 0.1. Absorption of biologically incorporated ^{210}Po was reported to be significantly higher, as studies of persons who ate meat from reindeer exposed to ^{210}Po indicated a fractional absorption of 0.3–0.5 (Ladinskaya *et al.*, 1973; ICRP, 1993c). In a study in six volunteers of the absorption of ^{210}Po from crabmeat, the absorbed fraction was estimated to be about 0.8 (Hunt & Allington, 1993). The absorption of ^{210}Po by rats was reported to be 0.03–0.06 for an unspecified chemical form and 0.06 for the chloride (ICRP, 1993c). In rats, the fractional absorption was 0.05

for ^{210}Po administered as the nitrate and 0.13 for ^{210}Po incorporated into liver obtained from rats given intravenous injections of ^{210}Po citrate. For ^{210}Po administered as the citrate, absorption was reported to be 0.07–0.09 in adult rats and guinea-pigs (Haines *et al.*, 1993).

(*c*) *Systemic distribution, retention and excretion*

^{210}Po is ubiquitous in the environment as a decay product of ^{226}Ra. It has been used to a certain extent in experimental radiation science over the past century (McKay, 1971). Although polonium belongs to Group VI of the periodic table, with sulfur and selenium, it is more metallic than either of the latter two elements and does not appear to be incorporated into organic compounds, such as the amino acids methionine and selenomethionine. There is a large body of information on the biodistribution and biokinetics of polonium in animals and a considerable amount of data on the biokinetics in humans after inhalation and ingestion of ^{210}Po. In rabbits injected with ^{210}Po nitrate, the main organ of deposition was the kidney (1.3–1.5%/g), followed by the blood, spleen, lung and liver; uptake in the skeleton was relatively low (< 0.01%/g; Parfenov & Poluboyarinova, 1973; see Table 2 in General Remarks). Polonium appears to be lost from the body relatively rapidly, predominantly in the urine. Analysis of the data on human excretion suggested that the half-time of whole-body retention of ^{210}Po ranges from 30 to 50 days (ICRP, 1993c).

In a person suffering from acute leukaemia, measurements six days after injection of ^{210}Po chloride showed a retention of 40% in the liver, 5% in kidneys and 4% in spleen (see ICRP, 1993c). These organs were also the main sites of deposition in rats. A study of the retention of ^{210}Po in marmoset tissues one week after intravenous injection as the citrate showed that the liver accounted for 26% of total body retention; the kidneys retained 21%, and < 1% was retained in the spleen and testes. The femora contained 1.5% of the retained activity, corresponding to a skeletal deposit of about 15%. Autoradiographs of marmoset and rat bone showed that the retained ^{210}Po was not associated with bone surfaces but was distributed throughout the bone marrow. On the basis of the data on excretion, the average retention half-time of polonium in the body was estimated to be about 50 days (ICRP, 1993c).

Two studies of ^{210}Po retention in children aged 6–15 years showed a half-time of about 40 days, which is not significantly different from the values for adults (ICRP, 1993c).

(*d*) *Placental transfer*

The fetal transfer of polonium has been studied mainly in rodents and baboons, showing low transfer of polonium to the fetus. These results are in accord with the limited data on humans.

Accumulation of ^{210}Po in the yolk sac and placenta of rats and guinea-pigs was demonstrated autoradiographically after administration of ^{210}Po citrate on various days during gestation (Haines *et al.*, 1995). Seven days after intravenous injection of ^{210}Po

citrate to two baboons in late pregnancy (five months after conception), the retention in the fetus was about 1% of the injected activity. The concentrations in fetal and maternal bone were similar (fetus:mother, 0.6–0.7), but those in fetal liver, kidneys and spleen were an order of magnitude lower than the corresponding values for maternal tissues. The overall fetal:maternal concentration ratio was estimated to be 0.3 (Paquet *et al*., 1998).

Elevated concentrations of ^{210}Po were reported in placentae of women in northern Canada who ate reindeer and caribou meat (Hill, 1966).

4.1.14 *Astatine-211*

Astatine is the fifth and heaviest element of the halogen series. Its chemical properties resemble those of iodine more closely than those of the lighter elements, fluorine, chlorine and bromine. Like iodine, astatine can readily form a number of organic compounds. No data are available on the biokinetics of astatine in humans, and few are available for animals.

Studies of the distribution and retention of ^{211}At in mice indicated that the radioactivity is distributed rapidly throughout the body after injection. The biological half-time of clearance from blood was 8 h. Astatine deposited in the thyroid appeared to be released to the systemic circulation with a biological half-time of about 36 h. The astatine deposited in liver, kidneys, spleen, stomach, small intestine and lungs appeared to be removed with biological half-times ranging from about 6 h (spleen) to about 21 h (stomach) (Garg *et al*., 1990).

During the development of ^{211}At-containing radiopharmaceuticals for endoradiotherapy, the biokinetics of a number of organic compounds of astatine were investigated in mice (see Garg *et al*., 1995; Foulon et al., 1998; Reist *et al*., 1999). In addition, a number of ^{211}At-labelled antibodies or antibody fragments have been investigated (Garg *et al*., 1990; Foulon *et al*. 1998). In almost all these studies, the paired-label technique was used in order to provide data that were directly comparable with those for the corresponding ^{131}I-labelled analogues. The studies indicated that the biological half-times of retention of ^{211}At from organoastatine compounds are generally longer than those of ^{131}I from the equivalent iodine compound, by factors up to about 2.5. Although most of the compounds investigated contained an astatine-substituted benzene moiety, the rates of dehalogenation appeared to be variable, and the fractional uptake in the different organs varied widely.

4.1.15 *Radon-222*

Data on the inhalation, dermal absorption, ingestion, systemic distribution, retention and excretion of ^{222}Rn were reviewed previously (IARC, 1988). More recent data on placental transfer of ^{222}Rn are presented below.

It is generally accepted that radon crosses the placenta, resulting in similar concentrations in fetal and maternal tissues. The specific activities of ^{214}Pb (a decay product of ^{222}Rn) were measured in tissues of pregnant rats after 13 consecutive 18-h-per-day exposures to radon on days 7–19 of gestation, and the corresponding dose equivalent rates were calculated. Because radon progeny were inhaled with radon gas, the lung had the highest activity concentrations, followed by the kidney, which showed concentrations more than an order of magnitude lower. The concentrations in other tissues, such as femur and liver, were several-fold lower than those in the kidney. The concentration of ^{214}Pb in the placenta was similar to that in the femur and liver of the pregnant rats, and the amount measured in the fetus was about one-fifth of that in the placenta. The difference in concentration between components of the fetoplacental unit on the last day of exposure (day 19 of gestation) contrasted with the results of the same authors for ^{85}Kr in rats, in which the concentrations were more uniform and the fetoplacental radiation doses were similar to those received by other tissues in the pregnant rats (Sikov *et al.*, 1992). Thus, while radon can be assumed to cross the placental barrier freely, all the short-lived decay products do not.

4.1.16 *Radium-224, radium-226 and radium-228*

(*a*) *Inhalation*

Radium has been shown to be highly soluble in studies in which $^{232}UO_2(NO_3)_2$ with its decay products and radium nitrate, with or without thorium nitrate, were administered to rats by intratracheal injection. Less solubility was reported in a person who accidentally inhaled a mixture of radium and barium sulfate and in a person who inhaled an unidentified radium-containing compound. Lung clearance half-time values of 90 and 120 days, respectively, were reported (ICRP, 1995b).

(*b*) *Ingestion*

Data from balance studies reviewed by the ICRP Task Group on Alkaline Earth Metabolism in Adult Man (ICRP, 1973) indicated that the fraction of radium absorbed from food or drinking-water is 0.15–0.21. The results of a study of a single volunteer who ingested a known quantity of radium suggested a higher fractional absorption value of around 0.5, while elderly subjects ingesting mock radium-dial paint containing $^{224}RaSO_4$ absorbed an average of about 20% (Maletskos *et al.*, 1969).

(*c*) *Systemic distribution, retention and excretion*

The alkaline earth elements strontium, barium and radium follow the migration and deposition of calcium in the body, but quantitative differences in their retention in tissues are found due to discrimination by biological membranes and bone minerals. In general, strontium is a better quantitative tracer for calcium than the heavier elements barium and radium. Discrimination against radium, relative to calcium, results in less

effective incorporation and retention in bone and more rapid urinary excretion. Long-term retention of radium, like that of calcium, is confined to the skeleton; the doses from radium isotopes absorbed in the blood are delivered largely to bone surfaces and red bone marrow (Leggett, 1992a; ICRP, 1993c).

The initial deposition of calcium, strontium, barium and radium from blood onto bone surfaces is similar in rats and rabbits, as determined from the skeletal content over the first few hours after injection. Limited data on humans also support the use of a single value for initial uptake of these elements by bone. These conclusions are derived from autoradiographic studies on bone samples taken after injection of ^{45}Ca 14 h or more before death, measurements of calcium and strontium in autopsy samples of bone from subjects injected with radioisotopes 3 h or more before death, and from external measurements of ^{45}Ca uptake and retention in the bones of the foot. The findings suggest that the initial uptake of the elements by bone in adults is about 25%. Measurements of the retention of radium in the human skeleton and in the whole body indicate that radium is less efficiently retained in bone than calcium, consistent with discrimination against inclusion of radium in hydroxyapatite crystals (Leggett, 1992a).

There is considerable experimental evidence that the initial uptake of radium and calcium by the skeleton is much greater in growing than in mature individuals (Leggett, 1992a; ICRP, 1993c). In mice, the uptake of injected ^{224}Ra by the skeleton decreased from about 50% of the total in young animals to 25% in mature animals, as measured two days after injection. Skeletal retention of ^{226}Ra in beagles 1–2 weeks after injection accounted for 85% of the injected amount in newborn animals, 65% in juveniles and 30–50% in adults. The available data are consistent with changes in the calcium addition rate to the skeleton with age. Bone turnover is also higher at younger ages, as indicated by histomorphometric measurements and turnover rates inferred from human studies on radionuclide retention (Leggett *et al*., 1982; Leggett, 1992a).

(*d*) *Placental transfer*

The normal radium content in various human tissues was measured in autopsy material from 12–56 persons of an average age > 60 years. The average amount of ^{226}Ra in the whole body was 4.8 Bq, of which approximately 60% was found in muscular tissue, 27% in the skeleton and the remainder in other tissues and organs. Analysis of eight placentae and nine samples of fetal tissue showed ^{226}Ra concentrations of 30 and 22 μBq/g of wet tissue, respectively (Muth *et al.*, 1960). The ^{226}Ra concentrations in the bone of about 200 human fetuses were similar to those in adult bone and were independent of the stage of gestation (Rajewsky *et al.*, 1965). The radium content was measured in a woman who had been a radium-dial painter for 5–7 years from the age of 16 and had died at the age of 26 in February 1928, on the day of delivery of her stillborn child. The reported ^{226}Ra activities in total mineral bone, measured in 1969, corresponded to concentrations at the time of death of 103 kBq and 64 Bq in the mother and infant, respectively. It was concluded that 0.06% of the mother's ^{226}Ra had been absorbed by the fetal skeleton, and 0.12% of the mother's

radium was absorbed by the whole fetus during the 8–9 months of fetal life (Schlenker & Keane, 1987).

4.1.17 *Thorium-232*

(*a*) *Inhalation*

Thorium decay products were measured in the chest and in exhaled air of former thorium refinery workers three or more years after the end of exposure to a range of compounds, from monazite ore to thorium nitrate; at least some of the material was highly insoluble in the lung (reviewed by ICRP, 1995b). Analysis of tissues from one worker at autopsy 30 years after exposure still showed retention in lung tissue and associated lymph nodes, consistent with low solubility. Concentration of thorium in lung tissue and lymph nodes was also reported in a study on tissues from former uranium miners. Measurements of thorium in autopsy tissues from members of the public showed that the proportion of total retained thorium accounted for by retention in the lungs (~ 25%) was greater than that for plutonium (~ 5%), indicating long-term retention in the lungs with a half-time of 1–8 years.

Studies in rats indicated that some compounds of thorium, including the citrate, chloride, nitrate and hydroxide, have intermediate solubility (ICRP, 1995b).

(*b*) *Ingestion*

Measurements of the absorption of ^{234}Th ingested as the sulfate in a mock 'dial' paint by six 63–83-year-old persons (reviewed by ICRP, 1995a) gave fractional absorption values in the range 10^{-4} to 6×10^{-4}, with a mean of 2×10^{-4}. Thorium absorption has also been estimated from data on skeletal content, dietary intake, estimated inhalation rates and excretion data, giving values of 0.001–0.01. The concentrations of thorium in tissues, body fluids and the daily diet of urban Indian populations suggested absorption values lower than 10^{-3}; it was concluded that inhalation was the dominant route of intake and that the contribution from ingestion was negligible.

Several reports on the absorption of inorganic thorium provided values of 5×10^{-5} to 0.006 for rats and about 6×10^{-4} for mice (ICRP, 1995a).

In a study of the effect of age on absorption of radionuclides, ^{228}Th nitrate was administered to two-day-old rats and adult mice. One week later, ^{228}Th was measured in various organs and in the skeleton. The amount absorbed in the neonatal rats, 1.1% of the activity administered, was nearly 20 times higher than the absorbed fraction in the mice. In parallel experiments, ^{233}Pa (protactinium) nitrate was given to two-day-old rats and adult rats. After one week, the absorbed fraction in the neonatal animals was 100-fold higher than that in the adults (Sullivan *et al.*, 1983).

(*c*) *Systemic distribution, retention and excretion*

A study was reported of the clearance of thorium from blood and its retention and excretion after intravenous injection of ^{234}Th citrate into normal human subjects (three men, two women) aged 63–83 years (reviewed by ICRP, 1995a). Whole-body retention was > 90% after three weeks in all five subjects. Cumulative urinary excretion was about 5% over the first five days and 2–3% over the following 19 days. The ratio of urinary to faecal excretion was approximately 12:1 for the men and about 25:1 for the women. External monitoring showed no significant reduction in body content over the following four months. Long-term measurements of ^{224}Th and ^{228}Th in the bodies and excreta of occupationally exposed persons suggested a half-time for clearance of thorium of at least 10–15 years and probably much longer (ICRP, 1995a).

When thorium isotopes were measured in autopsy samples from non-occupationally exposed subjects, the highest concentration was found in the lymph nodes, followed by bone, thyroid and lung (Ibrahim *et al.*, 1983).

In general, the behaviour of thorium in the body appears to be similar to that of the more frequently studied element, plutonium (ICRP, 1995a). Their patterns of distribution in bone are similar, with deposition on bone surfaces, burial in bone volume and removal by resorption. In persons with long-term exposure to environmental levels of thorium and plutonium, the content of the gonads as a proportion of the total systemic content appears to be similar for the two elements. There are, however, established differences: uptake by the liver is lower for thorium than for plutonium, and the urinary excretion and retention in the kidneys are higher.

(*d*) *Placental transfer*

In a preliminary report on the concentrations of environmental thorium in human fetoplacental tissues in the first trimester of pregnancy, they were found to be at the limit of detection. No thorium could be detected in fetuses obtained during the second or early third trimester (Weiner *et al.*, 1985). In rats, there was little transfer from the placenta to the fetus, and a strong decrease in the specific activity in the fetus (% of injected dose per g tissue) during the second half of gestation (Maurer *et al*., 1950).

4.1.18 *Uranium-234, uranium-235 and uranium-238*

(*a*) *Inhalation*

Accidental exposures of humans to UF_6 and UO_2F_2 resulted in rapid urinary excretion of radioactivity, consistent with high solubility in the lungs. Experiments in beagle dogs showed that most of the initial lung burden was rapidly absorbed to blood. High solubility has also been reported after intratracheal instillation of $UO_2(NO_3)_2$ in rats (ICRP, 1995b).

The reported behaviour of UF_4 is complex. Measurements of urinary excretion after inhalation by humans, rats and baboons showed that a large fraction of the lung deposit

was rapidly absorbed; however, the degree of solubility varied considerably between experiments (ICRP, 1995b).

The available data on UO_3, ammonium diuranate and U_3O_8 from cases of accidental intake by humans, occupational monitoring, studies in rats, dogs and monkeys and from studies *in vitro* show mainly intermediate levels of solubility, although U_3O_8 was sparsely soluble in some cases (ICRP, 1995b).

Studies in humans, rats, dogs and primates have shown that UO_2 is very insoluble (ICRP, 1995b).

(*b*) *Ingestion*

The absorption of uranium has been reviewed by Wrenn *et al*. (1985), Leggett and Harrison (1995) and ICRP (1995a).

In the first controlled study involving more than one subject, $UO_2(NO_3)_2$ was administered to four hospital patients. The results obtained were taken to suggest fractional absorption in the range 0.005–0.05 (Hursh *et al.*, 1969). Leggett and Harrison (1995) interpreted the data as suggesting absorption of 0.004, 0.01, 0.02 and 0.06 for the four subjects. A study of the absorption of uranium in 12 normal healthy adult volunteers was reported in which drinking-water with high concentrations of uranium was consumed (Wrenn *et al.*, 1989). As 40–60% of absorbed uranium was excreted in the urine within the first three days, Leggett and Harrison (1995) concluded that the mean fractional absorption was 0.01–0.015, maximum absorption was in the range 0.02–0.04, and that six subjects absorbed less than 0.25% of the ingested uranium. Results have also been reported (Harduin *et al.*, 1994) for the absorption of uranium from mineral water administered either on one day or over 15 days, resulting in fractional absorption of 0.005–0.05 with an average value of 0.015–0.02. After administration over 15 days, the fractional absorption was 0.003–0.02 (average, 0.01–0.015) (ICRP, 1995a; Leggett & Harrison, 1995).

A number of dietary balance studies have indicated mean absorption values for uranium in the range 0.004–0.04 (Leggett & Harrison, 1995).

Uranium absorption has been measured in rats, hamsters, rabbits, dogs and baboons (Wrenn *et al*., 1985; Leggett & Harrison, 1995), and these data provide the only quantitative information on the relative uptake of uranium ingested in different chemical forms. Absorption appears to be greatest when uranium is ingested as $UO_2(NO_3)_2$, UO_2F_2 or $Na_2U_2O_7$, roughly half as great for UO_4 or UO_3, and one to two orders of magnitude lower for UCl_4, U_3O_8, UO_2 and UF_4. A number of studies have shown that absorption is substantially greater in fasted than in fed animals. For example, uptake was increased by one order of magnitude in mice and baboons deprived of food for 24 h before administration of uranium (Leggett & Harrison, 1995).

The limited data available on the absorption of uranium in children over five years of age suggest that uptake does not vary substantially with age. However, the estimates were based on the assumption that the subjects were in uranium balance and could be underestimates of absorption in rapidly growing children, who may be expected to

show net retention of uranium. Increased absorption of uranium was demonstrated in neonatal rats and pigs; absorption in two-day-old rats was about two orders of magnitude greater than that in adult animals (Leggett & Harrison, 1995).

(*c*) *Systemic distribution, retention and excretion*

In experimental studies in humans, about two-thirds of uranium injected intravenously as the nitrate was excreted in urine within the first 24 h and a further 10% over the following five days (see ICRP, 1995a). Studies in humans and animals indicate that most of the remaining uranium is excreted over a few months but a small proportion is retained for years. Faecal excretion of uranium is low, accounting for less than 1% of total excretion in human subjects over the first few days after intravenous injection of $UO_2(NO_3)_2$.

Measurements of the systemic distribution of uranium at autopsy after injection of $UO_2(NO_3)_2$ showed that the skeleton, kidneys and other soft tissues accounted for 10%, 14% and 6%, respectively, of the injected activity in a person who died after 2.5 days, 4–13%, 6% and 4%, respectively, in a person who died after 18 days and 1.4%, 0.3% and 0.3%, respectively, for a third person who died 566 days after the injection. In animals, most of the retained uranium was confined to the kidneys and skeleton a few days after absorption into blood. For example, the kidneys and skeleton of beagles accounted for 90% of the retained uranium 2–6 days after injection (ICRP, 1995a).

A substantial proportion of the uranium filtered by the kidneys is retained temporarily in the renal tubules before being excreted in the urine. In humans and animals, 92–95% of the renal content is lost rapidly, but the remainder has a half-time of 30–340 days. Retention of uranium by the kidneys appears to increase with the mass absorbed into blood, complicating the interpretation of experimental studies, many of which involved administration of relatively large amounts of uranium.

The behaviour of uranium in the skeleton shows some qualitative similarities to that of the alkaline earth elements. It has been shown that uranyl ions exchange with Ca^{2+} on the surface of bone mineral crystals, although they do not participate in crystal formation or enter existing crystals. The early distribution of uranium in the skeleton is similar to that of calcium. Studies in dogs indicate that uranium may enter bone mineral by diffusion from the bone surface as well as by burial, but this has not been observed in rats or mice. As is the case for calcium, a substantial proportion of uranium deposited in bone is lost to the circulation by processes that occur more rapidly than bone resorption (ICRP, 1995a).

(*d*) *Placental transfer*

Significant concentrations of uranium were found in three of seven samples from first-trimester human abortuses and in 12 of 16 samples from second-trimester abortuses. The concentration range for all fetal tissues was 2–5 mBq/kg, whereas 5–9 mBq/kg were found in placenta and about 60 mBq/kg in umbilical cord (Weiner *et al.*, 1985). In rats, the fetal:dam concentration ratios were 2.5 for liver, ~ 1 for femur

and 0.01 for kidney 24 h after administration of ^{233}U citrate on day 19 of gestation, but the concentrations measured in the fetal tissues were highly variable (Sikov & Mahlum, 1968).

4.1.19 *Neptunium-237*

(*a*) *Inhalation*

Qualitative data on ^{237}Np in human lung tissue after exposure to fall-out suggested that its retention is lower and its absorption into blood higher than for ^{239}Pu. Studies in rats have shown intermediate levels of solubility for ^{237}Np inhaled as nitrate and oxalate aerosols (ICRP, 1995b).

(*b*) *Ingestion*

The absorption of ^{239}Np and ^{242}Cm was measured in five adult male volunteers who received solutions of the citrate complexes with a midday meal. The mean fractional absorption value, as measured in urine, was 2×10^{-4} for both radionuclides, with a range of $1–3 \times 10^{-4}$ in both cases (Popplewell *et al.*, 1991).

The results of studies of the absorption of neptunium in animals have been reviewed. After administration of milligram quantities of ^{237}Np to rats, the fractional absorption was about 0.01. Subsequent experiments established that absorption in a number of animal species after low doses is an order of magnitude or more lower. For example, in baboons, the absorbed fraction was about 0.001 in two animals given 11 ng of ^{239}Np as the nitrate and about 0.01 in those given 5 mg of ^{237}Np. Administration in a milk-supplemented diet reduced the fractional absorption of the low dose of ^{239}Np by a factor of five, to $1–2 \times 10^{-4}$, while administration in a potato diet increased absorption by a similar factor (ICRP, 1986; Métivier *et al.*, 1986; Harrison, 1991).

The effect of age on the absorption of neptunium and plutonium was also studied in baboons (ICRP, 1989; Harrison & Fritsch, 1992). In animals at four days of age, the maximum absorption of neptunium, administered as the nitrate, was about 2×10^{-2}, which was about 40 times higher than that in adult animals. At one week and four weeks after birth, absorption had decreased to 1.5×10^{-3} and 10^{-3}, respectively, which were three to four times the values found in adult animals.

(*c*) *Systemic distribution, retention and excretion*

Studies in adult animals, including baboons and cynomolgus monkeys, indicated that about half of the absorbed neptunium is deposited in the skeleton, 2–10% in the liver and about 5% in other soft tissues; the rest is excreted within a few days, primarily in urine (ICRP, 1989). The limited data on humans show a generally similar pattern (Popplewell *et al.*, 1991).

Like other actinide elements, neptunium is deposited on bone surfaces. Its distribution on various bone surfaces appears to be similar to that of americium, although

it also shows some similarities to that of strontium. Formation of aggregates in bone marrow after bone resorption has been observed (ICRP, 1989).

In rodents and primates, rapid loss of neptunium from the liver was seen with half-times of a few months or less (ICRP, 1989). In human autopsy samples, ^{237}Np was removed from the liver at least 15 times more rapidly than ^{239}Pu (Efurd *et al.*, 1986).

Studies of the uptake and retention of ^{237}Np in the gonads of rats have been reviewed (Thompson, 1982). It was concluded that the behaviour of neptunium can be assumed to be similar to that of plutonium.

(*d*) *Placental transfer*

A study of the placental transfer of neptunium and other radionuclides in two baboons in late pregnancy (five months after conception) showed that, seven days after intravenous injection of ^{237}Np citrate, the retention in the fetus represented 1–2% of the injected activity. Retention in the placenta accounted for 0.7–1.2%. The overall fetus:mother concentration ratio was estimated to be 0.6 (Paquet *et al.* 1998). When rats were given ^{237}Np citrate intravenously on day 15 or 19 of gestation, the amounts measured in the fetus (per g wet weight) 24 h later represented 0.01 and 0.02% of the injected activity, respectively (Sikov & Mahlum, 1968).

4.1.20 *Plutonium-238 and plutonium-239*

(*a*) *Inhalation*

Intermediate solubility has been reported for plutonium nitrate inhaled by rats and dogs and plutonium tributyl-phosphate inhaled by rats and baboons (reviewed by ICRP, 1995b).

The oxides of plutonium are the most thoroughly studied of the actinide aerosols. Generally, two phases of absorption from the respiratory tract to blood can be distinguished. A small fraction, typically less than 1%, is absorbed within about one day, and the remainder is cleared with half-times of the order of years. The solubility has been shown to be highly dependent on how the aerosol is formed. For example, $^{239}PuO_2$, formed by complete oxidation of the metal or a salt at about 1000 °C (high-fired), is sparsely soluble, while material formed at lower temperatures is more soluble, reflecting incomplete oxidation. The sparse solubility of high-fired $^{239}PuO_2$ has been demonstrated in studies in dogs and primates, and supporting data on lung retention have been reported for exposed workers (ICRP, 1995b).

The lung clearance characteristics of plutonium are also different when it is inhaled as a mixed metal oxide. Greater absorption was observed in rats exposed to oxides containing plutonium mixed with sodium, potassium, calcium or magnesium. In contrast, studies in which rats, dogs and primates inhaled mixed UO_2/PuO_2 aerosols showed the same sparse solubility as for PuO_2 (ICRP, 1995b).

Measurements in human autopsy material of ^{239}Pu resulting from the atmospheric testing of nuclear weapons show that a relatively high proportion of ^{239}Pu is retained in

lung tissue and tracheobronchial lymph nodes, consistent with low solubility (McInroy *et al.*, 1991). More soluble forms of ^{239}Pu have also been reported. For example, ^{239}Pu discharged into the sea from the Sellafield reprocessing plant and attached to sediments was of intermediate solubility when administered to rats by intratracheal instillation (Morgan *et al.*, 1990).

(*b*) *Ingestion*

The fractional absorption of ^{244}Pu administered in citrate solution with a midday meal to three volunteers was in the range 3×10^{-4}–9×10^{-4} (Popplewell *et al.*, 1994). Measurements on two further volunteers increased the range to 10^{-4}–10^{-3}, with an average of 6×10^{-4} (Ham & Harrison, 2000). In volunteers who ate winkles collected on the Cumbrian coast near to the nuclear-fuel reprocessing plant at Sellafield, the average fractional absorption of plutonium was 1.7×10^{-4}, with a range of 2×10^{-5}–5×10^{-4} (Hunt *et al.*, 1990; ICRP, 1993c). The fractional absorption from the gut of fall-out plutonium in reindeer meat was determined by comparing the ratio of body content to dietary intake of $^{239/240}$Pu in persons who had lived in Lapland or in the urban areas of southern Finland. The absorption was estimated to be 8×10^{-4}, but the estimate is uncertain (Mussalo-Rauhamaa *et al.*, 1984).

Studies on the absorption of plutonium in rodents, pigs, dogs and primates have been reviewed extensively (ICRP, 1986; Harrison, 1991). The lowest fractional absorption values were reported for the oxide, ranging from about 2×10^{-4} in rats to about 3×10^{-8} in pigs. This wide range probably reflects the solubility of the oxide preparation, which is affected by the temperature of production, the proportion of small particles present and the specific activity of the isotope. Mixed Pu–sodium oxides contain a higher proportion of very small particles (about 1 nm in diameter) than the pure oxides. Furthermore, because of their much higher specific radioactivity, suspensions of ^{238}Pu oxide (6.27×10^{8} kBq/g) are more prone than those of ^{239}Pu oxide (2.25×10^{6} kBq/g) to radiolytic breakdown to small particles (Fleischer & Raabe, 1977).

The fractional absorption values after uptake of plutonium administered to animals as the nitrate, chloride or bicarbonate are in the range 10^{-5}–10^{-4}. Fasting has been shown to increase absorption by up to an order of magnitude. Values of 10^{-3}–2×10^{-3} were reported for uptake of ^{237}Pu nitrate given as a single, low dose to rats and mice (Sullivan, 1980; Sullivan *et al.*, 1983). These results were taken as evidence of increased absorption at low masses; however, in experiments to determine the effect of long-term ingestion of low doses, a value of 3×10^{-5} was obtained for the nitrate in rats and 10^{-5} for the bicarbonate in hamsters (ICRP, 1986). In general, the ingested mass and valence appear to have little effect on absorption; however, when large masses of pentavalent plutonium are ingested, absorption may be increased by an order of magnitude, as demonstrated by Métivier *et al*. (1986) in baboons.

The fractional absorption of plutonium administered to animals as organic complexes or incorporated into food is generally greater than that of inorganic forms.

For example, most of the values reported for Pu citrate are in the range 6×10^{-5}–6×10^{-4}, while those for the nitrate are 10^{-5}–10^{-4}. An organic form of importance in fuel reprocessing is Pu tributylphosphate, for which the absorption in rats has been reported to be about 10^{-4}–2×10^{-4} (ICRP, 1986).

The absorption of plutonium in newborn hamsters and guinea-pigs has been shown to be greatest on the first day of life, with values of about 0.02–0.03, and to decrease progressively during the period of suckling to reach adult values by about the time of weaning at 21–22 days (Harrison & Fritsch, 1992; ICRP, 1986). In a study of the absorption of plutonium given as the nitrate to different animal species, a value of 2×10^{-2} was obtained for one-day-old rats, 6×10^{-2} for two-day-old dogs and 10^{-1} for one-day-old piglets. The values for the absorption of plutonium in baboons after administration of ^{239}Pu citrate were 2×10^{-2} at four days of age and 5×10^{-4} for adult animals (Sullivan & Gorham, 1982).

Increased absorption of plutonium has been shown to be associated with high levels of intestinal retention in rats and pigs but not in guinea-pigs or primates (Harrison & Fritsch, 1992). Autoradiographic studies have shown that the high levels of retention of plutonium in rats and pigs are confined mainly to epithelial cells. The kinetics of loss has been considered to involve the normal migration and sloughing of epithelial cells from the tips of villi. In guinea-pigs, baboons and macaques, low levels of plutonium were retained, mainly in macrophages in the lacteal region in the tips of villi (ICRP, 1986).

(*c*) *Systemic distribution, retention and excretion*

Studies on the distribution of plutonium in humans and experimental animals show that the main sites of deposition and retention are the liver and skeleton, with small fractions retained in the gonads (Leggett, 1985; ICRP, 1989, 1993c). In animals of all ages, about 90% of plutonium absorbed into blood is initially deposited in the liver and skeleton. In experiments with beagles, the distribution between liver and skeleton varied with age, skeletal uptake being almost 70% in juveniles and 40–60% in adults. In persons given intravenous injections of ^{239}Pu citrate, about 50% was retained in the skeleton and 30% in the liver 4–457 days after injection (Durbin, 1972; ICRP, 1986, 1989).

Within the skeleton, plutonium is deposited initially on bone surfaces, the highest concentrations being found at sites with red haematopoietic marrow and the lowest at sites with yellow fatty marrow. In adults, nearly all the red bone marrow is in trabecular bone, and deposition in these bones is likely to be greater than that in cortical bone. In children, some or all of the marrow in cortical bone is active, and a more uniform distribution in cortical and trabecular regions might be expected. Bone surfaces labelled with plutonium may remain unchanged, or they may be buried by the formation of new bone or resorbed by osteoclasts. The rate of removal from surfaces by burial or resorption depends on the age of the individual and on the bone surface type (trabecular or cortical). Plutonium resorbed by osteoclasts may be released and

concentrated by macrophages in bone marrow. In beagles injected with ^{239}Pu, the peak labelling of macrophages in bone marrow was found two years after injection, and no labelled macrophages were seen after four years. There is autoradiographic evidence that resorbed plutonium can be re-deposited on bone surfaces either locally or after entry into blood (ICRP, 1989).

Studies in rats and beagles indicate that hepatocytes are responsible for the initial uptake of plutonium by the liver, leading to association with the iron-storage protein, ferritin. Later, retained plutonium becomes associated with subcellular structures, including lysosomes, microsomes and mitochondria, and the proportion contained within reticuloendothelial cells increases with time. Studies of human autopsy samples show that plutonium may be retained for many years in the liver. Estimates of the ratio of total retained plutonium in liver and skeleton indicate that the ratio depends on the age at which exposure occurred, being near 1 for older subjects and 0.5 or less for younger individuals. The dominant factor in this age-related difference is the lower initial deposition in the liver at younger ages, although it is also possible that retention times may be shorter in children (ICRP, 1989).

Studies of actinide retention in human and animal gonads have been reviewed (Thomas *et al*., 1989) and show fractional uptake equivalent to about 10^{-5} per g of gonadal tissue for both testes and ovaries in humans and no evidence of loss with time in most of the animal species studied. Studies in beagles showed that the initial uptake of ^{239}Pu in testes and ovaries is greater in younger than in older animals (ICRP, 1993c).

(*d*) *Placental transfer*

Most of the data on the transfer of plutonium across the placenta have been obtained in rats, although some information is available for baboons, mice and guinea-pigs. Data on human placental transfer of plutonium are limited.

^{239}Pu was measured in human fetal tissue, obtained from second-trimester pregnancy terminations in the United Kingdom, by α-particle spectrometry and thermal ionization mass spectrometry. The typical concentration was < 50 μBq/kg. The whole-body concentration of ^{239}Pu of the mothers in this study was estimated to be approximately 0.3 mBq/kg (Prosser *et al.*, 1994).

A study of the placental transfer of ^{239}Pu in two baboons in late gestation (five months after conception; total gestation time, six months) showed that, seven days after intravenous injection of ^{239}Pu citrate, the fetus had retained about 4% of the amount injected. Retention in the placenta accounted for 8–12% of the injected activity. The concentrations of ^{239}Pu in fetal and maternal bone were similar, but those in fetal liver and other soft tissues were considerably lower than the corresponding values for maternal tissues. The overall fetal:maternal concentration ratio was about 1, while the concentration in the placenta was about four to five times the average maternal tissue concentration (Paquet *et al.*, 1998).

Less plutonium is transferred to the fetus in rodents than in baboons. When ^{238}Pu nitrate was administered to pregnant rats and guinea-pigs on various days of gestation

and the embryos or fetuses were analysed three days later, retention by a single rat embryo or fetus accounted for about 0.00004% of the injected activity on day 10.5, rising to 0.02% on day 17.5. In guinea-pigs, retention increased from 0.00001% of the injected activity for a day-17 embryo to 0.2% for a highly developed 57-day-old fetus (Morgan *et al.*, 1991).

4.1.21 *Americium-241*

(*a*) *Inhalation*

Most of the cases of human exposure for which adequate data from bioassays were available involved inhalation of oxides of americium. In these studies, a large proportion of the lung deposit (> 80%) was cleared with a half-time of tens of days, and the remainder had retention half-times of months or years. In general, the results of experiments in various animal species support the findings in humans *in vivo* (ICRP, 1995b).

^{241}Am inhaled or instilled as the nitrate in rats and dogs and as the chloride, citrate or hydroxide polymers in rats was highly soluble. Although various chemical forms of ^{241}Am have been shown to be more soluble than equivalent forms of ^{239}Pu, this appears not to be the case when both nuclides are present as minor components in an insoluble matrix. Similar levels of transfer of ^{241}Am and ^{239}Pu to blood were observed in rats, dogs and monkeys after inhalation of a mixed UO_2/PuO_2 aerosol. The rates of dissolution of ^{241}Am and ^{239}Pu from a number of industrial dusts were similar after intratracheal instillation in rats, but there was a trend towards greater absorption of ^{241}Am than ^{239}Pu from more soluble dusts (ICRP, 1995b).

(*b*) *Ingestion*

The only data on the absorption of americium in humans are from two studies of the absorption of plutonium and americium by volunteers who ate winkles collected on the Cumbrian coast near to the nuclear-fuel reprocessing plant at Sellafield. The average fractional absorption value obtained for americium was 1×10^{-4}, with a range of 4×10^{-5}–3×10^{-4} (Hunt *et al.*, 1990; ICRP, 1993c).

Studies on the absorption of americium in animals have been reviewed (ICRP, 1986; Harrison, 1991). Absorption after administration of americium to rodents as the nitrate or chloride was 2×10^{-4}–10^{-3}, while that of ^{241}Am oxide in fresh suspension was about 10^{-4} in rats and 6×10^{-5} in hamsters. The results for rodents and primates suggest that the absorption of americium, unlike plutonium, is not increased by binding to organic ligands (Harrison, 1991).

The absorption of americium in newborn hamsters and guinea-pigs was shown to be highest on the first day of life, with values of about 0.01–0.05, and to decrease progressively over the period of suckling to reach adult values by about the time of weaning at 21–22 days (Harrison & Fritsch, 1992).

(*c*) *Systemic distribution, retention and excretion*

In animals of all ages, most absorbed americium is deposited in the skeleton and liver within a few days of injection (ICRP, 1993c; Leggett, 1992b). Data on accidentally exposed humans and experimental data on baboons, monkeys and beagles indicate that the liver contains a major part of the systemic deposit soon after exposure, and a considerable proportion of the initial liver deposit is transferred to the skeleton within a few years. The skeletons of immature animals generally accumulate a greater proportion of injected americium than do mature animals. For example, the initial skeletal uptake accounted for 76–84% of injected ^{241}Am in newborn beagles and about 30% in mature animals (Stevens *et al.*, 1977).

In the skeleton, americium is deposited predominantly on bone surfaces, including resorbing and forming surfaces, in a more uniform manner than that of plutonium. Removal from bone surfaces occurs, as for plutonium, by burial and resorption, the burial rates probably being determined by age-specific bone formation rates, as for plutonium. Studies in experimental animals indicate that americium resorbed from bone is retained in the bone marrow to a lesser extent than plutonium (Leggett, 1992b).

Retention of americium in the liver has been shown to involve binding to ferritin and association with lysosomes, as for plutonium (Stover *et al.*, 1970). Transfer to liver reticuloendothelial cells was demonstrated after high doses. Data on humans and experiments in beagles indicate a removal half-time from liver of about one year (compared with about 10 years for plutonium). When account is taken of recycling of americium to the liver, this rate of loss corresponds to an apparent half-time of 2–3 years (Griffith *et al.*, 1983).

In humans, the testicular retention of the total systemic burden of ^{241}Am is about 0.03% long after exposure. This finding is consistent with results obtained in beagles. In adult baboons, the ovaries retained 4.8 and 1.5% of the injected dose per kilogram wet weight when measured 1 and 27 months after injection of ^{241}Am, respectively (Guilmette *et al.*, 1980; ICRP, 1986).

(*d*) *Placental transfer*

The transfer of americium to the embryo and fetus has been measured in mice, rats, guinea-pigs and baboons. The results obtained show that the levels of transfer are consistently lower than the corresponding values for plutonium.

A study of the placental transfer of ^{241}Am in two baboons in late gestation (five months after conception) showed that, seven days after intravenous injection of ^{241}Am citrate, retention by the fetus represented 0.3–0.4% of the amount injected. Retention in the placenta accounted for 2–3% of the injected activity. The concentrations of ^{241}Am in fetal bone and soft tissues were an order of magnitude or more lower than the corresponding values for maternal tissues. The overall fetus:mother concentration ratio was about 0.1 (Paquet *et al.*, 1998).

In rodents, the levels of transfer of americium to the fetus were lower than in baboons. The concentrations of ^{241}Am in guinea-pig fetuses in late gestation were two orders of magnitude higher when the mother had been treated one week previously than when they had been treated one month before conception (Levack *et al*., 1994).

4.1.22 *Curium-244*

(*a*) *Inhalation*

Follow-up of cases of accidental inhalation of ^{244}Cm oxides and a mixture of the nitrate, chloride and oxide, and the results of studies in rats and dogs exposed by inhalation show that curium isotopes generally behave similarly to americium. No large differences in solubility were observed between oxides and other chemical forms (ICRP, 1995b).

(*b*) *Ingestion*

The absorption of ^{239}Np and ^{242}Cm was measured in five adult male volunteers who received solutions of the citrate complexes with a midday meal. The mean fractional absorption value, as measured in urine, was 2×10^{-4} for both radionuclides, with a range of $1–3 \times 10^{-4}$ in both cases (Popplewell *et al.*, 1991).

The fractional absorption of curium in rats was in the range $3 \times 10^{-5}–7 \times 10^{-4}$. In guinea-pigs given ^{242}Cm prepared in the same way as for the study of Popplewell *et al*. (1991), described above, the fractional absorption was about 10^{-4}. High values have been reported for the absorption of curium in neonatal rats and pigs, similar to those for plutonium and americium. Leaving ^{244}Cm oxide in water for four days before administration to rats increased the absorption from 4×10^{-5} to 5×10^{-4} (ICRP, 1995b).

(*c*) *Systemic distribution, retention and excretion*

The biological behaviour of curium is similar to that of americium, particularly after absorption to blood, as shown in studies in rats and in more limited studies in dogs, baboons and sheep (ICRP, 1995b).

The systemic distribution and retention of ^{241}Am citrate, ^{241}Am nitrate and ^{244}Cm nitrate were virtually identical in rats during the first week after intubation into various regions of the respiratory tract. Similar behaviour of ^{241}Am nitrate and ^{242}Cm nitrate was also shown in rats after inhalation or intramuscular injection in a comparison of urinary excretion, uptake and retention in bone and sites of binding on bone. The long-term retention of ^{244}Cm in rat skeleton was similar to that of ^{241}Am. The distributions of americium and curium in beagles were also similar, although the initial liver:skeleton concentration ratio and the rate of faecal excretion appeared to be slightly higher for curium. Studies in a small number of baboons injected with ^{241}Am citrate or $^{243/244}$Cm citrate indicated similar patterns of distribution and retention. Studies of the transfer of

radionuclides to the milk of lactating ewes showed similar levels of transfer for ^{241}Am and ^{244}Cm (ICRP, 1995b).

(*d*) *Placental transfer*

^{244}Cm citrate was administered to a baboon by intravenous injection about four months after conception, and transfer to the fetus was measured after 45 days. The amount retained in the fetus represented 0.45% of total maternal retention, with 95% in the fetal skeleton. Placental retention represented 1% of total maternal retention. The average fetus:mother concentration ratio was estimated to be about 0.2 (Neton *et al.*, 1979). Studies of the transfer of americium and curium to rat fetuses gave similar results (Sikov & Mahlum, 1975; Sikov, 1987b).

4.1.23 *Biokinetics models and dose coefficients*

ICRP (1979, 1980, 1981) considered the behaviour of a large number of radioactive elements and calculated dose coefficients and limits of intake of their radioisotopes for workers by inhalation or ingestion. General models were proposed for the organs of intake, the respiratory and gastrointestinal tracts, and element-specific models were presented for the systemic distribution and retention of radionuclides after their entry into the blood. A model for the behaviour of bone-seeking radionuclides and dose delivery within the skeleton was also included. The doses to members of the public, including children, were also considered and models and dose coefficients have been published for isotopes of 31 elements (ICRP, 1989, 1993c, 1995a,b). When sufficient information was available, physiologically realistic, age-dependent models were developed, for example, taking account of the effects of bone remodelling on the distribution and retention of actinide and alkaline earth elements. A revised respiratory tract model has been developed (ICRP, 1994b), and revision of the model of the gastrointestinal tract is in progress. A CD-ROM has become available which gives the organ and tissue doses for intakes of radionuclides by workers and members of the public (ICRP, 1999). A report is in preparation on doses to the fetus after intake by the mother.

(*a*) *Respiratory tract model*

In the ICRP model (ICRP, 1994b), the respiratory tract is represented by five regions: the extrathoracic (ET) airways are divided into ET_1, the anterior nasal passages, and ET_2, which comprises the posterior nasal and oral passages, the pharynx and larynx. The thoracic regions are bronchial (BB: trachea, generation 0; bronchi, airway generations 1–8), bronchiolar (bb: airway generations 9–15) and alveolar–interstitial (AI: the gas exchange region). Lymphatic tissue is associated with the extrathoracic and thoracic airways (LN_{ET} and LN_{TH}, respectively). Reference values of dimensions and scaling factors for subjects of different ages are specified.

The deposition of radionuclides is calculated for each region of the respiratory tract, taking account of both inhalation and exhalation. This is done as a function of particle

size, breathing parameters and/or work load, according to the age and sex of the subject. Deposition parameters are given for a particle size range of 0.006–100 μm activity median aerodynamic diameter. Default deposition parameters for individuals are based on average daily patterns of activity. Table 102 shows values for the regional deposition of aerosols in a reference man who breathes through his nose and is engaged in light work, taking into account default aerosol particle sizes for environmental exposure (1 μm) and occupational exposure (5 μm). In general, deposition in the ET region is greater for larger particles, whereas smaller particles are more likely to reach the AI region of the lung.

Table 102. Deposition of inhaled aerosols in a reference man (%)

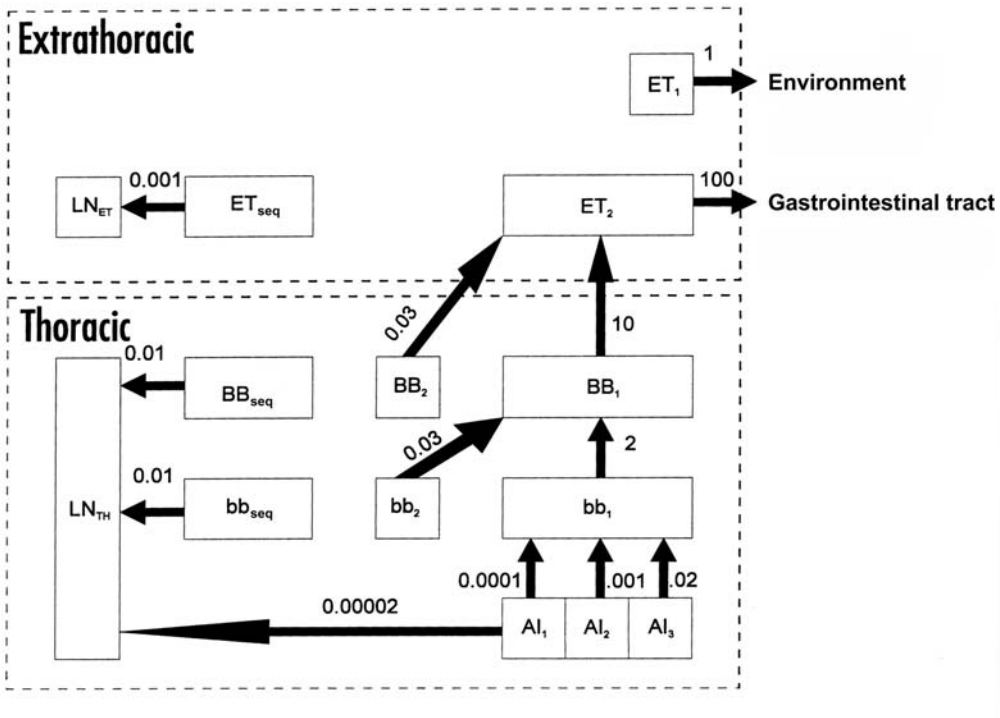
Region	Activity median aerodynamic diameter (μm)	
	1	5
ET_1	16.5	33.9
ET_2	21.1	39.9
BB	1.24	1.78
bb	1.65	1.10
AI	10.7	5.3
Total	51.2	82.0

From ICRP (1994b). ET_1, anterior nasal passages; ET_2, posterior nasal and oral passages; BB, trachea, generation 0; and bronchi, airway generations 1–8; bb, bronchioli, airway generations 9–15; AI, alveolar–interstitial gas exchange region

The model describes three clearance pathways. Material deposited in ET_1 is removed by extrinsic means such as nose-blowing. In other regions, clearance occurs either by particle transport to the gastrointestinal tract and lymphatic system or by absorption into blood. Transport to the gastrointestinal tract occurs by mucociliary clearance. It is assumed that the particle transport rates are the same for all materials. Absorption into blood is material-specific and is assumed to occur at the same rate in all regions except ET_1, where none occurs. Fractional clearance rates vary with time, but to facilitate calculations they are represented by combinations of compartments cleared at constant rates. It is assumed that the clearance rates by both processes are independent of age and sex.

Figure 10 shows the compartment model for particle transport. The rate constants shown are reference values (per day), which were derived, when possible, from studies in humans, since particle transport rates are known to vary greatly among mammalian

Figure 10. Particle transport in the respiratory tract



From ICRP (1994b)

ET_1, anterior nasal passages; LN_{ET}, lymphatic tissue associated with extrathoracic airways; ET_{seq}, extrathoracic walls; ET_2, posterior nasal and oral passages; BB_{seq}, trachea, generation 0; and bronchi, airway generations 1–8, fraction retained on walls; BB_2, fraction of deposit in BB that moves slowly; BB_1, fraction of deposit in BB that moves rapidly; LN_{TH}, lymphatic tissue associated with thoracic airways; bb_{seq}, airway generations 9–15, fraction retained on walls; bb_2, fraction of the deposit in bb that moves slowly; bb_1, fraction of the deposit in bb that moves rapidly; AI_1, AI_2, AI_3, deposits in three areas of the gas exchange region

species. It is assumed that the AI deposit is divided between AI_1, AI_2 and AI_3 in the ratio 0.3:0.6:1, with half-times of about 30, 700 and 7000 days, respectively. The fraction of the deposit in bb and BB that moves slowly (bb_2 and BB_2) depends on particle size (up to 50% for particles < 2.5 μm), 0.7% being retained in the walls (bb_{seq} and BB_{seq}).

Absorption of radionuclides into blood depends on the chemical nature of the element and the chemical form deposited. The use of material-specific dissolution rates is encouraged, but default values are given for types F (fast), M (medium) and S (slow). Expressed as approximate half-times for one or two components of clearance, these absorption rates correspond to: type F, 10 min (100%); type M, 10 min (10%), 140 days (90%); and type S, 10 min (0.1%), 7000 days (99.9%). The amounts of 1-μm activity median aerodynamic diameter aerosol that reach the blood from the respiratory tract can

be calculated as 24% (F), 9% (M) and 1% (S). In each case, a further fraction of the inhaled material will reach the blood by absorption from the gut after mucociliary clearance from the respiratory system and swallowing; this fraction will be greatest for type F materials (most soluble) and least for type S materials. The recommended default dissolution rate for most of the elements considered in this monograph is type M; the exceptions are iodine and caesium (type F) and thorium (type S).

Doses are calculated for each region of the respiratory tract, taking account of the location of target cells for induction of cancer. In the ET region, the target is taken to be the basal cells of the epithelial layer. In the bronchial epithelium, both secretory cells and basal cells are included as targets, while in the bronchiolar epithelium only secretory (Clara) cells are considered to be a target. In the AI region, Clara cells, type II epithelial cells and epithelial cells of blood capillaries are considered tissues from which tumours can arise.

(*b*) *Gastrointestinal tract model*

The model of the gastrointestinal tract used by ICRP (1979) is that developed for calculation of doses to workers. It has since been applied to members of the public, including children (ICRP, 1989, 1993c, 1995a,b), taking into account the smaller tissue masses in children.

The model has four compartments: the stomach, small intestine, upper large intestine and lower large intestine. Material is transferred successively between the four compartments of the model in an exponential manner, with half-times taken to be 0.69, 2.8, 9.2 and 17 h (relative clearance rates of 24, 6, 1.8 and 1 per day), respectively; immediate mixing within the contents of the different compartments is assumed, and doses are calculated separately for the mucosal wall of each compartment. As specific information on the age-dependence of the half-time in the different compartments is not available, these rates are taken to apply to all age groups. Since the total transit time in children is shorter than in adults, the dose to the gastrointestinal tract in children may be overestimated.

Radionuclides are absorbed mainly in the small intestine. Absorption is usually expressed as the fraction of the ingested radionuclide reaching the blood. ICRP has specified values for the intake of each radioactive element by workers and has recommended intake limits by children for 31 radionuclides. The recommended absorption values for the radioisotopes included in this monograph for intakes by members of the public are given in Table 103. Absorption by infants refers to intakes at three months of age.

The colon (large intestine) receives doses from radionuclides passing unabsorbed through the gut and from radionuclides excreted into the gut. Systemic models for the behaviour of radionuclides after their entry to blood specify the proportions excreted in urine and faeces. For mathematical convenience in the current model, excretion into the gut is generally assumed to occur in the upper large intestine, whereas absorption takes place in the small intestine.

Table 103. Fractional absorption of radionuclides from the gastrointestinal tract by members of the public

Element	Adult	Infant
H, C, Cs, S, I, At	1	1
P, Re	0.8	1
Tc, Po	0.5	1
Sr[a]	0.3	0.6
Ra[a]	0.2	0.6
Bi	0.05	0.1
U	0.02	0.04
Ga	0.001	0.01
Th, Np, Pu, Am, Cm	0.0005	0.005

From ICRP (1989, 1993c, 1995a,b)

[a] Intermediate values for 1-, 5- 10- and 15-year-old children: Sr, 0.4; Ra, 0.3

For penetrating radiations, the average dose to the wall of each region is used as a measure of the dose to the mucosal layer. For non-penetrating radiations, the fraction absorbed by the mucosal layer is taken to be equal to 0.5 v/M where M is the mass of the contents of that section of the gastrointestinal tract and v is a factor between 0 and 1 representing the proportion of radiation energy reaching sensitive cells. The factor 0.5 is introduced because the radiation dose from non-penetrating radiations near the intestinal wall is approximately half that within the contents. For β-particles, v is taken to be 1; for α-particles, an arbitrary value of 0.01 is used. The cells sensitive to cancer induction are thought to be the stem cells in the base of the crypts, which in this model are likely to receive negligible doses from α-emitting nuclides in the gut lumen.

(*c*) *Bone models*

In ICRP Publication 30 (ICRP, 1979), radionuclides deposited in bone were classified as either volume or surface seekers, and the initial distribution was assumed to persist throughout the retention of the radionuclide in the bone. For example, plutonium and related actinide elements were classified as surface seekers, while the alkaline earth elements calcium, strontium and radium were classified as volume seekers. The target regions were taken to be a 10-μm layer of marrow adjacent to endosteal bone surfaces for induction of solid tumours and of red bone marrow for induction of leukaemia. Table 104 shows the proportion of energy from decay of α- and β-particle-emitting radionuclides deposited in these two target regions.

In practice, all the radionuclide deposited in bone is initially on bone surfaces, and then migrates within the bone. Dynamic models for the skeleton have been adopted by ICRP (1993c) for the main groups of bone-seeking radionuclides, those of the alkaline earth elements, calcium, barium, radium and strontium, and the actinides, plutonium,

Table 104. Absorbed fractions of energy from radionuclides deposited in bone

Source organ	Target organ	Class of radionuclide				
		α-emitter		β-emitter		
		Uniform in volume	On bone surfaces	Uniform in volume	On bone surfaces	
					$\bar{E}_\beta \geq 0.2$ MeV	$\bar{E}_\beta < 0.2$ MeV
Trabecular bone	Bone surface	0.025	0.25	0.025	0.025	0.25
Cortical bone	Bone surface	0.01	0.25	0.015	0.015	0.25
Trabecular bone	Red bone marrow	0.05	0.5	0.35	0.5	0.5
Cortical bone	Red bone marrow	0.0	0.0	0.0	0.0	0.0

From ICRP (1979); $\bar{E}_\beta$, average energy of β-particles

americium, neptunium and thorium. The alkaline earth model is also used for lead and uranium. These models take account of the burial of surface deposits, transfer of radioactivity to marrow and recycling to the circulation and between organs.

(*d*) *Assumptions concerning elements*

The following sections describe some assumptions made in the ICRP model for ^{3}H, ^{131}I, ^{137}Cs and for radionuclides of the alkaline earth elements and the actinide elements.

(i) *Hydrogen*

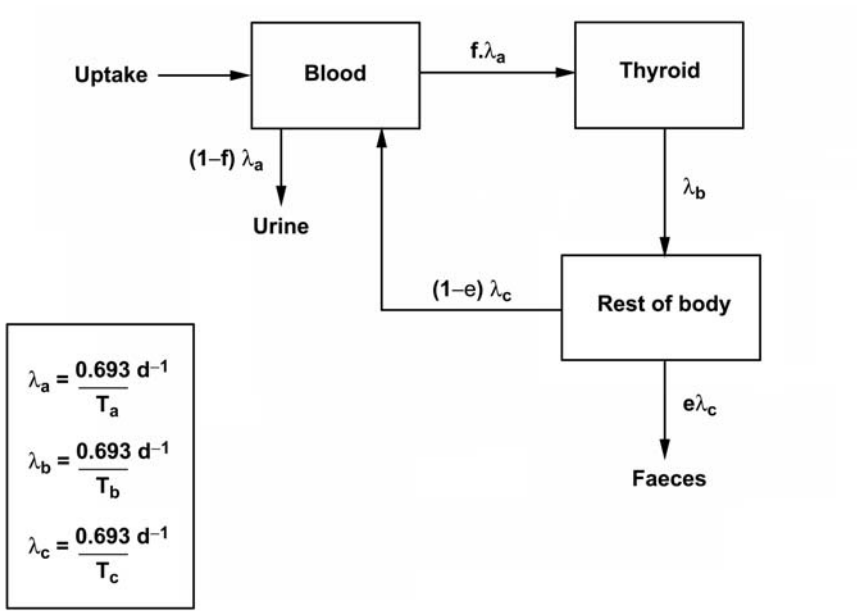
For ^{3}H entering body fluids as $^{3}H_2O$, the doses to tissues are calculated by assuming that 97% equilibrates with body water and is retained with a half-time of 10 days in adults (range, 4–18 days). On the basis of studies in animals, the remaining 3% is assumed to be incorporated into organic molecules and retained with a half-time of 40 days. For ^{3}H absorbed after ingestion of organically bound ^{3}H, it is assumed that 50% is readily exchangeable with hydrogen from the body water pool and will therefore be retained with a half-time of 10 days in adults. A half-time of 40 days is applied to the remaining 50%. On the basis of these assumptions and given a uniform distribution of retained ^{3}H, the dose to all body tissues is the same and is about 2.5 times higher for organically bound ^{3}H than for $^{3}H_2O$.

The half-times of retention are lower in children than in adults when account is taken of their smaller mass of total body water, the values for daily water balance based on their energy expenditure and, for the organically bound component, carbon content and balance. For example, half-times of three and eight days are applied for a three-month-old-infant and 10- and 40-day values for adults (see above). Despite the more rapid loss of ^{3}H from the body of children, the doses per unit intake are higher than for adults because of the dominating effect of smaller body mass (ICRP, 1989).

(ii) *Iodine*

The systemic model used for radioiodines is shown in Figure 11, and the parameters used are listed in Table 105. For children, there is no evidence that the level of uptake of iodine into the thyroid varies with age, although it may be higher in the first few days of life. As there is some evidence, however, that the half-time of retention in the thyroid is reduced in children, shorter half-times were used for children in the model (ICRP, 1989).

Figure 11. Model for biokinetics of iodine



From ICRP (1989). *f*, fractional uptake by thyroid; *e*, fractional excretion in faeces; λ, coefficient of transport from blood to thyroid (λ_a), thyroid to rest of body (λ_b), rest of body to faeces (λ_c); T_a, biological half-time in blood; T_b, biological half-time in thyroid; T_c, biological half-time in rest of body

(iii) *Caesium*

Human retention of ^{137}Cs has two components. The first accounts for about 10% of the administered activity and is excreted mainly in the urine with a half-time of about two days in adults. The second component has a half-time of about 110 days in men (range, 50–150 days) and is shorter in women (mean, 60–65 days). The use of the ICRP value of 110 days is therefore likely to be conservative for women (ICRP, 1989).

The rate of loss of caesium from the body appears to be higher in children than in adults, and, in newborns, the short-term component accounts for an increasing proportion of the activity entering the blood with decreasing age (Table 106). The dose

Table 105. Parameters used for model of biokinetics of iodine

Age	Uptake by thyroid (%)	Faecal excretion (%)	Biological half-time (days)			'Apparent half- time' (days)
			Blood (T_a)	Thyroid (T_b)	Rest of body (T_c)	Thyroid[a]
3 months	30	20	0.25	11.2	1.12	15
1 year	30	20	0.25	15	1.5	20
5 years	30	20	0.25	23	2.3	30
10 years	30	20	0.25	58	5.8	70
15 years	30	20	0.25	67	6.7	80
Adult	30[b]	20	0.25[b]	80[b]	12[b]	91

From ICRP (1989)
[a] 2–16 days after intake
[b] From ICRP (1979)

Table 106. Biokinetics of caesium

Age	Total body distribution (%)		Total body biological half-time (days)	
	A	B	A	B
3 months	–	100	–	16
1 year	–	100	–	13
5 years	45	55	9.1	30
10 years	30	70	5.8	50
15 years	13	87	2.2	93
Adult[a]	10	90	2	110

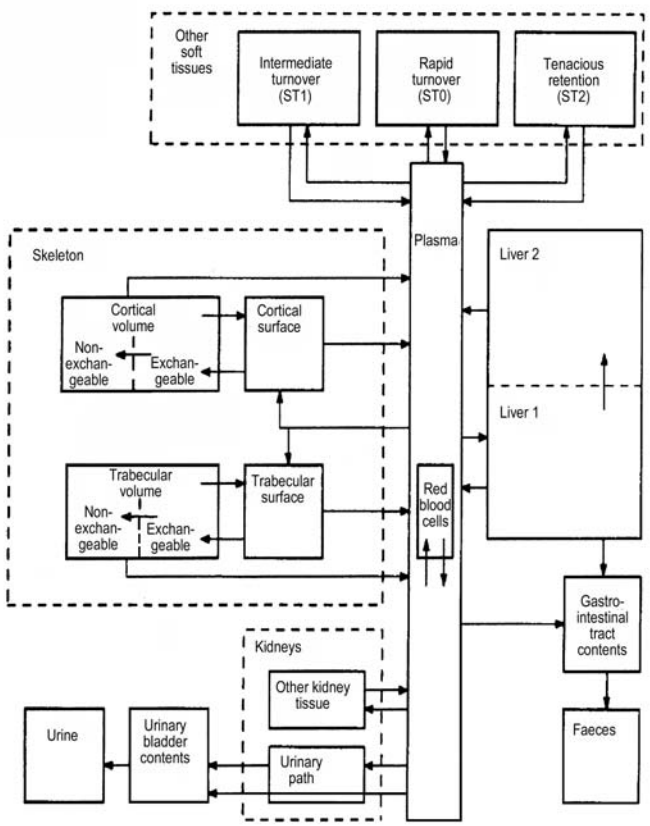
From ICRP (1989). A, short-term component; B, long-term component
[a] From ICRP (1979); the half-time of 110 days would yield a conservative estimate for women

coefficients for ^{137}Cs are largely independent of age, the maximum difference being less than a factor of two, because the shorter biological half-times at younger ages counteract the effect of smaller body mass (ICRP, 1989).

(iv) *Alkaline earth elements*

The model shown in Figure 12 was applied by ICRP (1989, 1993c, 1995a,b) to the alkaline earth elements calcium, strontium, barium and radium and to lead and uranium. Some features added to the model to enable its extension to the latter two elements do not apply to the alkaline earth elements. Thus, retention in red blood cells and kidneys is not considered for the alkaline earth elements, and the liver is included with other soft tissues.

Figure 12. Model for the biokinetics of alkaline earth elements (and Pb and U)



From ICRP (1993c)

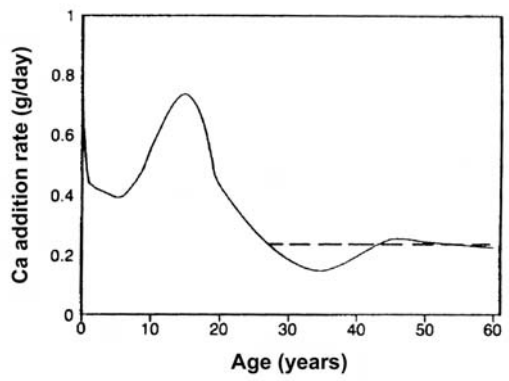
From blood, 25% of each alkaline earth element is assumed to deposit on bone surfaces in adults. A large proportion (60% for strontium, 68% for calcium) is deposited in soft tissues, mostly with a rapid turnover (ST0) with a half-time of retention of a few hours (representative of tissue fluids), and the remainder is excreted in the urine and faeces. About three times more strontium is excreted in the urine than calcium, as a result of less efficient reabsorption by kidney tubules; that is, the kidneys discriminate against strontium. The faecal excretion of calcium and strontium is similar.

Much of the bone surface deposit returns to blood plasma over the next few days, but a fraction is transferred inside the bone. Radionuclides returning to plasma from bone surfaces or soft tissues are available for uptake by these tissues again or for excretion. Cortical and trabecular regions of bone are distinguished, although many of the parameters used for these compartments are the same. Bone volume is separated into

'exchangeable' and 'non-exchangeable' regions, and discrimination among the alkaline earth elements by bone is accounted for by fractional transfer of activity from exchangeable to non-exchangeable bone volume. It is assumed in effect that the elements are equally likely to become temporarily incorporated into bone mineral but that the likelihood of reaching non-exchangeable sites in bone crystal decreases in the order calcium > strontium > barium > radium (fractional transfers exchangeable → non-exchangeable of 0.6, 0.5, 0.3 and 0.2, respectively). Release from non-exchangeable bone volume is assumed to result from the relatively slow process of bone turnover, involving resorption and remodelling. In adults, the bone turnover rates are assumed to be 3% per year for cortical bone and 18% per year for trabecular bone (ICRP, 1995b).

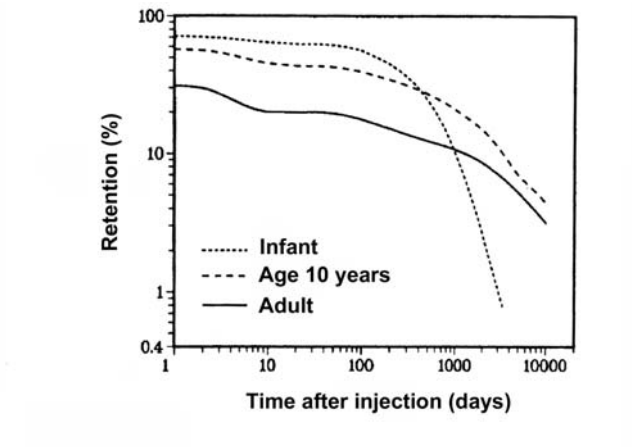
There are extensive data for humans and animals indicating that there is greater early retention of alkaline earth elements in growing than in mature individuals and that much of the variation with age is due to increased uptake by the immature skeleton. However, individuals exposed at younger ages also have a higher rate of loss of these elements from the skeleton than do mature individuals, owing to their higher rate of bone turnover. Accordingly, the most important changes to the model parameters to account for intake by infants and children are increased initial deposition in the skeleton in relation to the calcium addition rate (Figure 13) and increased release of elements from the non-exchangeable bone volume, proportional to the bone turnover rate. Figure 14 illustrates the resulting retention of strontium in the skeleton after intake at different ages, showing the higher initial uptake but more rapid subsequent loss after intake at younger ages.

Figure 13. Estimated calcium addition rate to the human skeleton as a function of age



From Leggett (1992a)

Figure 14. Model predictions for the retention of strontium in the skeleton as a function of time after entry into blood (% total entering blood)



From ICRP (1993c)

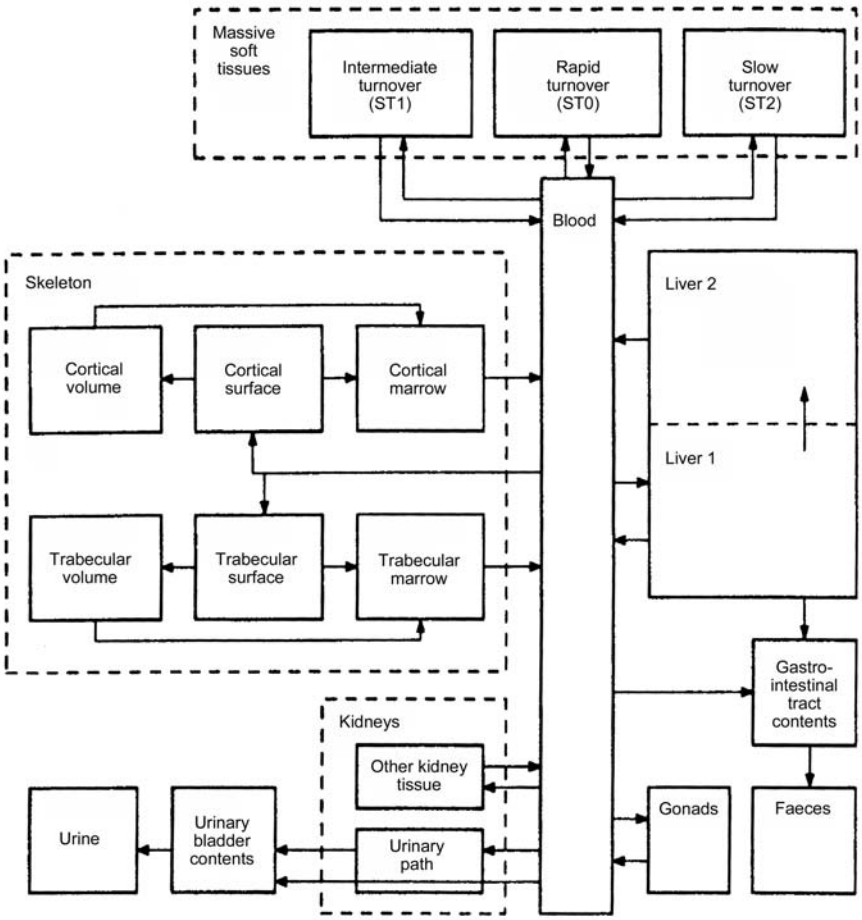
(v) *Actinide elements*

After absorption to blood, the principal sites of deposition of plutonium and related elements are the skeleton and liver. ICRP (1979) assumed that, for adults, 45% of the absorbed dose from blood is deposited in skeleton and in the liver, a small amount is deposited in gonads (0.042% in testis, 0.01% in ovary), and the remainder is promptly excreted. The half-times of retention were assumed to be 100 years for the skeleton and 40 years for the liver; no loss was considered to occur from gonads. In the skeleton, plutonium and related elements were treated as bone-surface seekers; that is, they remain on bone surfaces throughout their retention in the skeleton.

ICRP (1989, 1993c) later developed a physiologically realistic, age-dependent model and applied it to plutonium, americium and neptunium and subsequently to thorium and curium (ICRP, 1995a,b). The model (Figure 15) is similar to that for the alkaline earth elements with respect to the compartments considered, the main difference being in the migration of elements within the skeleton. The model is based on and validated against data in humans and animals for the behaviour of the actinide elements.

The main differences between plutonium and the other elements with regards to the parameters used in the model are in the rates of urinary and faecal excretion (e.g. plutonium < americium < neptunium for urinary excretion), the proportions deposited in the skeleton and liver and retention by the liver. The main age-dependent differences are in the relative proportions deposited in the skeleton and liver and the rates of migration in the skeleton (and hence skeletal retention). Table 107 illustrates the age dependence of uptake of plutonium and americium by the skeleton and liver.

Figure 15. Model for the biokinetics of actinide elements, Pu, Am, Cm, Th and Np



From ICRP (1993c)

Table 107. Age-dependent uptake of Pu and Am by the skeleton and liver (% reaching blood), excluding 4% Pu and 7% Am excreted

Tissue	Infant (3 months)		Child (1–15 years)		Adult (20 years)	
	Pu	Am	Pu	Am	Pu	Am
Liver	10	10	20	30	30	50
Skeleton	70	70	60	50	50	30

From ICRP (1993c)

As in the model for the alkaline earth elements, cortical and trabecular regions of the skeleton are treated separately, with initial deposition on bone surfaces. While subsequent migration of the alkaline earth elements to the interior of the bone is related to the chemical processes involved in the transfer of calcium to bone crystal, incorporation of plutonium and related elements into bone volume depends on burial by surface deposition of new bone. Different regions of bone surfaces may be growing by the deposition of new bone (by osteoblasts), losing mineral by resorption (by osteoclasts) or resting.

There is evidence that plutonium removed from the bone surfaces may be retained in bone marrow. Accordingly, the model considers transfer of actinide elements to bone volume and to bone marrow. It also includes transfer from bone volume to bone marrow due to resorption. Activity is eventually released from bone marrow to blood and becomes available for recycling to all tissues, including the skeleton. For simplicity, the rates of bone growth and resorption are taken to be the same and to show the same age-dependence.

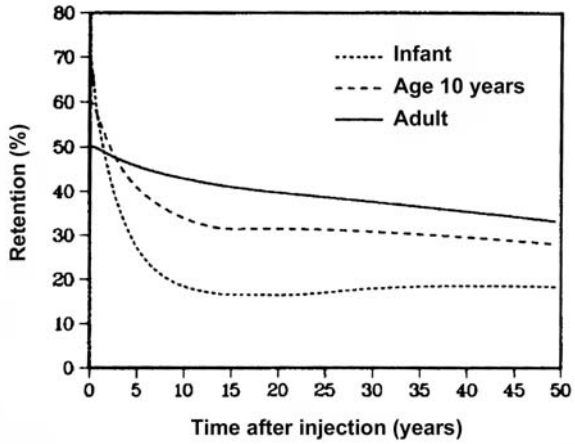
The liver has two compartments in the model, for all elements except americium and curium, for which one compartment is used. Activity is taken up by Liver 1 and transferred to Liver 2, except for a small proportion that is removed to blood or excreted in bile to the gastrointestinal tract. Material leaving Liver 2 is released to blood. Uptake and retention in the gonads is similar to that assumed in the previous models of ICRP (1979). Figures 16 and 17 illustrate the retention of Pu in the skeleton and liver predicted by the model for different ages at intake. The predictions of the model are consistent with data for autopsy samples from occupationally exposed persons. The model is also consistent with the data on urinary and faecal excretion (ICRP, 1993c).

(*e*) *Dose coefficients*

Having established the distribution of radionuclides between body organs and tissues and the time course of their retention, the resulting distribution of the absorbed energy and absorbed dose, defined as absorbed energy per unit mass (expressed in J/kg or Gy), can be calculated. For non-penetrating radiations, the energy is usually deposited largely in the region in which the radionuclide is located. For penetrating radiations, however, it is necessary to take account of 'cross-fire' between tissues. This is done by using a 'mathematical phantom' (i.e. a phantom that can be described with simple mathematical equations), which describes the geometric relationship between the different tissues and organs of the body. Such phantoms have been developed for various age groups (ICRP, 1989). Tissue doses are commonly integrated over a 50-year period for adults or up to age 70 years for children, and the resulting values are referred to as 'committed doses'.

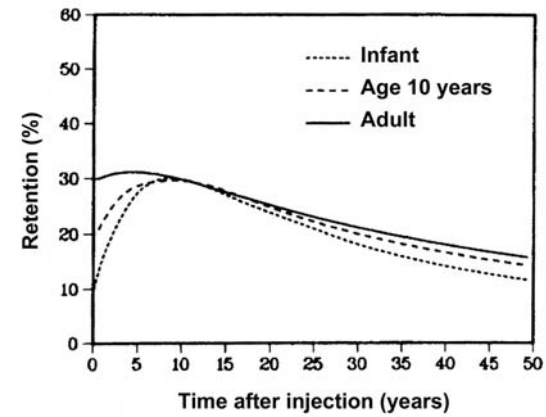
Tables 108–113 give the committed doses to selected tissues (in Gy per Bq of radioactivity) for intakes by adult members of the public by inhalation or ingestion. ICRP (1995a,b) specified default assumptions for the solubility of inhaled radionuclides: type M is assumed for all the radionuclides considered here except isotopes of caesium and iodine (type F) and thorium (type S). The values used for the fractional absorption of ingested radionuclides are as shown in Table 103.

Figure 16. Model predictions for the retention of plutonium in the skeleton as a function of time after entry into blood (% total entering blood)



From ICRP (1993c)

Figure 17. Model predictions for the retention of plutonium in the liver as a function of time after entry into blood (% total entering blood)



From ICRP (1993c)

The doses received vary from a low value of 1.8×10^{-11} Gy/Bq from inhaled or ingested $^{3}H_2O$, with uniform dose to all tissues, to a high value of about 8×10^{-5} Gy/Bq to bone surfaces from inhaled ^{239}Pu or ^{241}Am.

Table 108. Committed doses from inhalation of β- and γ-emitting radionuclides by adults (Gy/Bq)

Nuclide	Lung	Stomach	Colon	Liver	Red bone marrow	Bone surface	Testis	Thyroid
^{3}H								
$^{3}H_2O$	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}
Organically bound	4.1×10^{-11}	4.1×10^{-11}	4.1×10^{-11}	4.1×10^{-11}	4.1×10^{-11}	4.1×10^{-11}	4.1×10^{-11}	4.1×10^{-11}
^{14}C	1.6×10^{-8}	8.2×10^{-11}	4.1×10^{-10}	6.8×10^{-11}	6.8×10^{-11}	6.8×10^{-11}	6.8×10^{-11}	6.8×10^{-11}
^{32}P	2.4×10^{-8}	3.4×10^{-10}	1.2×10^{-9}	1.7×10^{-10}	2.1×10^{-9}	2.1×10^{-9}	1.7×10^{-10}	1.7×10^{-10}
^{35}S	1.2×10^{-8}	2.1×10^{-11}	3.4×10^{-11}	7.7×10^{-12}	7.7×10^{-12}	7.7×10^{-12}	7.7×10^{-12}	7.7×10^{-12}
^{67}Ga	1.6×10^{-9}	2.6×10^{-11}	2.5×10^{-10}	1.8×10^{-11}	1.7×10^{-11}	4.5×10^{-11}	3.8×10^{-12}	8.1×10^{-12}
^{89}Sr	4.5×10^{-8}	2.0×10^{-10}	3.9×10^{-9}	4.6×10^{-11}	1.1×10^{-9}	1.4×10^{-9}	4.6×10^{-11}	4.6×10^{-11}
^{90}Sr	2.1×10^{-7}	3.8×10^{-10}	5.2×10^{-9}	2.8×10^{-10}	7.0×10^{-8}	1.6×10^{-7}	2.8×10^{-10}	2.8×10^{-10}
^{99}Tc	3.2×10^{-8}	5.2×10^{-10}	8.9×10^{-10}	1.2×10^{-11}	9.2×10^{-12}	9.2×10^{-12}	9.2×10^{-12}	2.4×10^{-10}
^{125}I	1.5×10^{-11}	1.1×10^{-11}	1.6×10^{-11}	8.9×10^{-12}	1.2×10^{-11}	6.0×10^{-11}	7.9×10^{-12}	1.0×10^{-7}
^{131}I	6.0×10^{-11}	4.0×10^{-11}	2.5×10^{-11}	1.7×10^{-11}	3.7×10^{-11}	4.6×10^{-11}	1.4×10^{-11}	1.5×10^{-7}
^{137}Cs	4.3×10^{-9}	4.4×10^{-9}	5.1×10^{-9}	4.6×10^{-9}	4.4×10^{-9}	4.6×10^{-9}	4.2×10^{-9}	4.4×10^{-9}
^{141}Ce	2.4×10^{-8}	9.8×10^{-11}	1.2×10^{-9}	1.4×10^{-9}	2.9×10^{-10}	2.9×10^{-9}	2.1×10^{-11}	3.8×10^{-11}
^{144}Ce	1.9×10^{-7}	2.1×10^{-9}	1.2×10^{-8}	1.4×10^{-7}	2.8×10^{-8}	4.9×10^{-8}	1.7×10^{-9}	1.8×10^{-9}
^{186}Re	6.4×10^{-9}	1.2×10^{-9}	9.1×10^{-10}	3.2×10^{-11}	2.4×10^{-11}	2.6×10^{-11}	2.3×10^{-11}	1.1×10^{-9}
^{188}Re	2.0×10^{-9}	1.0×10^{-9}	6.4×10^{-10}	2.4×10^{-11}	1.9×10^{-11}	1.9×10^{-11}	1.8×10^{-11}	1.5×10^{-9}

Default assumptions for members of the public: H is vapour and completely absorbed; 1-μm activity mean aerodynamic diameter aerosol for others; type F for Cs and I; type M for all others

Table 109. Committed doses from ingestion of β- and γ-emitting radionuclides by adults (Gy/Bq)

Nuclide	Lung	Stomach	Colon	Liver	Red bone marrow	Bone surface	Testis	Thyroid
^{3}H								
$^{3}H_2O$	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}	1.8×10^{-11}
Organically bound	4.1×10^{-11}	4.8×10^{-11}	4.3×10^{-11}	4.8×10^{-11}	4.8×10^{-11}	4.8×10^{-11}	4.8×10^{-11}	4.8×10^{-11}
^{14}C	5.7×10^{-11}	6.3×10^{-11}	5.9×10^{-11}	5.7×10^{-11}	5.7×10^{-11}	5.7×10^{-11}	5.7×10^{-11}	5.7×10^{-11}
^{32}P	6.7×10^{-10}	1.5×10^{-9}	5.6×10^{-9}	6.7×10^{-10}	8.2×10^{-9}	8.2×10^{-9}	6.7×10^{-10}	6.7×10^{-10}
^{35}S								
Inorganic	9.6×10^{-11}	1.5×10^{-10}	2.5×10^{-10}	9.6×10^{-11}	9.6×10^{-11}	9.6×10^{-11}	9.6×10^{-11}	9.6×10^{-11}
Organic	7.6×10^{-10}	8.1×10^{-10}	8.3×10^{-10}	7.6×10^{-10}	7.6×10^{-10}	7.6×10^{-10}	7.6×10^{-10}	7.6×10^{-10}
^{67}Ga	2.2×10^{-12}	8.9×10^{-11}	1.2×10^{-9}	1.3×10^{-11}	2.6×10^{-11}	1.9×10^{-11}	1.2×10^{-11}	1.9×10^{-13}
^{89}Sr	2.0×10^{-10}	8.8×10^{-10}	1.4×10^{-8}	2.0×10^{-10}	4.8×10^{-9}	6.0×10^{-9}	2.0×10^{-10}	2.0×10^{-10}
^{90}Sr	6.6×10^{-10}	9.1×10^{-10}	1.3×10^{-8}	6.6×10^{-10}	1.8×10^{-7}	4.0×10^{-7}	6.6×10^{-10}	6.6×10^{-10}
^{99}Tc	3.9×10^{-11}	2.2×10^{-9}	2.5×10^{-9}	5.2×10^{-11}	3.9×10^{-11}	3.9×10^{-11}	3.9×10^{-11}	1.0×10^{-9}
^{125}I	4.1×10^{-11}	6.3×10^{-11}	5.5×10^{-11}	2.6×10^{-11}	3.3×10^{-11}	1.7×10^{-10}	2.3×10^{-11}	3.1×10^{-7}
^{131}I	1.0×10^{-10}	3.1×10^{-10}	1.2×10^{-10}	4.9×10^{-11}	1.0×10^{-10}	1.3×10^{-10}	4.0×10^{-11}	4.3×10^{-7}
^{137}Cs	1.3×10^{-8}	1.3×10^{-8}	1.5×10^{-8}	1.4×10^{-8}	1.3×10^{-8}	1.4×10^{-8}	1.3×10^{-8}	1.3×10^{-8}
^{141}Ce	1.4×10^{-12}	2.3×10^{-10}	5.5×10^{-9}	2.4×10^{-11}	1.9×10^{-11}	4.9×10^{-11}	7.9×10^{-12}	2.9×10^{-13}
^{144}Ce	1.3×10^{-11}	1.1×10^{-9}	4.2×10^{-8}	9.6×10^{-10}	1.9×10^{-10}	3.3×10^{-10}	1.7×10^{-11}	1.2×10^{-11}
^{186}Re	5.4×10^{-9}	5.4×10^{-9}	4.2×10^{-9}	1.3×10^{-10}	9.9×10^{-11}	1.0×10^{-10}	9.8×10^{-11}	4.8×10^{-9}
^{188}Re	7.9×10^{-11}	4.8×10^{-9}	3.1×10^{-9}	1.1×10^{-10}	8.0×10^{-11}	8.1×10^{-11}	7.9×10^{-11}	6.6×10^{-9}

Table 110. Committed doses from inhalation of α-emitting radionuclides by adults (Gy/Bq)

Nuclide	LET[a]	Lung	Stomach	Colon	Liver	Red bone marrow	Bone surface	Testis	Thyroid
^{210}Po	High	1.3×10^{-6}	2.5×10^{-9}	2.9×10^{-9}	5.8×10^{-8}	2.3×10^{-8}	1.4×10^{-8}	2.4×10^{-9}	2.4×10^{-9}
^{211}At	High	4.4×10^{-8}	1.3×10^{-10}	1.1×10^{-10}	1.1×10^{-10}	1.1×10^{-10}	1.1×10^{-10}	1.1×10^{-10}	1.1×10^{-10}
^{212}Bi	High	9.8×10^{-9}	9.3×10^{-12}	3.3×10^{-12}	9.4×10^{-13}	9.4×10^{-13}	9.4×10^{-13}	9.4×10^{-13}	9.4×10^{-13}
	Low	1.5×10^{-10}	8.7×10^{-11}	2.7×10^{-11}	2.5×10^{-12}	2.5×10^{-12}	1.9×10^{-12}	4.3×10^{-13}	1.9×10^{-12}
^{224}Ra	High	1.2×10^{-6}	1.7×10^{-10}	1.4×10^{-9}	6.7×10^{-10}	2.0×10^{-9}	2.1×10^{-8}	1.2×10^{-10}	1.3×10^{-10}
	Low	1.3×10^{-8}	1.1×10^{-10}	3.8×10^{-9}	1.4×10^{-10}	1.8×10^{-10}	2.6×10^{-10}	2.9×10^{-11}	6.1×10^{-11}
^{226}Ra	High	1.4×10^{-6}	1.2×10^{-9}	2.0×10^{-9}	5.3×10^{-9}	2.6×10^{-8}	3.7×10^{-7}	1.2×10^{-9}	1.2×10^{-9}
	Low	2.1×10^{-9}	3.8×10^{-10}	2.6×10^{-9}	4.7×10^{-10}	6.5×10^{-9}	1.6×10^{-8}	3.2×10^{-10}	5.7×10^{-10}
^{228}Ra	High	4.8×10^{-7}	1.0×10^{-8}	1.5×10^{-8}	1.2×10^{-7}	2.3×10^{-7}	2.8×10^{-6}	2.5×10^{-8}	1.0×10^{-8}
	Low	1.2×10^{-7}	2.6×10^{-9}	1.9×10^{-8}	7.7×10^{-9}	2.1×10^{-8}	3.9×10^{-8}	1.4×10^{-9}	2.4×10^{-9}

Default assumptions for members of the public: 1-μm activity mean aerodynamic diameter aerosol; type M for each nuclide. LET, linear energy transfer

[a] Doses from high-LET α- and low-LET β- or γ-radiation given separately; low LET not shown when < 1%

Table 111. Committed doses from ingestion of α-emitting radionuclides by adults (Gy/Bq)

Nuclide	LET[a]	Lung	Stomach	Colon	Liver	Red bone marrow	Bone surface	Testis	Thyroid
^{210}Po	High	1.4×10^{-8}	1.4×10^{-8}	1.5×10^{-8}	3.3×10^{-7}	1.3×10^{-7}	8.0×10^{-8}	1.4×10^{-8}	1.4×10^{-8}
^{211}At	High	5.3×10^{-10}	6.0×10^{-10}	5.4×10^{-10}	5.3×10^{-10}	5.3×10^{-10}	5.3×10^{-10}	5.3×10^{-10}	5.3×10^{-10}
^{212}Bi	High	3.4×10^{-13}	5.4×10^{-11}	1.4×10^{-11}	3.4×10^{-13}	3.4×10^{-13}	3.4×10^{-13}	3.4×10^{-13}	3.4×10^{-13}
	Low	2.7×10^{-12}	5.3×10^{-10}	1.6×10^{-10}	6.2×10^{-12}	6.1×10^{-12}	2.9×10^{-12}	1.5×10^{-12}	3.6×10^{-13}
^{224}Ra	High	5.4×10^{-10}	7.5×10^{-10}	6.3×10^{-9}	2.8×10^{-9}	8.3×10^{-9}	8.7×10^{-8}	5.2×10^{-10}	5.4×10^{-10}
	Low	6.0×10^{-11}	2.0×10^{-10}	1.6×10^{-8}	2.4×10^{-10}	5.4×10^{-10}	8.7×10^{-10}	1.2×10^{-10}	4.6×10^{-11}
^{226}Ra	High	2.0×10^{-9}	2.0×10^{-9}	4.6×10^{-9}	8.9×10^{-9}	4.3×10^{-8}	6.2×10^{-7}	2.0×10^{-9}	2.0×10^{-9}
	Low	9.3×10^{-10}	6.4×10^{-10}	7.1×10^{-10}	7.7×10^{-10}	1.1×10^{-8}	2.7×10^{-8}	5.5×10^{-10}	9.5×10^{-10}
^{228}Ra	High	7.4×10^{-9}	7.4×10^{-9}	8.6×10^{-9}	5.2×10^{-8}	1.1×10^{-7}	1.1×10^{-6}	1.0×10^{-8}	7.4×10^{-9}
	Low	1.9×10^{-9}	1.7×10^{-9}	2.0×10^{-8}	4.1×10^{-9}	2.4×10^{-8}	4.0×10^{-8}	1.3×10^{-9}	1.8×10^{-9}

[a] Doses from high-LET α- and low-LET β- and γ-radiation given separately; low LET not shown when < 1%

Table 112. Committed doses from inhalation of α-emitting actinide radionuclides by adults (Gy/Bq)

Nuclide	LET[a]	Lung	Stomach	Colon	Liver	Red bone marrow	Bone surface	Testis	Thyroid
^{232}Th	High	8.0×10^{-6}	4.0×10^{-8}	4.4×10^{-8}	2.5×10^{-7}	6.2×10^{-7}	1.4×10^{-5}	1.3×10^{-7}	4.0×10^{-8}
	Low	5.5×10^{-7}	1.1×10^{-8}	1.5×10^{-8}	1.8×10^{-8}	3.8×10^{-8}	1.1×10^{-7}	3.2×10^{-9}	9.9×10^{-9}
^{234}U	High	1.4×10^{-6}	6.8×10^{-9}	7.2×10^{-9}	2.7×10^{-8}	2.0×10^{-8}	1.9×10^{-7}	6.8×10^{-9}	6.8×10^{-9}
^{235}U	High	1.2×10^{-6}	6.3×10^{-9}	6.6×10^{-9}	2.5×10^{-8}	1.9×10^{-8}	1.8×10^{-7}	6.3×10^{-9}	6.3×10^{-9}
	Low	5.5×10^{-8}	7.7×10^{-10}	1.9×10^{-9}	2.0×10^{-9}	4.8×10^{-9}	1.3×10^{-8}	5.0×10^{-10}	7.4×10^{-10}
^{238}U	High	1.1×10^{-6}	6.0×10^{-9}	6.3×10^{-9}	2.4×10^{-8}	1.8×10^{-8}	1.7×10^{-7}	6.0×10^{-9}	6.0×10^{-9}
	Low	1.2×10^{-7}	1.4×10^{-9}	2.5×10^{-9}	5.6×10^{-9}	1.9×10^{-8}	4.6×10^{-8}	1.6×10^{-9}	1.4×10^{-9}
^{237}Np	High	1.4×10^{-6}	6.7×10^{-8}	6.7×10^{-8}	8.2×10^{-7}	2.0×10^{-6}	5.1×10^{-5}	6.9×10^{-7}	6.7×10^{-8}
	Low	6.0×10^{-8}	9.3×10^{-9}	1.3×10^{-8}	5.9×10^{-8}	1.6×10^{-7}	2.6×10^{-6}	4.5×10^{-8}	1.1×10^{-8}
^{238}Pu	High	1.8×10^{-6}	1.2×10^{-7}	1.2×10^{-6}	1.5×10^{-5}	3.4×10^{-6}	7.0×10^{-5}	9.3×10^{-7}	1.2×10^{-7}
^{239}Pu	High	1.7×10^{-6}	1.4×10^{-7}	1.4×10^{-7}	1.6×10^{-5}	3.7×10^{-6}	7.7×10^{-5}	1.0×10^{-6}	1.4×10^{-7}
^{241}Am	High	1.9×10^{-6}	1.4×10^{-7}	1.4×10^{-7}	5.2×10^{-6}	2.9×10^{-6}	8.0×10^{-5}	1.6×10^{-6}	1.4×10^{-7}
	Low	1.2×10^{-8}	2.6×10^{-9}	3.6×10^{-9}	6.3×10^{-8}	4.0×10^{-8}	8.4×10^{-7}	1.8×10^{-8}	2.8×10^{-9}
^{244}Cm	High	2.0×10^{-6}	6.4×10^{-8}	6.5×10^{-8}	3.8×10^{-6}	1.9×10^{-6}	4.6×10^{-5}	9.1×10^{-7}	6.4×10^{-8}

Default assumptions for members of the public: 1-μm activity mean aerodynamic diameter aerosol; type S for Th; type M for all others

[a] Doses from high-LET α- and low-LET β- and γ-radiation given separately; low LET not shown when < 1%

Table 113. Committed doses from ingestion of α-emitting actinide radionuclides by adults (Gy/Bq)

Nuclide	LET[a]	Lung	Stomach	Colon	Liver	Red bone marrow	Bone surface	Testis	Thyroid
^{232}Th	High	1.8×10^{-9}	1.8×10^{-9}	3.1×10^{-9}	9.2×10^{-9}	2.3×10^{-8}	5.9×10^{-7}	5.4×10^{-9}	1.8×10^{-9}
	Low	1.8×10^{-10}	1.7×10^{-10}	7.8×10^{-10}	2.5×10^{-10}	1.2×10^{-9}	4.6×10^{-9}	1.3×10^{-10}	1.9×10^{-10}
^{234}U	High	1.4×10^{-9}	1.4×10^{-9}	2.9×10^{-9}	5.4×10^{-9}	4.0×10^{-9}	3.9×10^{-8}	1.4×10^{-9}	1.4×10^{-9}
^{235}U	High	1.3×10^{-9}	1.3×10^{-9}	2.6×10^{-9}	5.0×10^{-9}	3.7×10^{-9}	3.7×10^{-8}	1.3×10^{-9}	1.3×10^{-9}
	Low	1.3×10^{-10}	2.2×10^{-10}	4.8×10^{-9}	3.4×10^{-10}	9.6×10^{-10}	2.6×10^{-9}	1.2×10^{-10}	1.2×10^{-10}
^{238}U	High	1.2×10^{-9}	1.3×10^{-9}	2.5×10^{-9}	4.7×10^{-9}	3.6×10^{-9}	3.5×10^{-8}	1.2×10^{-9}	1.2×10^{-9}
	Low	2.6×10^{-10}	2.8×10^{-10}	1.7×10^{-9}	1.0×10^{-9}	3.2×10^{-9}	8.3×10^{-9}	2.6×10^{-10}	2.6×10^{-10}
^{237}Np	High	3.5×10^{-10}	4.1×10^{-10}	1.9×10^{-9}	4.3×10^{-9}	1.0×10^{-8}	2.7×10^{-7}	3.7×10^{-9}	3.5×10^{-10}
	Low	6.1×10^{-11}	1.4×10^{-10}	2.7×10^{-9}	3.1×10^{-10}	8.4×10^{-10}	1.4×10^{-8}	2.4×10^{-10}	5.7×10^{-11}
^{238}Pu	High	6.4×10^{-10}	7.1×10^{-10}	2.4×10^{-9}	7.8×10^{-8}	1.8×10^{-8}	3.7×10^{-7}	4.9×10^{-9}	6.4×10^{-10}
^{239}Pu	High	7.2×10^{-10}	7.8×10^{-10}	2.4×10^{-9}	8.6×10^{-8}	2.0×10^{-8}	4.1×10^{-7}	5.5×10^{-9}	7.2×10^{-10}
^{241}Am	High	7.6×10^{-10}	8.3×10^{-10}	2.5×10^{-9}	2.8×10^{-8}	1.5×10^{-8}	4.5×10^{-7}	8.7×10^{-9}	7.6×10^{-10}
	Low	1.9×10^{-11}	8.8×10^{-11}	1.9×10^{-9}	3.4×10^{-10}	2.2×10^{-10}	4.4×10^{-9}	9.9×10^{-11}	1.5×10^{-11}
^{244}Cm	High	3.4×10^{-10}	4.1×10^{-10}	2.2×10^{-9}	2.0×10^{-8}	1.0×10^{-8}	2.5×10^{-7}	4.8×10^{-9}	3.4×10^{-10}

[a] Doses from high-LET α- and low-LET β- and γ-radiation given separately; low LET not shown when < 1%

The values given for ^{3}H, inhaled as either $^{3}H_2O$ or organically bound, are for intakes as a vapour, with complete absorption to blood. The doses are therefore the same. For very soluble radionuclides such as ^{137}Cs and ^{131}I, the doses from ingestion are higher than those from inhalation, because the ingested radionuclide is assumed to be completely absorbed to the blood while a proportion of the inhaled material is immediately exhaled (see Table 102). For the least soluble radionuclides, including those of thorium, plutonium and other actinides, the doses are greater after inhalation because of their low absorption to blood from the intestine (see Table 103) and their longer retention in the lungs.

While a number of radionuclides, including ^{3}H, ^{14}C and ^{137}Cs, deliver similar doses to all tissues, many others deliver most of their dose to a small number of tissues. The radioiodines ^{125}I and ^{131}I deliver more than 99% of their dose to the thyroid gland. Ingested ^{90}Sr delivers most of its dose (> 90%) to bone surfaces and red bone marrow. Inhaled ^{90}Sr delivers about half of its dose to the lungs and half to bone surfaces and red bone marrow. For inhaled ^{89}Sr, because of its shorter half-life (50 days as compared with 29 years for ^{90}Sr), a greater proportion of the dose is delivered to the lungs. Similar considerations apply to doses from isotopes of radium and differences between ^{224}Ra (half-life, 3.6 days) and ^{226}Ra (half-life, 1600 years).

The presentation of committed doses conceals differences between the radionuclides in the temporal pattern of dose delivery, resulting from differences in their physical half-lives and their retention times in tissues. For example, doses from ^{3}H as $^{3}H_2O$ or organic matter are delivered in weeks or months because of their short retention times; doses from ^{89}Sr are negligible the first year after intake because of the short half-life of this radionuclide, while doses from ^{90}Sr and particularly from actinide isotopes such as ^{239}Pu and ^{241}Am are delivered over the entire 50-year integration period specified for calculation of the committed dose.

ICRP do not give dose coefficients for ^{222}Rn and its progeny; however, various estimates have been made of the doses delivered under various conditions of exposure. The doses to the lungs from exposure to radon and its progeny are usually expressed in terms of working-level months (WLM). The values given by Birchall and James (1994) and Marsh and Birchall (2000) allow calculation of the doses to the lung after inhalation of radon progeny as about 3×10^{-9} Gy/Bq ^{222}Rn after exposures in mines and about 5×10^{-9} Gy/Bq ^{222}Rn after domestic exposures. The higher value after domestic exposure is attributable to the larger contribution to the dose from unattached decay products. An analysis of the doses from ingested and inhaled radon gas suggests that the dose to the stomach dominates after exposure by ingestion, with a value of about 4×10^{-9} Gy/Bq, and that the red bone marrow may receive doses of approximately 6×10^{-11} Gy/Bq after ingestion and 2×10^{-11} Gy/Bq after inhalation (Khursheed, 2000).

4.1.24 *Models for the embryo and fetus*

ICRP task groups are developing models for embryos and fetuses; the approaches being used are described briefly below.

(*a*) *Dosimetry*

Implantation in the uterus occurs 2–3 days after the fertilized egg enters the uterus or about six days after fertilization. The implanted embryo is imbedded in the epithelial lining of the uterus and becomes closely surrounded by maternal tissue, the progressive erosion of this tissue constituting a source of nourishment for the embryo before development of the placenta. The period of organ formation in the embryo may be considered to last up to about the end of the second month, at which time the developing embryo still weighs less than 10 g. Because of the close apposition between the embryo and the uterine wall, it may be assumed, in the absence of more specific information, that the dose to the embryo up to the end of the second month of gestation can be approximated by the dose to the uterus.

The mass of the fetus increases rapidly from eight weeks to term at 38 weeks (birth). Calculation of doses to the fetus requires consideration of contributions from 'cross-fire' from penetrating radiation emitted in maternal organs and tissues and contributions from penetrating and non-penetrating radiations from radionuclides incorporated into the fetus. The absorbed fractions resulting from cross-fire from maternal tissues have been calculated for the fetus (average for all tissues) by the use of geometric 'phantoms' for the first, second and third trimesters of pregnancy. The doses to fetal organs and tissues from radionuclides retained in the fetus depend on the masses of the organs and tissues during the period of interest and the geometric relationships between them. Postnatal doses from activity retained in the fetus at term are also calculated.

Dose coefficients will be provided for maternal intakes by ingestion or inhalation, for long-term and single intake, before and during pregnancy for radioisotopes of the 31 elements considered in ICRP publications (ICRP, 1989, 1993c, 1995a,b).

(*b*) *Biokinetics*

For a number of radioactive elements, sufficient data for humans and animals exist to allow the development of specific models of transfer to the fetus. This applies principally to iodine and the alkaline earth elements. These models account for placental transfer throughout the fetal period and distribution within the fetus. A general approach has been applied to all other elements on the basis of limited data. The concentrations of the element in maternal and fetal tissues are compared, and doses are calculated from the ratio of the whole-body concentrations in the fetus and the mother (C_F/C_M).

For plutonium and related elements, C_F:C_M ratios are specified for each trimester. The distribution of activity between fetal organs and tissues is taken to be the same as that specified for three-month-old infants (ICRP 1989, 1993c, 1995a,b). The concentrations in the placenta may contribute doses to the fetus in some cases; the placental concentrations are specified as C_{Pl}:C_M ratios (Table 114).

Table 114. Ratios of concentrations of elements in the fetus and the mother (C_F:C_M) for intake before or during pregnancy

Element	Intake	
	Before pregnancy	During pregnancy
^{3}H	1.4	1.4
Cs	1	1
Pu	0.03	0.1/0.3/1[a]
Am	0.01	0.1

Modified from Stather & Phipps (1998)
[a] 1st, 2nd and 3rd trimesters

A model for the transfer of alkaline earth elements is being developed (Fell *et al.*, 1998), which takes into account information on: (i) calcium deposition in the human fetus, i.e. skeletal development; (ii) bidirectional flow of calcium and strontium across the placenta (in animals); (iii) the placental content of calcium and strontium (low); (iv) placental discrimination in transfer to the fetus (calcium > strontium > barium > radium); and (v) the following maternal changes during pregnancy: increased gut transfer of radionuclides, increased urinary excretion and increased bone turnover.

Table 115 gives examples of model predictions for strontium reaching maternal blood after ingestion or inhalation. The highest transfer to the fetus, in which 20% of total strontium reaches the maternal blood, occurs after intake late in pregnancy (36

Table 115. Intakes of Sr before conception or during pregnancy

Time of intake	Retention at term (%) in maternal blood		
	Fetus	Mother	C_F:C_M[a]
1 year before conception	0.1	11	0.1
8 weeks	0.3	9	0.5
12 weeks	0.7	9	1
24 weeks	3	16	3
30 weeks	7	18	6
36 weeks	14	26	9
8–38 weeks[b]	5	16	5

From Fell *et al.* (1998)
[a] Fetus:mother whole-body concentration ratio at term
[b] Long-term intake

weeks) and corresponds to a C_F:C_M ratio of 9. For calcium, the corresponding C_F:C_M ratio at 36 weeks is 19. Preliminary estimates of the doses after intake of ^{90}Sr at this late stage of pregnancy gave committed doses, to e.g. the red bone marrow, in offspring that are twice those for adults.

4.1.25 *Studies of decorporation (chelation)*

Several physical methods and a number of pharmacological approaches have been developed for the removal of radioactive materials from the body. The physical approaches include, for example, the use of lung lavage to remove recently inhaled material (Muggenburg *et al.*, 1977). The pharmacological approaches include the use of diuretics to promote urinary excretion and administration of chelating compounds. Various chelating compounds have been described, and their use has been extensively reviewed (Levine, 1979; Bulman, 1990). The presumption in most of these studies is that the likelihood of adverse effects will decrease by accelerating the removal of the radioactive material from the body. Thus, the 'efficacy' of a particular treatment or therapeutic strategy is based on its ability to reduce the body burden of the radioactive material in comparison with that in untreated controls. Table 116 lists some of the compounds used in 'decorporation' studies, the animal model used and the radionuclide targeted.

4.2 Toxic effects

4.2.1 *Deterministic effects*

Incorporated radionuclides may induce a wide variety of deterministic effects in irradiated tissues and organs. These effects, which may be related to carcinogenesis in some tissues (see, e.g., Lord *et al.*, 1991) and may precede neoplasia (Ober *et al.*, 1994), were formerly referred to as non-stochastic effects. Deterministic effects may arise in any tissue or cell system, provided that the radiation dose is sufficient to initiate the necessary cellular and matrix changes. The effects produced by incorporated radionuclides are, in most respects, qualitatively similar to those produced by external irradiation from X-rays, γ-rays and neutrons, although the latter effects are better understood, partly because of the vast experience accumulated from the medical uses of radiation for radiotherapy (see, e.g., Withers, 1986, 1989; IARC, 2000).

Deterministic effects result from cell damage or cell death and give rise to impairment of tissue function. Within any tissue or organ, the effect may be either the direct result of irradiation of component cells or an indirect effect of damage to vascular components. With respect to the latter, damage to blood vessels may be particularly important (Field & Upton, 1985). The extent of tissue damage is a function of the number of damaged cells, and a large number is frequently required to produce the effect (UNSCEAR, 1993). The minimum radiation dose needed to cause enough cellular damage to have an effect is usually more or less well defined and is referred to

Table 116. Studies of 'decorporation' (chelation)

Chelating compound tested	Species	Route of administration	Nuclide(s)	Reference
N-(2,3-Dimercaptopropyl)phthalamidic acid; meso-dimercapto-succinic acid	Rat	Injection	^{210}Po	Bogdan & Aposhian (1990)
2,3-Dimercaptopropanol; *N*,*N*′-diethylamine-*N*-carbodithioate (diethyldithiocarbamate); *N*-(2,3-dimercaptopropyl)phthalamidic acid	Rat	Injection	^{210}Po	Rencova *et al*. (1993)
N,*N*′-Diethylamine-*N*-carbodithioate (diethyldithiocarbamate); *N*,*N*′-di(2-hydroxyethyl)ethylenediamine-*N*,*N*′-biscarbodithioate	Rat	Injection	^{210}Po	Rencova *et al*. (1995)
Alginate	Mouse	Oral	^{226}Ra	Schoeters et al. (1983)
Zn-Diethylenetriaminepentaacetic acid; Ca-diethylenetriamine-pentaacetic acid	Rat	Injection	^{239}Pu, ^{241}Am, ^{242}Cm	Seidel & Volf (1972)
Zn-Diethylenetriaminepentaacetic acid	Mouse	Injection	^{239}Pu	Jones *et al*. (1986)
N^1,N^5,N^{10},N^{15}-Tetrakis(2,3-dihydroxy-4-carboxybenzoyl)tetra-azatetradecane; diethylenetriaminepentaacetic acid (Ca or Zn salt); desferrioxamine	Mouse, rat, hamster	Injection, oral	^{238}Pu, ^{241}Am	Volf (1986)
N^1,N^5,N^{10},N^{15}-Tetrakis(2,3-dihydroxy-4-carboxybenzoyl)tetra-azatetradecane	Mouse, rat, baboon	Injection	^{238}Pu, ^{239}Pu	Gerasimo *et al*. (1986)
Diethylenetriaminepentaacetic acid (Ca or Zn salt)	Rats	Injection, oral	^{238}Pu	Sullivan & Ruemmler (1986)
N^1,N^5,N^{10},N^{15}-Tetrakis(2,3-dihydroxy-4-carboxybenzoyl)tetra-azatetradecane; *N*,*N*′,*N*″,*N*‴-tetra(2,3-dihydroxybenzoyl)-spermine	Mouse	Injection	^{239}Pu	Szot *et al*. (1986)
N^1,N^5,N^{10},N^{15}-Tetrakis(2,3-dihydroxy-4-carboxybenzoyl)tetra-azatetradecane	Mouse	Injection	^{239}Pu	Durbin *et al*. (1989)

Table 116 (contd)

Chelating compound tested	Species	Route of administration	Nuclide(s)	Reference
Zn-Diethylenetriaminepentaacetic acid; Ca-diethylenetriamine-pentaacetic acid	Dog	Injection	^{239}Pu	Bruenger *et al*. (1991b)
Hydroxypyridinone desferrioxamine; dihydroxamic diethylene-triaminepentaacetic acid; diethylenetriaminepentaacetic acid (Ca or Zn salt)	Rat	Injection	^{238}Pu, ^{241}Am	Stradling *et al*. (1991)
Linear hydroxypyridinone derivative, $C_{34}H_{34}O_{12}N_8Na_4$; di-ethylenetriaminepentaacetic acid (Ca or Zn salt)	Rat	Injection	^{238}Pu, ^{241}Am	Stradling *et al*. (1992)
Diethylenetriaminepentaacetic acid (Ca or Zn salt)	Dog	Injection, infusion	$^{238}Pu(NO_3)_4$	Guilmette & Muggenburg (1993)
Docosyltriethylenetetraminepentaacetic acid	Rat	Oral	^{239}Pu	Miller *et al*. (1992)
Docosyltriethylenetetraminepentaacetic acid	Rat	Oral	^{239}Pu, ^{241}Am	Miller *et al*. (1993)
Zn-Diethylenetriaminepentaacetic acid	Rat	Oral	^{238}Pu, ^{241}Am	Gray *et al*. (1995)

as the 'threshold dose' (Field & Upton, 1985). With increasing radiation dose, both the fraction of damaged cells and the severity of the effect increase (UNSCEAR, 1982). This contrasts to radiation-induced cancer, in which the frequency of the effect is a function of radiation dose but the severity is independent of dose. The effects of radiation may be greater in children, whose tissues and organs are rapidly growing, than in adults. In contrast, the severity of the effect decreases with dose protraction; this is attributed to the increased time available for either repair of cell damage or tissue repopulation by undamaged cells (ICRP, 1984). Dose–response curves established for deterministic effects are sigmoidal (UNSCEAR, 1993). The deterministic effects of radiation may be enhanced by administered drugs, e.g. in radiotherapy patients who receive chemotherapy (Withers, 1986). Other factors that affect the expression of deterministic effects include oxygen tension, hormone status, temperature, sex, stress and trauma (Hall, 1978; Elkind, 1980; UNSCEAR, 1982, 1993).

Deterministic effects are commonly initiated by radiation damage to the stem cells within a tissue. As a result, the number of maturing cells and mature, functional cells recruited by the irradiated tissue is reduced, leading to impaired tissue function. The time of onset of overt tissue damage is commonly a function of the cell kinetics, the adverse effects being produced faster in tissues with a rapid turnover of cells, such as the bone marrow, than in tissues and organs comprising cells with long cycle times, such as the liver (Coggle, 1983).

Deterministic effects of radiation are found at the sub-cellular, cellular, tissue and whole-body levels. The most serious short-term effect of radiation is acute radiation syndrome, which leads to death. Smith and Stather (1976) estimated that the radiation dose that leads to a 50% rate of death within 60 days ($LD_{50/60}$) in humans is 3.5 Gy, with a threshold dose of 2 Gy; in the absence of substantial medical intervention, the mortality rate after whole-body exposure to 4 Gy or more is nearly 100%. External, whole-body doses exceeding 100 Gy result in cerebral and cardiovascular death — usually within two days. The effects include nausea, vomiting, diarrhoea, headache, erythema, disorientation, agitation, ataxia, weakness, somnolence, coma, convulsions, shock and finally death. At doses exceeding 20 Gy, death normally results from gastrointestinal complications within two weeks. At doses of 3–4 Gy, death is delayed, perhaps for a month, and is caused by bone-marrow ablation. The effects include nausea, vomiting, diarrhoea, weakness, fatigue, anorexia, fever, haemorrhage, epilation and, without medical intervention, death (Young, 1987).

Acute radiation syndrome is unlikely to result from internal deposition of radionuclides. In contrast, specific tissues and organs may be damaged after exceptional intake of some radionuclides, in particular when they are deposited in a single organ or a small volume of tissue. Experience with the use of radiotherapy (Rubin & Casarett, 1972) suggests a wide range of threshold doses for effects in different tissues and organs, depending on the radiosensitivity of the tissue and the age of the subject. The thresholds for effects in different tissues are given by ICRP (1984). At tissue doses of 5–10 Gy, bone-marrow hypoplasia and permanent sterility of the ovary may occur

in 25–50% of irradiated patients. At tissue doses of 10–30 Gy, the threshold doses for cataract of the lens, permanent sterility of the testis and siderosis of the kidney may be exceeded. The threshold doses for liver failure, pneumonitis and fibrosis of the lung, nervous tissue necrosis and skin ulceration lie in the region 40–70 Gy. Effects such as bone necrosis and fracture, hypothyroidism and hypopituitarism occur when the local tissue dose exceeds 100–300 Gy. In children, the threshold doses for deterministic effects are generally lower: 15 Gy for failure of breast development, 30 Gy for arrested growth and 40–50 Gy for muscle hypoplasia (ICRP, 1984).

In other mammalian species, the $LD_{50/30}$ varies from about 2 Gy in pigs to 7 Gy in rats, 8 Gy in rabbits and 10 Gy in gerbils.

The radiation-induced effects at the cellular level include DNA strand breakage and micronucleus formation, which are reviewed in section 4.4.

4.2.2 *Effects on specific tissues and organs*

Of the wide range of deterministic effects described above, relatively few are important under most conceivable conditions of human exposure to internally deposited α- and β-emitting radionuclides, since most radionuclides tend to be deposited in a limited range of tissues within the body. Only the Group I metals, such as sodium and caesium, and some non-metals, such as the noble gases and hydrogen, are relatively uniformly distributed in the body and capable of delivering a similar radiation dose to a wide range of tissues, approximating whole-body irradiation. For this reason, the deterministic effects of, e.g., ^{137}Cs, an important component of fall-out resulting from nuclear fission, have generally been assumed to be deducible from observations made following exposure to similar doses of whole-body external X-radiation (McClellan *et al.*, 1962; McClellan & Bustad, 1964).

Studies with $^{3}H_2O$ in mice suggest that β-radiation from tritium is more damaging to spermatogonia than γ-rays from ^{137}Cs. Similarly, enhanced effects were seen in assays of post-implantation death of mouse embryos and injury to haematopoietic tissue, suggesting that the biological effectiveness of ^{3}H relative to that of external γ-rays is 2–6 (Balonov *et al.*, 1993). Care must therefore be exercised in extrapolating data collected after external exposures to electromagnetic radiations to exposures from more or less uniformly distributed internally deposited radionuclides.

After their intake, metals other than those in Group I and some non-metals become located in a limited number of tissues as they follow the metabolic pathways for use of essential elements (Priest, 1990). For example, radium and strontium, which are alkaline earth elements, follow the metabolic pathways of calcium and are deposited almost exclusively in the skeleton. Therefore, the radionuclides of these elements are likely to substantially irradiate only skeletal tissues. The lanthanide isotopes and most actinide isotopes are deposited in the skeleton, but these nuclides also attach to iron transport proteins and are deposited to variable extents in the liver, spleen and bone marrow. As a consequence, internal exposure to such radionuclides could result in

deterministic effects within a wider range of organs (ICRP, 1984; UNSCEAR, 1993). The inhalation of radioisotopes — either as radioactive gases or as particles — results in irradiation of tissues within the respiratory tract. In a review (Park *et al*., 1997) of the outcome of life-span studies in beagle dogs that inhaled ^{238}Pu (an α-particle emitter), a wide range of deterministic effects was seen in many tissues of animals that had received an initial lung deposit in excess of 3 kBq. The effects included radiation pneumonitis, osteodystrophy, hepatic nodular hyperplasia, lymphopenia, neutropenia, sclerosing tracheobronchial lymphadenitis, hypoadrenocorticism and increased activity of serum alanine aminotransferase, which is indicative of liver damage.

Another important difference between exposure to external electromagnetic radiation and to internal radiation from deposited radionuclides is the temporal distribution of radiation dose. Under most circumstances, the deterministic effects after X- and γ-irradiation were quantified after exposure to high doses, either at a single exposure or to relatively few fractionated doses (Withers, 1986). In contrast, incorporated radionuclides may deliver their radiation dose over periods of days or years. Under such circumstances, the tissue repair processes may be more effective, and the doses required to produce the same effect under various exposure conditions may be quite different. The many models used to quantify the relationship between the extent of tissue damage, total dose, dose protraction and overall duration of exposure have been described by ICRP (1984).

The deterministic effects that have been observed in a limited but important range of tissues are described below. The most important target tissues are often the lungs, lymph nodes and liver for inhaled radioactive particles, and the liver, bone and bone marrow and thyroid for dissolved deposits. All ingested radionuclides may irradiate the gastrointestinal tract.

(*a*) *Bone*

Deterministic effects of radionuclides incorporated within the human skeleton were first described in the late 1920s after observation of osteonecrosis and fractures in the bones of dial painters who had ingested the α-particle-emitting radionuclide ^{226}Ra (Martland *et al.*, 1925; see also section 1.2.2(*k*)). The first author also described changes in blood and radiation-induced bone cancers (Martland, 1926, 1931). Since then, studies of the skeletons of dial painters and of experimental animals exposed to α-particle-emitting, bone-seeking radionuclides have demonstrated many radiation-induced changes, including areas of bone sclerosis, abnormally large resorption cavities and blocked haversian canals within individual osteons (Rowland & Marshall, 1959; Taylor *et al*., 1965). Other disparate effects observed after intakes of both ^{226}Ra and ^{239}Pu include significant peritrabecular fibrosis (Jee *et al*., 1969) and the formation of a fibrotic layer between the mineralized endosteal bone surface and marrow cells (Lloyd & Henning, 1983), as seen in a female radium-dial painter with osteosarcoma 60 years after intake of ^{226}Ra. The layer was up to 50 μm in depth and occurred at a cumulative skeletal dose of 66 Gy. The filling of osteocyte lacunae, the presence of

hypermineralized osteons and new regenerative bone production have also been described after contamination with radium (Pool *et al.*, 1983).

Radiation 'osteitis', 'osteodystrophy' and 'osteodysplasia' are terms used to describe the entire spectrum of radiation-induced disturbances to the remodelling mechanism of bone tissue. The process is characterized by areas of bone infarction, i.e. bone necrosis, vascular damage, peritrabecular fibrosis and new bone formation (Stover & Jee, 1963). A proliferative fibro-osseous response is frequently seen in the marrow. This response resembles those seen in the active phases of Paget disease and fibrous dysplasia. The pathology of these deterministic bone lesions has been described in detail in persons exposed to ^{226}Ra. Lisco (1956) published a detailed analysis of the bone lesions in a dial painter with a fibrosarcoma of the ischium. Osteodysplasia was distributed widely in many of the non-tumorous bones available for study. It was postulated that the tumour developed at a site of radiation-induced skeletal damage, presumably originating from the cells of the peritrabecular fibrous tissue.

Radiation osteodysplasia has been studied extensively in mice treated with the short-lived radionuclides ^{224}Ra and ^{227}Th (Gössner *et al.* 1976; Gössner, 1986). A comprehensive survey of the literature on the pathology of deterministic radiation effects on bone has been published (Luz *et al.*, 1991).

Simmons and Holzmann (1983) and Morgan *et al*. (1983) showed that the severity of deterministic effects, within a dose range to 200 Gy, is a function of average skeletal α-particle dose, with a threshold of approximately 1 Gy. It has been claimed that in ultrastructural studies of ^{238}Pu-injected mice the changes were somewhat analogous to those that occur in ageing (Mohelská *et al*., 1988), the primary effect on bone cells being cell hypertrophy and destruction of endosteal cell organelles, followed by deformation and hypertrophy of osteocytes and then abnormalities in osteocyte self-burial and abnormal formation of bone tissue structure.

In all species, α-particle emitters have been shown to produce different effects in cortical and trabecular bone — a function of the different structures and turnover of these tissues. A landmark study on the effects of ^{239}Pu on dog bone was published by Jee (1972). A wide variety of histopathological lesions was induced by a single intravenous injection of ^{239}Pu (IV) citrate in beagles. The changes noted in trabecular bone were cell death, including the death of osteoblasts, osteocytes and osteoclasts; a reduction in cell division and DNA synthesis in bone cells; endothelial cell damage and reduced marrow-space vascularity; suppressed bone resorption in regions of high plutonium concentration; atypical bone formation, with mosaic trabeculae of woven bone, growth arrest lines and peritrabecular fibrosis; bone necrosis with spontaneous microfractures; altered bone remodelling rates; and pathological bone resorption and osteosarcoma. In cortical bone from the same dogs, haversian canal plugging and inhibited canalicular transport were observed, as well as excessive bone resorption, decreased vascularity, osteocyte death, atypical bone formation, endothelial cell depletion and, in rare cases, osteosarcoma. In an earlier paper (Jee *et al*., 1962), it was suggested that these effects are attributable not only to the direct interaction of α-

particles with bone cells but also to indirect effects caused by radionuclide- and dose-dependent radiation damage to both small and larger blood vessels within the bone marrow. The attribution of effects to these different causes is problematic, but both are likely to be important. The lowest average skeletal doses that produced significant vascular depletion were reported to be 23 Gy for ^{226}Ra, 3.5 Gy for ^{239}Pu, 5 Gy for ^{228}Ra and 2.5 Gy for ^{238}Th. In contrast, vascular effects were not seen up to a dose of 80 Gy in dogs injected with the β-particle emitter ^{90}Sr. The differences in the toxicity of these radionuclides is a consequence of their different deposition patterns or those of their progeny and, hence, dose distribution within the skeleton (Priest, 1990), and of the lower toxicity of β-particle-emitting isotopes. Momeni *et al.* (1976) used X-ray radiography to visualize endosteal and periosteal cortical sclerosis and thickening, osteolytic lesions, fractures and trabecular coarsening in beagles that were fed diets containing ^{90}Sr chloride in equilibrium with ^{90}Y or were given ^{226}Ra chloride by repeated injections. The α-particle-emitting alkaline earth isotope ^{226}Ra was estimated to be five to six times more toxic than the β-particle-emitting alkaline earth isotope ^{90}Sr and its co-located decay product ^{90}Y. Effects were seen with the β-particle emitters only when the skeletal dose rate exceeded 0.025 Gy per day.

Changes such as those described above, other than the occlusion of vessels, have also been seen in mice after administration of the short-lived, α-particle-emitting isotopes ^{227}Th and ^{244}Ra (Müller *et al*., 1978) and after injection of ^{241}Am (Nilsson & Broomé-Karlsson, 1976). In the latter study, the effects that were not seen in dogs included a reduction in the numbers of nucleated cells in the epiphyseal growth plate cartilages, loss of a substantial fraction of the long-bone metaphyseal trabeculation and a reduction in longitudinal bone growth. Growth retardation has also been demonstrated in rabbits injected with ^{224}Ra and in boys and girls injected with this short-lived, α-particle-emitting isotope for the treatment of tuberculosis during the period 1946–50. Significant growth inhibition was observed among these children at a mean skeletal dose of 3–25 Gy (Spiess *et al*., 1986). Hitchman and colleagues (1978) failed to reproduce this effect in three-month-old dogs that had been given 2.86 μCi (106 kBq)/kg bw ^{239}Pu, perhaps because plutonium, unlike radium, does not concentrate in the mineralizing zones of the epiphyseal growth plate cartilages.

Given the relatively low doses at which skeletal deterministic effects were observed in animals injected with the bone surface-seeking radionuclides ^{239}Pu and ^{241}Am, efforts were made to see if similar effects could be demonstrated in humans. In a recent publication (Stebbings, 1999), radiographs prepared from the bones of five persons injected with 11–15 kBq ^{239}Pu in the years 1945–47 were described. Two of these subjects died within two years of injection, but the others survived for 29–47 years. The cumulative skeletal doses calculated up to 1977 were 0.04–0.05 Gy and 0.81–1.4 Gy, respectively. Although the underlying disease complicated the analysis, bony changes were seen in all cases, and changes attributable to the plutonium were suspected for three subjects, comprising two cases of osteoporosis and non-specific degenerative changes associated with hip and vertebral fractures and areas of increased bone density. At a

higher dose of internal α-radiation, pathological changes resembling those described in dogs were found in the bones of a worker at the Hanford nuclear weapons plant who had been extensively contaminated with ^{241}Am (Priest *et al*., 1995b). When he died 11 years after his accident from a pre-existing heart condition, his skeleton contained an estimated 500 kBq of radionuclide — an amount that had already been much reduced by decorporation therapy from an initial estimated intake of 185 MBq. The bones examined were the patella, clavicle, sternum, rib, vertebral body and ossified thyroid cartilage; all showed evidence of radiation damage. The cellularity of most bones was reduced, and little evidence of recent active bone remodelling was seen in any bone other than the vertebra, as concluded from the redistribution of the americium in the vertebral body. In several bones, the architecture was disrupted, with woven bone, abnormal appositional bone deposits, bizarre trabecular structures and marked peri-trabecular fibrosis. Growth arrest lines were common. When compared with trabecular bone modelling, that of cortical bone in the rib appeared less disrupted. Overall, the results obtained are consistent with those observed in dogs (Jee, 1972) at a similar level of actinide intake.

Sharpe (1983) discussed the possibility that the bone infarcts and osteonecrosis seen in radium-dial painters might be linked to the production of bone cancers. While such links have not been confirmed, it is clear from the above, given the low dose thresholds for some effects and the apparent 10-Gy threshold for osteosarcoma induction by ^{226}Ra in humans (Rowland, 1997), that osteosarcoma is unlikely to develop in bone that is free of radiation-induced damage.

Benign radiation-induced tumours such as osteochondromas (cartilagenous exostosis) usually arise in growing bone and cartilage. They are recorded in children who have received external irradition and have also been observed in children and adolescents treated with ^{224}Ra for osteoarticular tuberculosis. Spiess and Mays (1979a) reported 55 exostoses in 28 of 218 children and adolescents treated with this radio-nuclide. These lesions developed in the long bones, usually at sites where the growing metaphysis had been irradiated. This suggests that disturbance of normal skeletal growth was the mechanism of induction. Patients who were younger at the time of injection of ^{224}Ra had a higher incidence of exostosis. None of these radiation-induced exostoses has been reported to have become malignant, although 36 of the 218 children developed bone sarcomas elsewhere in the skeleton.

(*b*) *Teeth*

Several publications have described the effect of ^{226}Ra intake on teeth. The term ‘radium jaw’ was coined by Blum (1924) to describe the tooth loss that was common in the radium-dial painters. Radiation damage to either dental tissues or to their blood supply initiates excessive resorption of dentine, particularly around the gum line, causing teeth to break with a minimum of trauma. In the dial painters, one tooth after another broke until all were lost. A similar loss was seen in young persons injected with the short-lived α-particle emitter ^{224}Ra (Sonnabend *et al*., 1986). This effect was

greatest (20–30%) in patients injected at the age of 16–21 years, with much lower frequencies at earlier and later ages of administration. Radiation-induced tooth loss has also been described in beagles injected with either ^{226}Ra or ^{239}Pu (Jee & Arnold, 1960) and in mice injected with ^{224}Ra (Humphreys *et al*., 1985). Robins (1990) described osteopenia equivalent to radium jaw in mice after injection of > 16 kBq of ^{224}Ra.

(*c*) *Eye*

Cataracts were described in 119 of 813 women who were radium-dial painters before 1930 (Adams *et al*., 1983) and in 58 of 831 patients injected with high doses of ^{224}Ra (Chmelevsky *et al*., 1988). In the dial painters, latency was negatively correlated with accumulated radiation dose; in the ^{224}Ra-injected patients, the incidence was dose-dependent, with a 14% incidence in those patients receiving the highest doses of radium and an overall mean of 5–6% for patients injected either as children or as adults (Stefani *et al*., 1986). In this population, about 55–60% of the cataracts were thought to be associated with irradiation; the remainder were accounted for by the normal age-related incidence. By plotting incidence against dose, Chmelevsky *et al*. (1988) concluded that the incidence increased either as a function of the square of the dose or linearly with dose, with an intake threshold of 0.5 MBq/kg. Griffith *et al*. (1985) described the case of a worker who had been potentially exposed to external β- and γ-radiation and had possibly ingested or inhaled plutonium and other radionuclides. In three known incidents, his face had been contaminated with plutonium, some of which must have reached the bloodstream. After 24 years of work, the man had developed impaired vision due to cataract. The estimated radiation dose to the eye — measured by external dosimeters — was ~ 0.8 Sv, which is below the threshold for this effect derived for γ-radiation in the atomic bomb survivors, 1.1–1.5 Gy (Griffith *et al.*, 1985; see also Otake & Schull, 1990). The authors noted that ^{239}Pu concentrates in the iris of dogs and suggested that the cataract seen in this worker may have arisen because of the additional dose of α-particles from his internal body-burden of ^{239}Pu, which was 2 nCi (74 Bq).

(*d*) *Skin*

Unlike in most other tissues, damage to the skin from α- and β-particle-emitting radionuclides generally results from energy released by externally deposited radionuclides, rather than internally deposited isotopes; these external sources may be in the form of diffuse deposits or hot particles. Experimental studies on pig and mouse skin show that the effects produced are dependent on the range of the radiation emission, the area of skin irradiated, the thickness of skin and the degree of skin penetration achieved by the radionuclide (Hopewell *et al*., 1986, 1993). For example, application of sources of ^{90}Sr, ^{170}Tm and ^{147}Pm (high-, medium- and low-energy β-particle emitters, respectively) to the skin of pigs (thick) or mice (thin) *in vivo* resulted in a range of deterministic effects, varying from slight breakdown of the most superficial

layers of the epidermis, produced by high doses from ^{147}Pm, to extensive local damage and moist desquamation, produced at ~ 28 Gy from large-area ^{90}Sr sources (22.5 mm in diameter). To produce the same effect with thulium, 80 Gy of β-radiation from this radionuclide were required. The thresholds for acute tissue breakdown due to the larger-diameter sources of β-radiation were 17 Gy for ^{90}Sr/^{90}Y and 30 Gy for ^{170}Tm. In contrast, the threshold for less serious epidermal necrosis after irradiation by ^{147}Pm was 150 Gy. This is important, since exposure of 50% or more of the total body surface led to death of Chernobyl liquidators due to skin desquamation and subsequent infection when the doses to the skin exceeded 30 Gy for penetrating β-radiation and 200–300 Gy for less energetic emitters (Barabanova & Osanov, 1990).

Similar dermal effects of radionuclides deposited externally were seen in Marshall Islanders exposed to fall-out rich in β-particle emitters from a thermonuclear explosion at Bikini atoll in March 1954 (Cronkite *et al*., 1995; see section 1.1.1(*c*)(ii)). On Rongelap atoll, where the exposure was greatest (~ 1.9 Gy total dose of γ-radiation in air), hair loss and hyperpigmentation of the skin were seen. Some of the skin lesions were painful. The lesions were initially small but gradually coalesced. Later, scaly, dry desquamation proceeded from the centre of each lesion, and the skin colour was lost. Repigmentation began in the central region of each lesion and spread, so that after a few weeks the skin appeared normal. In some more severe cases, lesions, mostly on the head and neck, became necrotic with moist desquamation, followed by ulceration. By three months after the explosion, the hair had begun to grow, and within 6–12 months the skin had returned to normal.

(*e*) *Liver*

The deterministic effects of radionuclides deposited in the human liver have been studied extensively in patients who received the radiographic contrast agent Thorotrast and in animals given a variety of α- and β-particle-emitting isotopes. Thorotrast is a colloidal preparation of $^{232}ThO_2$, which, after its injection into the bloodstream, is deposited within reticuloendothelial organs, principally the spleen, liver and bone marrow. Thorotrast is essentially insoluble and continues to irradiate tissues at all times after its entry (radioactive half-life, 1.1×10^{10} years), with a mixture of α- and β-emissions from ^{232}Th and its progeny (principally ^{228}Ra, ^{228}Th and ^{230}Th).

A special study was made of one Thorotrast patient who died from myelodysplasia in June 1989, 36 years after receiving an injection of Thorotrast, and who donated her body to the Transuranium and Uranium registries in the USA. At autopsy, the patient's liver was found to contain 44.3% of the whole-body ^{232}Th content, and the estimated accumulated radiation dose received by this organ was 15 Gy (Kathren & Hill, 1992). The liver was of normal weight, but its exterior appearance was characterized by widespread, reticulated capsular fibrosis (Graham *et al*., 1992). Histological examination showed generalized, moderate, subcapsular and portal fibrosis. The hepatocytes were iron-loaded — a consequence of multiple blood transfusions. Foci of mild hepatocellular dysplasia, occasionally associated with intranuclear inclusions, were identified.

Focal extramedullary haematopoiesis, consistent with myelodysplasia, was present. No neoplasm was identified.

Liver cirrhosis was seen in groups of Japanese patients 20 years after receiving Thorotrast, and the incidence rose to 10% after 36 years (Mori *et al*., 1983). Cirrhosis occurred at organ dose rates of 0.15–0.6 Gy/year, with a mean cumulative dose of 9.5 Gy (Kato *et al*., 1983). In an equivalent group of 2326 German patients with a longer latency since injection (approaching 50 years), the incidence of cirrhosis was somewhat higher at 12.6% (van Kaick *et al*., 1989). However, no cirrhosis was present in the liver of the whole-body donor.

Moroz and Parfenov (1972) summarized changes in the livers of 10 children and four adolescents exposed accidentally to polonium from polonium–beryllium sources. The amounts of polonium deposited in these two groups ranged from 18.5 kBq to over 370 kBq. Transitory changes were observed in liver function, and decreased numbers of leukocytes and platelets was seen during the first few months after exposure.

In dogs injected with the α-particle emitter ^{239}Pu at doses ranging from 0.0168 to 2.9 μCi (620 Bq–107 kBq)/kg bw, hepatic-cell necrosis was a consistent finding. However, regeneration was sufficient to maintain the normal liver mass in all dogs except those that received the highest dose. Changes in the distribution of plutonium produced by regeneration were seen at lower doses and at average cumulative doses to the liver ≤ 0.8 Gy. The dogs given the highest dose of plutonium showed severe centrilobular degeneration and fibrosis (Taylor *et al*., 1972b).

In dogs that had inhaled ^{238}Pu, the initial lung was 3–200 kBq, which, after translocation of the radionuclide, gave rise to doses of α-radiation ≤ 3.4 Gy to the liver. Effects were seen at doses below those at which cancer was induced. At necropsy, the most consistent change was an increased incidence of adenomatous hyperplasia as the dogs aged. These regions were typically 20–30 mm in diameter, well-circumscribed and pale grey, with cells that were enlarged and often distended with glycogen or cytoplasmic vacuolation. Excess activity of liver enzymes, including alanine aminotransferase and alkaline phosphatase, in serum indicated liver damage. The increased activity was positively correlated with the dose rate and the cumulative dose of α-radiation (Weller *et al*., 1995c).

Similar changes were described in the livers of mice given 8 or 16 μCi (300 or 600 kBq)/kg bw, i.e. high doses, of ^{241}Am (Nilsson & Broomé-Karlsson, 1976) and in dogs given 6 mg/kg bw (corresponding to 150 kBq) of ^{237}Np citrate (Mahlum & Clarke, 1966). In the mice, slight periportal fibrosis was a common finding. The parenchymal changes varied from changes in cell nuclei to extensive fatty degeneration, multiple focal necroses and microabscesses. Binucleate cells were increased in number. In a significant number of mouse livers, the epithelial cells of the bile canaliculae were swollen, and multi-focal proliferations of these structures were seen. In the dogs, the liver damage comprised cloudy swelling of tissues, fatty degeneration, lobular necrosis, biochemical changes and a marked increase in the number and size of the littoral cells. Given the low specific activity of ^{237}Np, the effects seen might have been

due to the chemical toxicity of the compound rather than the emitted radiations (Boulahdour & Galle, 1998).

Hepatic changes have also been described after intake of β-particle-emitting radionuclides. Injections of $^{144}Ce/^{144}Pr$ at 0.33–0.42 mCi (12.2–15.5 MBq)/kg bw to sheep produced effects in the liver similar to those described above, including cell swelling and death. The hepatocyte nuclei were clearly damaged by nine days after injection, when the effects were most frequent near the central veins of the lobules; later, all parts of the lobule were affected. By 18–24 days after injection, foci of necrotic fibril material containing gram-positive pleomorphic cocci were seen, which resulted in terminal bacteraemia (Sullivan *et al.*, 1969).

Hepatic effects have also been seen in dogs that inhaled ^{144}Ce at doses resulting in long-term body burdens of 0.096–13.3 MBq/kg bw. In the dogs that lived longer than five years after treatment, the radionuclide produced an average cumulated dose of β-radiation to the liver of 60 Gy per MBq ^{144}Ce/kg bw. The animals survived 1–10 years after exposure. Hepatocellular degeneration or hepatic atrophy with fibrosis and hepatic failure was either the primary cause of death or contributed to death in 18 animals that received cumulative doses of 6.4–210 Gy. It may be recalled that 10 animals died from liver tumours after exposure to doses over the same range (10–240 Gy) (Hahn *et al.*, 1995).

(*f*) *Haematopoietic bone marrow*

The effects of α-radiation on the bone marrow of humans and of α- and β-radiation on the bone marrow and stem cells of animals have been studied extensively. In the patient who died in 1989 and donated her body to the Transuranium and Uranium registries in the USA (see section *e*, above), the estimated accumulated dose of radiation to the skeleton and bone marrow from a Thorotrast injection given 36 years previously was 3.9 Gy (Kathren & Hill, 1992). A bone-marrow biopsy from the iliac crest *post mortem* showed failure of cell maturation beyond the myelocyte stage of the granulocytic series, with virtually no polymorphonuclear cells. Blasts and pro-myelocytes comprised about 15% of all the elements. Erythropoiesis was virtually absent. Megakaryocytes were present in adequate numbers but were often mononuclear or binuclear. No significant fibrosis was seen. The authors concluded that the findings in bone marrow were compatible with refractory anaemia with an excess of blast cells. Consistent with this diagnosis was the presence of extramedullary haematopoiesis in the liver.

Similar changes were described in the bone marrow of the worker in Hanford who had been contaminated with ^{241}Am (Priest *et al.*, 1995b). The bone marrow of this patient had been substantially damaged by α-irradiation from americium, principally on the bone surfaces. A common finding was a marked decrease in bone marrow cellularity associated with dilatation of blood sinusoids. The severity of these effects varied according to site and was greatest in the vertebral body, where the marrow was almost acellular, and least in the clavicle. In addition, extensive peritrabecular marrow

fibrosis was present in some bones, including the rib and clavicle. As noted above, fibrosis is a common observation in bones irradiated by bone-seeking radionuclides and has been linked to bone sarcoma induction (Rowland, 1994).

Aplastic anaemia resulting from α-irradiation by Thorotrast was seen at high frequency in all groups of Thorotrast-treated patients studied (Mole, 1986), although at a slightly lower frequency than that of leukaemia. However, the bone marrow of all the patients was damaged. Similarly, slight or severe bone marrow damage was recorded in 38% of patients given 10 MBq or more of the short-lived α-particle emitter ^{224}Ra more than 5 years previously (Arnold & Weber, 1989).

Male Wistar rats were given a single intravenous injection of $^{239}PuO_2$ (particle size, 1–2 μm) at a dose of 23.2, 46.3 or 92.5 kBq/kg bw, and the numbers of cells in the bone marrow and peripheral blood were analysed for 365 days at different times after injection. Dose-dependent impairment of haematopoiesis was observed, with an increase in the number of lymphocytes and a reduction in the pool of maturating granulocytes in the bone marrow. The number of circulating lymphocytes was decreased for a long time after injection (Murzina *et al.*, 1988).

In dogs, ^{239}Pu-labelled macrophages accumulated in the bone marrow at lower injected doses of plutonium (0.5 kBq/kg bw), but at higher doses (up to 10 kBq/kg bw) the influx of macrophages was depressed because of inhibition of bone resorption by radiation. At 0.5 kBq, the number of macrophages reached a maximum 100 days after injection. After four years, ^{239}Pu-labelled macrophages were no longer detectable. Other responses in the bone marrow included fibrosis, hypoplasia and hyperplasia (Jee, 1972). In mice irradiated to a level of about 2 Gy from ^{239}Pu injected one year previously at a dose of 13.3 kBq/kg bw, the bone-marrow tissues were about 10 times more sensitive to subsequent irradiation with X-rays (Svoboda *et al.*, 1987).

^{241}Am administered to mice at 8 or 16 μCi (300 or 600 kBq)/kg bw also had profound effects on the marrow, the effects ranging from slight hypoplasia to complete aplasia. All cell types were usually depleted, but the erythroid series was most sensitive. Most of the marrows were reported to have become loaded with fat, and the blood sinusoids were heavily congested. In some mice, the sinusoids were destroyed and replaced by blood lakes. The effects were most severe in the vertebral column, where americium is concentrated, and least severe in the long bones (Nilsson & Broomé-Karlsson, 1976).

In mice, both ^{239}Pu and ^{226}Ra have been shown to damage haematopoietic stem cells and their regulatory stromal microenvironment (Lord *et al*., 1991). After a single injection of 960 Bq of ^{239}Pu (35 Bq/g bw) per mouse (strain $B_6D_2F_1$), the number of viable stem cells in the femur fell to about 50% of the normal number eight days after injection, with a gradual recovery to 90% of control values 120 days after injection. In contrast, the total cell numbers in the marrow remained at control levels for 300 days then decreased to 60% after 1.5–2 years. After a single injection of ^{224}Ra to CBA/H mice (555 Bq/g bw), the total cell number in the bone marrow of the femur fell to 60% of the control value by 4 h after injection, before reaching a minimum of 25% at four

days then recovering to 75% at about 90 days. The number of viable stem cells was initially unaffected but then decreased rapidly, reaching < 5% of control values eight days after treatment; the number then recovered slowly to a level of 50% of the control value by 90 days. The failure to recover fully was attributed to microenvironmental damage. Similar effects on the numbers of stem cells have been described in adult and neonatal mice after administration of ^{241}Am. Even at a dose of 33 Bq/g bw, the stromal cells in the bone marrow showed a reduced capacity to support viable stem-cell proliferation (Van den Heuvel *et al*., 1987). The inability of a damaged microenvironment to host a complement of normal stem cells can induce extraproliferative activity and stress on the pluripotent progenitor cells outside that microenvironment, which is required to maintain normal cellular output. It has been suggested that such perturbation, while not leading to the development of leukaemia *per se*, could be a prerequisite for its induction by other, non-radiological hazards. Damage to stroma may, however, directly precede the development of osteosarcoma (Lord *et al*., 1991).

Studies with β-particle emitters have also revealed effects on the haematopoietic system. Mice were maintained on $^{3}H_2O$ at 11×10^7 Bq/L starting at four weeks of age, and the bone marrow of the femur and tibia from these animals and from controls given tap water was analysed at regular intervals. No significant difference between treated and control mice was found in the total cellularity of the bone marrow over the entire 80-week observation period. A decrease was seen in the relative number of colony-forming cells as early as 12 weeks in the males and 20 weeks in the females. After a brief recovery, the decrease continued throughout the experiment, indicating maintenance of normal cell numbers in the bone marrow with fewer than normal stem cells (Carsten *et al*., 1977).

In mice given $^{3}H_2O$ at a concentration of 1.9×10^{10} Bq/L, haematopoietic failure resulted in death after 45 days. The marrow became severely hypoplastic, and replacement by fatty tissue was observed. At concentrations > 1.5×10^{11} Bq/L, all bone-marrow cells were destroyed, the marrow space became filled with diffuse haemorrhage, and death occurred within 15 days. At a dose of 9.25×10^9 Bq/L, the mice survived, but the marrow showed decreased cellularity (Yamamoto *et al*., 1990).

The β-particle emitters ^{90}Sr/^{90}Y, ^{32}P-phosphate and ^{144}Ce/^{144}Pr are bone-seeking radionuclides that attach to bone surfaces, from which they irradiate the marrow, and the depth of penetration of the radiation often exceeds that of similarly located α-particle emitters. Inhalation of aerosols containing ^{90}Sr chloride produced dose-related pancytopenia in dogs with a retained burden of > 0.37 MBq/kg bw. Thrombocytopenia and neutropenia were persistent until the death of the animals. The effects were reported to be similar to those seen after external irradiation (Gillett *et al*., 1987b). In rodents given 1 μCi (37 kBq)/g ^{32}P-phosphate per day for 14 days per month for three months, bone-marrow damage was inferred from decreases in the numbers of erythrocytes and lymphocytes and an increase in the fraction of circulating neutrophils and immature cells (Malhotra & Srivastava, 1978).

After administration of 0.33–0.42 mCi (12.2–15.5 MBq)/kg ^{144}Ce, in equilibrium with its decay product ^{144}Pr, to sheep, the production of granulocytes within the bone marrow decreased rapidly, and it ceased by three days after injection. The replacement cells were judged to be lymphoid in appearance, and haemorrhage was common. Megakaryocytes were also damaged, showing nuclear fragmentation and pyknosis. Regeneration of the bone marrow was seen 24 days after injection, but the delivery of granulocytes to the peripheral circulation was impaired (Sullivan *et al.*, 1969).

Given the importance of iron metabolism within the bone marrow, the effects of administration of the Auger electron-emitter ^{55}Fe were studied in mice. Doses in excess of 1.3 mCi (48 MBq) per mouse resulted in a dose-dependent depletion in the population of nucleated red blood cell precursors in the bone marrow that was similar to that seen after external whole-body irradiation. However, at very high doses, the effect was less severe than expected, probably because of diversion of excess iron to the liver. At an administered dose of 15 mCi (550 MBq) per mouse, the number of bone-marrow erythrocyte precursors decreased to 10% of the control value, a 60% reduction in the number of granulocyte precursors was seen, and total bone-marrow cellularity was decreased by 50%; the number of viable stem cells was also decreased. The absence of marked changes in the granulocyte-cell population probably reflects both the deposition of iron in the erythroblasts and on bone surfaces and the short range of Auger electrons (track length in tissue, < 1 μm) (Reincke *et al.*, 1975).

(*g*) *Gonadal tissues*

The effects of radiation on gonadal tissues are also discussed in section 4.3. Less is known about the deterministic effects of internally deposited radionuclides in the human testis and ovary than about the effects of external exposure to ionizing electromagnetic radiation (UNSCEAR, 1982, 1993); however, studies have been conducted with both α- and β-particle-emitting radionuclides in experimental animals.

Single intraperitoneal injections of $^{3}H_2O$ at a dose of 92.5 or 185 kBq/g bw to female Swiss albino mice caused a reduction in ovarian volume and an almost total depletion of follicles. Oocytes showed atretic changes, including fragmentation of nuclear materials, pseudo-maturation, spindle formation and shrinkage of the oocyte membrane. Cells in the granulosa layer showed pyknosis and cell lysis (Kapoor *et al.*, 1985). The survival of oocytes was studied in juvenile ICR mice given single injections of $^{3}H_2O$ at doses of 170–1020 kBq/g bw, corresponding to cumulative doses of 0.039–0.3 Gy. Other groups of mice were exposed to comparable doses of either external γ-rays from ^{60}Co or external neutrons from ^{252}Cf. An exponential decrease with increasing dose in the number of surviving oocytes was found. The effectiveness of the different radiation types decreased in the order: external ^{252}Cf neutrons > $^{3}H_2O$ β-radiation > ^{60}Co γ-radiation.

The effects of $^{3}H_2O$ and [^{3}H]thymidine (which is incorporated into DNA) on the mass of the testis of CBA mice was measured. A 30% reduction in testicular mass was observed five weeks after injection of $^{3}H_2O$ at 40 μCi (1.5 Mbq)/g bw, whereas a dose of 10 μCi (0.37 MBq)/g bw [^{3}H]thymidine resulted in a 20% reduction. The mass of

the testes had recovered by 16 weeks. The biological effectiveness of the β-radiation from $^{3}H_2O$ relative to that from external γ-radiation, calculated on the basis of the average absorbed dose to the testis, was 1.43. The equivalent ratio for [^{3}H]thymidine was 2.07, illustrating the stronger effect of the short-range β-emitter when incorporated directly into DNA (Carr & Nolan, 1979).

Injection of ^{241}Am into mice at a dose of 0.04, 8 or 16 μCi (1.5, 300 or 590 kBq)/kg bw also resulted in a reduction in testicular mass. Histological examination of the treated mice showed either marked hypospermia or aspermia and tubular degeneration. In older mice, slight interstitial fibrosis was seen, with a reduction in the number of Leydig cells. Necrosis of superficial testicular vessels with fibrosis and calcification were observed. In the smaller arteries, proliferation of the endothelium, generally in association with proliferation of adventitial tissue, was seen. Effects were found even at 0.04 μCi/kg bw (Nilsson & Broomé-Karlsson, 1976).

(*h*) *Lung*

In patients treated with Thorotrast, the lungs were irradiated by both thorium and its decay products, including ^{220}Rn, deposited within the lung and by ^{220}Rn emanating from thorium deposits throughout the body and transported to the lungs by the blood. Calculation of an average α-radiation dose to the lung is therefore complicated. For a Thorotrast intake of 18.5 kBq, the cumulative dose to basal cells in the region of the terminal bronchi (assuming 40 years of exposure) has been estimated to be about 2.5 Gy (Hornik & Kaul, 1995). At this level of irradiation, increased incidences of pulmonary cancer are not seen (Hoffmann & Daschil, 1986), but deterministic effects have been described in the woman who donated her body to the Uranium and Trans-uranium registries in the USA (Graham *et al*., 1992). In this case, the lungs showed focal emphysematous changes and atelectasia (areas of deflated lung associated with failure of surfactant production).

The time course of pulmonary changes was studied in beagle dogs after inhalation of $^{239}PuO_2$ particles in an aerosol, to give lung burdens of 0.1–48 μCi (3.7 kBq and 1.8 MBq) and a cumulative dose of α-particles to the lung of 0.004–140 Gy. Most animals at the higher doses that were not killed died from lung disease within one year. Examination of autopsy specimens showed that few changes had occurred in the lungs during the first week after inhalation. Between one week and one month after inhalation, some small bronchioles were swollen, with desquamation of epithelial cells. Multiple foci of septal, peribronchiolar and perivascular fibrosis also appeared. Between 55 and 63 days, moderate septal thickening was seen, as was alveolar collapse, infiltration of fibrotic areas with neutrophils and the first signs of alveolar cell metaplasia. By 63–79 days after inhalation, the focal fibrosis had become increasingly severe and resulted in local obliteration of the normal pulmonary architecture. The alveolar-cell metaplasia was now focal and moderate, but it was overshadowed by the appearance of moderate-to-severe peribronchiolar squamous and bronchiolar-type metaplasia, the alveolar lining cells taking on the appearance of squamous or simple columnar epithelium. Alveolar

macrophages were common, and giant cells were present within fibrotic foci. Between 80–107 days, the septal fibrosis had become increasingly severe, and diffuse fibrosis associated with increased alveolar and squamous metaplasia was also described. At 120–124 days, the developing metaplasia was extensive, and thickening of the alveolar septa and foci of advanced dense fibrosis caused considerable distortion of the entire lung architecture. In some bronchi, the lining surface was either denuded of epithelium or covered with a layer of flat cells. Focal areas of alveolar 'fibrin balls', neutrophil clusters, giant cells and haemorrhage were present. After 168 days, the pathological changes to the lung were severe; the lungs were twice their normal mass and visibly damaged. Emphysematous spaces were associated with the most severely damaged areas (Clarke & Bair, 1964). Nevertheless, the immune responses in dogs that had inhaled $^{239}PuO_2$ (initial lung burden, 19–35 kBq) were not suppressed by large continuous doses of α-particles, indicating that pulmonary immune responses are preserved despite severe radiation-induced alteration of tissues (Galvin *et al*. 1989).

At lower doses, the effects of α-radiation are less severe. In the study of Thomas *et al*. (1972), the average cumulative radiation dose to the lungs of four dogs at various times after inhalation of ^{241}Am oxide as an aerosol was determined to be 30 Gy at 127 days, 32 Gy at 256 days, 38 Gy at 512 days and 53 Gy at 1022 days after exposure. Only minor pulmonary changes were found 127 days after inhalation, with a few isolated areas of inflammation and minor alterations in bronchiolar and alveolar epithelia. By 256 days, these changes were more extensive. Some local dense fibrosis was present, which was predominantly sub-pleural and associated with marked pleural thickening, but was also present as a diffuse deposit throughout the lungs. At times up to 1022 days, some focal mineralization was seen, with local proliferation of alveolar cells and minimal squamous metaplasia. The fibrosis was more severe, with obliterative fibrosis of small arteries and some dense parabronchial fibrosis.

The lesions induced by internal exposure to α-radiation have been described in mice (Talbot & Moores, 1985), rats (Sanders, 1972; Métivier *et al*., 1975, 1978), dogs (Galvin *et al*., 1989; Diel *et al*., 1992) and baboons (Métivier *et al*., 1975) after irradiation by $^{239}PuO_2$ and in hamsters after inhalation of $^{238}PuO_2$ (Pickrell *et al*., 1983).

The changes after administration of $^{239}PuO_2$ to rats were similar to those produced by external irradiation. At cumulative doses of α-particles ranging from 3 to 130 Gy, the severity of the effects produced was a function of dose. During the intermediate stages of developing pneumonitis, the number of type II alveolar epithelial cells was increased, and these cells contained an increased number of osmiophilic inclusions. Also found was accumulation of a membranous–proteinacious exudate in the air spaces, accumulation of lipid in the septal walls, severe disruption of endothelia and accumulation of collagen, elastin, fibroblasts, plasma cells and mast cells in greatly thickened septal walls. Type I cells were relatively unchanged, the changes being restricted to a few areas of focal cytoplasmic disruption; however, about one week before the death of the animals, generalized oedema was present, with swelling of type I cells. A decrease was also seen in the proliferation of macrophages, and these

cells were less able to phagocytose latex spheres. Fewer macrophages were recoverable by lavage, suggesting a long-term cytocidal effect of plutonium on these cells (Sanders, 1972). A similar plutonium-induced reduction in macrophage activity was found in dogs with an accumulated lung dose of 23 Gy from single or repeated exposure. At this dose, about 80% of the animals died from deterministic effects (radiation pneumonitis, pulmonary fibrosis) and most of the remainder from pulmonary cancer (Diel *et al*., 1992). Similarly, in mice that had inhaled an aerosol of $^{239}PuO_2$ providing an average lung dose of 32 Gy, marked changes were seen in the lungs, including increased lung mass, protein and total collagen, fibrotic patches with accumulation of foamy cells and decreased cellularity with areas of compensatory hypertrophy (Talbot & Moores, 1985).

The survival rate of baboons exposed to an aerosol of $^{239}PuO_2$ was three times shorter than that of dogs in comparable studies, and varied from about 15 days at a lung burden at death of 400 nCi/g (14.8 MBq/kg) to 900 days at 3 nCi/g (111 kBq/kg). Scar tissue and fibrosis associated with local accumulation of plutonium were found. Some early deaths resulted from cell necrosis and alveolar oedema; later deaths resulted from interstitial pneumonitis and respiratory insufficiency due to fibrosis and were preceded by high arterial pCO_2 and low arterial pO_2 (Métivier *et al.*, 1975). In rats, the lung fibrosis observed 200 days after administration of $^{239}PuO_2$ aerosol at lung doses of up to 3 Gy regressed as the dose rates gradually decreased due to clearance of plutonium particles, so that, at 400 days, the lung collagen content had returned to normal (Métivier *et al*., 1978). A similar pattern of collagen reabsorption was observed in hamsters that had received 50 nCi (1.85 kBq) of relatively soluble $^{238}PuO_2$ by inhalation. Diffuse interstitial fibrosis was evident 10 weeks after inhalation, which had peaked by 15–20 weeks and then reached a plateau before returning to control values at 50 weeks. In this group of animals, dense fibrotic scars were rare; however, in animals that received twice as much ^{238}Pu, areas of heavy fibrosis was more common and, in these, the collagen concentration remained high. The authors concluded that diffuse fibrosis resolves spontaneously under conditions of limited exposure to α-radiation (Pickrell *et al*., 1983).

Pneumosclerosis and malignant lung tumours were also described in rats after intratracheal administration of ^{237}Np as the nitrate or oxalate. These changes occurred at cumulative lung doses of 0.05–32.2 Gy. The oxalate resulted in more severe fibrosis than the more soluble neptunium nitrate. As in other tissues, ^{237}Np may induce effects as a consequence of both its radiotoxicity and its chemical toxicity (Levdik *et al*., 1972).

The responses of pulmonary tissues to irradiation have also been studied in dogs after administration of β-particle-emitting radionuclides (McClellan *et al*., 1970; Hobbs *et al*., 1972; Slauson *et al*., 1976, 1977). Pneumonitis and fibrosis (as well as carcinogenesis) developed after inhalation of insoluble aerosols containing either ^{90}Sr, $^{90/91}$Y or ^{144}Ce, and the sequential alterations in the function of the lungs leading to death from pulmonary failure were described. In a later study (Mauderly *et al*., 1980),

the time course of histological and functional changes in the lungs of dogs exposed by inhalation to 230–630 μCi (8.5–23.3 MBq) of ^{144}Ce incorporated in aluminosilicate particles were evaluated comprehensively. The total score for histological changes in serially sacrificed animals was found to rise exponentially with cumulative radiation dose within the dose range 0–500 Gy; once disease was clinically evident, it progressed little with further increases in dose. The effects produced were changes to the vasculature (inflammation and thrombosis of arteries and veins, dilatation of lymphatic vessels and perivascular fibrosis), changes in bronchioles (inflammation and epithelial degeneration, metaplasia), changes in alveolar structures (interstitial-cell proliferation, alveolar lining-cell proliferation, fibrosis, collagenous scars, changes in macrophages and leukocytes, fibrin, oedema, emphysema) and changes to the pleura (fibrosis). Changes in pulmonary function were also observed. In dogs with pulmonary failure, a fourfold increase in respiratory frequency, a 50% reduction in tidal volume, a fourfold increase in alveolar dead space and many changes in gas exchange were noted. Cardiac output and blood pressure were also increased. Overall, it was concluded that the dogs developed progressive radiation pneumonitis and pulmonary fibrosis similar to that produced by external irradiation of the lungs. Moderate functional impairment was associated with more severe inflammatory and proliferative changes in the airways and alveoli. The severe impairment was found to have resulted from progressive fibrosis and scarring.

(*i*) *Thyroid*

The thyroid gland in adults is considered to be radioresistant in terms of cell death and failure of function. It has the capacity to actively concentrate iodine [and presumably the chemically related element astatine, although no experimental evidence exists to support this suggestion]. Radioiodine can, therefore, deliver considerable doses to the gland. Both medical diagnostic and therapeutic procedures are based on this effect: irradiation of the thyroid is a common treatment for the purposes of reducing its metabolic rate and controlling symptoms of angina in patients with cardiac insufficiency. A dose of at least 300 Gy is required to cause total ablation of the thyroid within a period of two weeks. This can be achieved with a single oral dose of 1850–3700 MBq of ^{131}I, resulting in an uptake of about 37 MBq by the thyroid (Goolden & Davey, 1963).

Reduced thyroid function caused by internal irradiation with ^{131}I or ^{125}I has been reported frequently. Orally administered ^{131}I is widely used for treatment of a hyperactive thyroid, which is more radioresponsive. After fractionated doses of 1.5–3.7 MBq, giving estimated total doses of 2–8 Gy, a return to normal activity or even hypothyroidism was observed (Werner *et al.*, 1952; UNSCEAR, 1982). When it occurs, hypothyroidism after treatment with radioiodine develops slowly: in 7.5% of the cases it appeared within the first year after treatment, and this percentage increased by approximately 3% each subsequent year, until approximately 26% of the patients had symptoms of hypothyroidism at seven years (Beling & Einhorn, 1961). It is not clear whether the rate of delayed hypothyroidism caused by ^{125}I is different from that after

treatment with ^{131}I (Bremner *et al.*, 1973). The loss of thyroid function in hypothyroid patients can be compensated by administration of synthetic thyroid hormone.

Little is known about the incidence of hypothyroidism after exposure to low doses of ^{131}I, e.g. during diagnostic tests for uptake. Hypothyroidism occurred in three of 146 patients who had received doses in the range of 0.31–0.80 Gy and in five of 151 patients at 0.81–19 Gy (UNSCEAR, 1982). However, the incidence of overt hypothyroidism in children exposed to ^{131}I in fall-out was not significantly different from that in unexposed controls (Rallison *et al*., 1974).

Radioactive fall-out from a thermonuclear explosion at Bikini in the Pacific Ocean was deposited on the Marshall Islands in 1954 (see section 1.1.1(*c*)(ii)). Inhalation and ingestion of radioactive iodine (mainly ^{131}I, ^{132}I, ^{133}I, ^{134}I) by the population resulted in significant internal exposure. Twenty-five years later, the population on the nearby atoll of Rongelap still showed a significantly impaired thyroid reserve, while at least four of 43 persons suffered from thyroid malfunction. Three of these were estimated to have received doses < 3.5 Gy (Larsen *et al.*, 1978).

Radiation from ingested ^{131}I and iodine deficiency have a combined effect on the development of thyroid abnormalities. The frequencies of diffuse euthyroid goitre and nodular abnormalities were significantly increased among children who received doses to the thyroid > 1 Gy and lived in areas with iodine deficiency (renal excretion, 7.5–5.0 μg/mL) than in children who received similar doses but lived in regions with adequate iodine provision (> 10 μg/mL) (Tsyb *et al*., 1999).

When children are exposed to radiation during the first two decades of life, the thyroid gland is susceptible to radiation-induced effects. Few data are available on the effects of absorbed doses of ^{131}I in the thyroid of children. In a study cited by the National Council on Radiation Protection and Measurements (1977; UNSCEAR, 1993), eight of 443 children < 16 years of age showed hypothyroidism after diagnostic tests with ^{131}I. The incidence of hypothyroidism increased with dose from 0% at < 0.3 Gy to 0.23% per year after > 0.8 Gy. Hypothyroidism was observed in eight of 30 young patients (8–18 years) receiving ^{131}I therapy for hyperthyroidism after administration of a mean amount of 244 MBq, during a nine-year follow-up (Hayek *et al*., 1970). A 92% prevalence of hypothyroidism was found among 51 patients aged 6–18 years after ^{131}I therapy (mean activity, 240 MBq) for hyperthyroidism (Freitas *et al*., 1979).

Within nine years after the thermonuclear explosion at Bikini in 1954, thyroid nodules were noted in children on Rongelap atoll, who had received the highest dose (Larsen *et al.*, 1978). Of those aged < 10 years, 67% developed nodules. The doses to the thyroid were estimated to be 10–43 Gy. Five children who were exposed when below the age of five years showed growth retardation, which was most prominent among children aged 1–1.5 at the time of exposure (Sutow *et al.*, 1965). The incidence of subclinical hypothyroidism was 31% among children who were < 10 years old at the time of exposure to estimated doses of > 2 Gy from ^{131}I (Conard, 1984).

A 23-year-old woman with Graves disease was given symptomatic treatment with propanolol and then received ^{131}I at 370 MBq as a definitive treatment. Three weeks

later, she was hospitalized with acute radiation thyroiditis. The clinical symptoms and signs persisted for over 30 days, and one month later she developed hypothyroidism. Of the three therapeutic options for the treatment of Graves disease — antithyroid drugs, radioiodine and surgery — treatment with radioactive iodine, without pretreatment with antithyroid drugs, can lead to acute thyroiditis or 'thyroid storm' (Zúñiga-González, 2000).

Detrimental effects on the thyroid of the developing human fetus may occur as a result of ^{131}I treatment for thyrotoxicosis of the mother during the first trimester of pregnancy. Estimates of the dose received under typical clinical circumstances indicate that the effective dose to the fetus is 100–450 Sv. This dose may be considerably higher if the blood concentration of ^{131}I in the mother remains high. Under such circumstances there may be fetal thyroid dysfunction, which can lead to severe abnormalities (Pauwels *et al.*, 1999).

The effects of a low dose of ^{131}I and ^{131}I-induced maternal hypothyroidism on the development of the thyroid gland and brain were studied in rat embryos. The dose given (150 μCi [5.6 MBq]) produced an estimated absorbed thyroid dose of 0.5 Gy, a dose similar to that received by the populations of the regions polluted by radioactive isotopes of iodine as a result of the Chernobyl accident in 1986. Thirty-five female Wistar rats and their 168 newborn pups were divided into a control group and four experimental groups distinguished by the time of ^{131}I injection: group I, no less than 12 days before mating; groups II, III and IV, days 5, 10 and 16 of gestation, respectively. In all tested females, the incorporated dose of ^{131}I led to hypothyroidism, accompanied by a 43% reduction in the thyroxin level and a nearly eightfold increase in the amount of thyroid-stimulating hormone. It was found, however, that the effect of maternal hypothyroidism on the development of the thyroid gland and brain of the embryo depends on the time at which ^{131}I took effect. The weight of the newborn brain and thyroid gland and total body mass were reduced. The hormonal status of the newborns' thyroid gland was also changed (Usenko *et al.*, 1999).

The radiotoxicity of ^{123}I, ^{125}I and ^{131}I to the thyroid gland was compared in groups of mice injected with the three isotopes at doses ranging from 100 kBq to 100 MBq. Thyroid function was determined 15 months later on the basis of the 24-h uptake of tracer activity of ^{131}I. A reduction in uptake to 20% of the control value for untreated mice was found for mice injected with 35 MBq of ^{123}I, 13 MBq of ^{125}I or 2.2 MBq of ^{131}I. The average absorbed dose in different parts of the thyroid was estimated by means of a refined method. The absorbed dose in the cell layers surrounding the follicles seemed to be most indicative of impairment of thyroid function (Van Best, 1982).

(*j*) *Gastrointestinal tract*

Animals receiving single doses of radiation (10–50 Gy) to the gastrointestinal tract died with signs of the gastrointestinal syndrome (Stather *et al.*, 1988; UNSCEAR, 1988). The symptoms in humans include anorexia, lethargy, diarrhoea, infection and loss of

fluids and electrolytes. Other signs include weight loss, reduced food and water intake, gastric retention and decreased intestinal absorption. Haemorrhage and bacteraemia may be present which aggravate injury and contribute to death. In various animal species, the mean time to death after doses of the order of 50 Gy is 4–10 days.

Given that the gastrointestinal tract is less radiosensitive than the bone marrow, death due to irradiation of the gut is likely to predominate over death due to irradiation of the bone marrow only when radioactivity delivering large internal doses has been ingested. Owing to the normal clearance times through the gastrointestinal tract, the dose would be delivered within a few days. Severe injury to the intestinal mucosa has not been reported after ingestion of radionuclides in humans, although many cases of accidental intakes have been published (Fry & Sipe, 1986).

Dose–effect relationships for intestinal damage have been calculated from data for animals, showing that different species respond in a similar way to irradiation of the gut (Bond *et al.*, 1965; Maisin *et al.*, 1971). After ingestion of radiotoxic doses of insoluble β-particle emitters, death was due to damage to the large intestine in both rats and dogs. Values for the LD_{50} of about 33 Gy for rats (25–41 Gy) and 40 Gy for dogs (20–52 Gy) were obtained in experiments in which rats ingested either $^{106}Ru/^{106}Rh$ (average, 1.4 MeV β) or ^{147}Pm (average, 0.06 MeV β) and dogs were given $^{106}Ru/^{106}Rh$ (Cross *et al.*, 1978; Sullivan *et al.*, 1978). The estimated dose to crypt cells in rats was the same with both $^{106}Ru/^{106}Rh$ and ^{147}Pm (about 35 Gy), although the dose to the mucosal surface was 30–35 times greater with ^{147}Pm than with $^{106}Ru/^{106}Rh$. On the basis of these data, an LD_{50} of 35 Gy has been suggested, with a simple linear function (LD_0, 20 Gy; LD_{100}, 50 Gy) (Pochin, 1983).

Comparison of the toxicity — on the basis of dose per body weight — of $^{106}Ru/^{106}Rh$ in rats of different ages showed decreasing sensitivity in the order: newborn > adults > weanlings (Sullivan *et al.*, 1987). The greater sensitivity of adults than of weanlings probably reflects the longer residence time of the gastrointestinal contents in the small bowel and caecum in adult animals. The newborn is more sensitive because of the uptake and retention of these radionuclides in the mucosal cells of the intestine, particularly in the proximal small intestine. Other radionuclides, including the actinides, are also retained in the mucosa of the immature gut of neonatal rats (see, e.g., Sullivan & Gorham, 1982). It would appear that at the high levels of retention observed in young rats, doses of up to 100 Gy/day may be received by cells located towards the tips of the intestinal villi, without evidence of mucosal injury. Indeed, a much lower concentration of radionuclide was seen in the region of the more sensitive crypt cells.

4.2.3 *Association between deterministic effects and cancer*

It has been suggested (Van den Hooff, 1984; Islam, 1985; Mole, 1986; Lord *et al.*, 1991; Gössner *et al.*, 2000) that cancer induction in humans and animals is linked to the occurrence of deterministic effects in the tissues in which the cancer arises. This suggestion has been made for several tissues, but the arguments have been most fully

explored in the case of human bone tumours resulting from skeletal irradiation by α-particle-emitting radium isotopes, and this is considered in detail below.

The first cases of malignant bone tumours occurring after therapeutic X-irradiation were reported by Beck (1922) in patients treated for tuberculous arthritis. Since then, detailed reports of post-irradiation neoplasia in bone after therapeutic external irradiation have been published (reviewed by Huvos, 1991; Schajowicz, 1993; Unni, 1996). The latent period, the time between exposure to external irradiation and the appearance of sarcoma, varies between three and 55 years with an average of about 15 years. It has been suggested that a dose of at least 30 Gy and a 3–4-year latent period is sufficient to establish a universally acceptable cause-and-effect relationship between exposure to radiation and tumour (Huvos & Woodard, 1988; Huvos, 1991).

Bone sarcomas associated with internal irradiation from ^{226}Ra and ^{228}Ra were first reported as an industrial hazard in radium-dial workers by Martland *et al.* (1925; see section 2.2.1). The long-term analysis of bone sarcomas in radium dial-painters is a classic epidemiological study in occupational medicine. In studies in the USA covering about 2600 individuals, 64 cases of malignant bone tumours were observed among persons in whom measurements were made (Rowland, 1994; Fry, 1998). A detailed study of the histopathology of ^{226}Ra- and ^{228}Ra-induced bone sarcomas in humans has been published (Schlenker *et al.*, 1989). There appears to be a practical threshold dose of 10 Gy for bone sarcomas in radium-dial painters (Rowland, 1997; Thomas, 1999).

Bone sarcomas have been induced in humans after incorporation of the short-lived α-particle-emitting ^{224}Ra. In the most recent reports on a group of 899 patients treated with ^{224}Ra in Germany (1945–55) (see section 2.2.2), 56 malignant bone tumours were described in 55 patients in this cohort (one person developed a second bone sarcoma two years later). Most of the cases occurred within the first 25 years after exposure; only four bone sarcomas have been diagnosed since 1980. According to data extracted from the cancer registries of the Saarland and of the former German Democratic Republic, the expected number of bone sarcomas in a group of this size would have been < 1 (about 0.3) over the entire observation period. The age at first injection of the patients who developed bone sarcomas ranged between 2 and 55 years. The time to tumour appearance peaked eight years after exposure. Thirty-seven bone sarcomas were reported in the 217 patients under the age of 21, whereas only 19 bone sarcomas occurred in 18 patients among the 682 adults. In the group of 393 patients with ankylosing spondylitis, only six bone sarcomas were seen. The lowest dose to the bone surface associated with a bone sarcoma in the total study cohort of patients exposed to ^{224}Ra was 9 Gy (Nekolla *et al.*, 1999, 2000).

More recent treatment of 1577 patients with ankylosing spondylitis with ^{224}Ra led to a mean bone surface dose of about 5 Gy. Among 626 deceased patients, only four cases of malignant primary bone tumour (compared with 1.3 cases expected in the general population) were observed, comprising one fibrosarcoma of the bone, one malignant fibrous histiocytoma, one reticulum-cell sarcoma (malignant lymphoma) of

the bone and one medullary plasmacytoma (myeloma), originally observed in the bone marrow of the sternum and pelvis. There was no osteosarcoma. In the control group, only one case, a medullary plasmacytoma, was observed (Wick *et al*., 1999).

Several studies have been devoted to the anatomical distribution of radiation-induced bone sarcomas in humans and beagles and their correlation to the distribution of radiation dose and bone mass or bone surface area (Spiers *et al.,* 1977*;* Spiers & Beddoe, 1983; Lloyd *et al.*, 1991). Spiers *et al.* (1977) observed a strong correlation between tumour frequency and the extent of the trabecular areas (endosteal surface areas). ^{226}Ra- and ^{224}Ra-induced bone sarcomas predominantly involved the appendicular skeleton; however, comparison of the sites of bone sarcomas induced by ^{226}Ra and and ^{224}Ra showed an axial:appendicular ratio of 14:85 with ^{226}Ra and 24:75 with ^{224}Ra. In contrast to spontaneously occurring tumours or those induced by external radiation, relatively few radium-induced tumours are located in the knee joint (Gössner, 1986).

In a retrospective study of patients who developed histopathologically confirmed bone tumours after receiving ^{224}Ra, the two commonest histological types were bone-producing osteosarcomas and non-bone-producing sarcomas of the fibrocytic and fibrohistiocytic type (Gössner *et al*., 1995). The first case of malignant fibrous histiocytoma of the bone after internal irradiation was described in this study. The unusually high incidence of this tumour type in ^{224}Ra patients, with a ratio of osteosarcoma:fibrosarcoma or malignant fibrous histiocytoma of 1.9:1 differs significantly from that among spontaneously occurring skeletal tumours (ratio, 5.9:1) (Gössner, 1999).

The types of bone tumour in patients exposed to ^{224}Ra have been compared with those in persons exposed to ^{226}Ra and ^{228}Ra (Schlenker *et al*., 1989), patients exposed to external irradiation (Huvos, 1991; Unni, 1996) and unirradiated patients who developed bone tumours at the sites of pre-existing bone lesions, such as Paget disease (Schajowicz, 1993) and bone infarct (Desai *et al*., 1996). The types of bone sarcomas among both radiation-induced and ‘secondary’ bone tumours are different from those among spontaneously occurring bone tumours (Table 117), with a higher incidence of bone tumours of the fibrosarcoma–malignant fibrous histiocytoma type and a lower incidence of chondrosarcomas in the first two groups than among the spontaneous tumours. These observations strongly suggest a close histogenic relationship between changes in the microenvironment (deterministic effects on bone remodelling and the fibro-osseous response, i.e. ‘radiation osteitis’) and the production of bone-producing and non-bone-producing tumour types (Gössner, 1999).

4.3 Reproductive and developmental effects

In the broad sense, the effects of perinatal exposure to radionuclides include a wide array of stage-dependent reproductive and developmental alterations. The adverse effects seen after prenatal exposure fit the classic model of developmental toxicity: prenatal and neonatal deaths, reduced growth and malformations. The effects of neonatal exposure, especially in rodents, follow a parallel pattern.

Table 117. Differential distribution of osteosarcomas, fibrosarcomas–malignant fibrous histiocytomas and chondrosarcomas among radiogenic, non-radiogenic 'secondary' bone tumours and spontaneous bone tumours

Source of bone tumours	No. of tumours (%)		
	Osteosarcomas	Fibrosarcomas/malignant fibrous histiocytomas	Chondrosarcomas
Radium-224	22 (53)	14 (33)	6 (14)
Radium-226 and -228	32 (70)	14 (30)	0 (–)
External irradiation	155 (63)	82 (33)	9 (4)
Paget disease	39 (64)	17 (28)	5 (8)
Spontaneous	3148 (55)	538 (10)	1990 (35)

From Gössner *et al*. (2000)

Dosimetric considerations are important in determining the qualitative and quantitative nature of the responses. When the overall content of the radionuclide remains constant, absolute and differential growth lead to continuing decreases in the concentration of the radionuclide, so that the distribution of radiation dose over time is different after perinatal deposition of most nuclides than after administration to adults. Differences in sensitivity cannot be dissociated completely from dose rate and dose rate reduction. Although precise timing can be achieved with external irradiation, the persistence of a radionuclide after perinatal deposition inevitably results in exposure of successive developmental stages. With many radionuclides, fetal deposition, retention and radiation dose are greater when they are administered at late stages of gestation.

In order to establish dose–effect relationships by stage of development for perinatal exposure to radionuclides, placental transfer and deposition and retention in the embryo, fetus or neonate must be quantified. The conceptus may receive radiation from radionuclides external to or within the mother's body. The radionuclide must be absorbed by the mother, enter her blood circulation and be transferred through the placenta, and these processes are influenced by the route of entry, the physicochemical form and the chemical characteristics of the radionuclide. Depending on the element and its biological behaviour in the mother and conceptus, the placenta may act as a 'transparent' intermediate compartment between the circulation of the mother and the conceptus; its structures may serve as barriers or may facilitate transfer (Sikov & Kelman, 1989; von Zallinger & Tempel, 1998). Passive diffusional transfer from the uterine mucosa may occur very early during gestation, but thereafter transfer is governed by ordinary transfer kinetics involving concentration gradients in the maternal and placental blood circulation. Selective deposition of a radionuclide in a fetal organ or tissue reduces its concentration in fetal blood and enhances transfer rates, whereas deposition of the nuclide in placental structures restricts transfer but

could lead to selective irradiation of the placenta *per se* or of primitive stem cells that originate in the blood island of the yolk sac placenta.

Most of the information about stage-dependent effects of radiation on prenatal development derives from studies of mice and rats exposed to X-rays or γ-rays at relatively high dose rates (UNSCEAR, 1986; Sikov & Hui, 1996; National Council for Radiation Protection and Measurements, 1998; IARC, 2000), and the discussion below is based on those studies.

The developmental processes constituting embryonic induction, differentiation and histogenesis are unique events. Thus, the effect of radiation on cancer induction and subsequent promotion in embryos or fetuses may differ from that in adults. Although the actual carcinogenic responses should be similar, the responses and consequences may change with the stage of neonatal development.

Effects are often categorized as early, delayed and late on the basis of their nature and the time at which they arise. The responses of embryos and early fetuses to irradiation are similar in human, non-human primate and lower mammalian species, reflecting the comparability of the developmental patterns. Differences between species in the relative and absolute duration of individual developmental stages lead to species-specific response characteristics. These differences become more prominent later in gestation, and differences in maturity at birth are associated with differences in response and apparent sensitivity. The distinctions become less clear with protracted exposure, and the spectrum often shifts with different radionuclides.

Early effects arise from alterations of cells present at the time of irradiation or of the first several daughter-cell generations, and may comprise mitotic inhibition, cell death and interruption of pregnancy. Depending on the species and the time of exposure, early prenatal deaths may manifest as reduced fertility, miscarriage or abortion, or as decreased litter size or increased resorptions in rodents. Defects in the developmental process that lead to malformations of surviving embryos may also manifest as alterations of metabolism or physiology.

Delayed effects produced by prenatal exposure to radiation are considered to be overt or latent defects that arise later or biologically modified expressions of previously induced defects. Prenatal exposure may result in decreased body or organ weights, with minor stage differences among species. The more severe effects occur after exposure during organogenesis and at the beginning of fetal development, but the period of sensitivity to postnatal growth retardation extends throughout the perinatal period, at least in rats and mice. Particularly in the case of exposure during the fetal period, effects on the weights of certain organs, e.g. the brain, may be disproportionate to the effect on body weight, resulting in substantially larger decreases in absolute and relative brain weights.

Differences in the nature of the response to radiation are also related to compensatory cell proliferation, which may occur later in gestation and during the postnatal period. Histopathological and cytological examinations of the human central nervous system after prenatal exposure to radiation consistently indicate that the effects of high

radiation doses on neurogenic processes are similar in humans and in experimental animals; this is true particularly of those effects that involve changes in the matrix and cell migration in specialized neural epithelia (ICRP, 1986). There is a programmed sequence of events that leads to qualitatively different cell populations at successive stages, which is probably also related to the lower capacity of neural tissue to repair lesions. Neuronal cell formation ceases early in the postnatal period, so that subsequent compensation of tissue damage is accomplished through gliosis, which can lead to an imbalance between neural and glial cells. In humans and in experimental animals, microcephaly or cerebral dysmorphology and underdevelopment are the most distinctive and frequent retardation effects.

After early cell inactivation, gametogenesis appears to be one of the most radiosensitive developmental processes. Nevertheless, germ cells have a great capacity for regeneration in the early stages of gametogenesis and also high rates of redundancy and natural elimination in adults. After acute and chronic irradiation, postnatal fertility is one of the most sensitive indicators of prenatal damage.

Late effects include the various degenerative diseases, solid tumours and leukaemia, or lesions of later life. A number of factors make it difficult to extrapolate the results of animal experiments to risk estimates for radiation-induced late effects in humans. In many experiments, the animals were selectively bred to have a high spontaneous incidence of neoplasms or degenerative diseases, so that the predisposition to development of various lesions in later life may be specific to the stock of animals studied. Factors such as interactions between differences in life span, altered endocrine status, competing risk factors in mortality, tumour latency and destruction of cells of target tissues are known to play a role in the development of late effects after prenatal irradiation of animals. Extrapolations should therefore be restricted to general features rather than to quantitative estimates of risk.

4.3.1 *Sensitivity at different stages of gestation*

The effects of irradiation depend on the period of gestation. Moreover, transfer of radionuclides to the conceptus, their subsequent biological disposition and the doses of radiation are also related to the stage of gestation.

(*a*) *Preimplantation period*

The earliest phases of development involve pluripotent cells with high mitotic activity, which develop into the blastocyst that is implanted into the uterine mucosa. Individual cells are radiosensitive during this period, when there is a high capacity for regeneration and reorganization.

The effects of exposure to radiation during the preimplantation period are characterized by a moderately high threshold, and most studies of rodents exposed during this period have not shown persistent effects. There is an all-or-none response over a wide range of doses, i.e. preimplantation or early postimplantation death, or complete

restitution, so that the survivors develop into fetuses with normal morphology. No other clear-cut types of effects have been found after exposure to radiation during this period.

(*b*) *Embryonic stage*

The period of organ formation in developing embryos is referred to as organogenesis. Cell death, mitotic delay or genomic alterations during organogenesis can lead to defects in the developmental process and have been considered the major cause of morphological lesions or malformations. Cell proliferation during this phase is accompanied by remodelling: the neural plate forms into the neural tube, outpouchings develop into the primitive brain, the complex structure of the heart is attained and the external body form develops. Extensive intrauterine selection, especially in humans, often avoids further prenatal development of embryos with major defects. Malformations are the characteristic effect of exposure to radiation during the period of major organ formation. Changes in radiosensitivity have been noted in various stages of organ differentiation.

(*c*) *Fetal period*

Gestation from organogenesis through term is referred to as the fetal period. It is characterized by growth and histogenic development, through which organs and tissues progress from primordial structures into more differentiated histological entities that are present at birth. This phase of development is relatively brief in many rodent species, but it comprises more than two-thirds of the prenatal period in primates. Acute exposure of rats or mice to radiation during later stages of this period has less effect on intrauterine mortality than exposure during organogenesis. Irradiation tends to result in developmental retardation but has little effect on the basic shape or structure of most organs. The sensitivity at the cellular level remains essentially the same, however, which is important in the formation of specific populations such as germ cells and structures in the central nervous system.

Irradiation often yields a mosaic of surviving and reproductively inactive cells in embryonic or fetal tissues. Damage to the cell nucleus or chromosomes may lead to acute cell death, chromosomal aberrations or aneuploidy and to inactivation or delayed death of daughter cells. Depending on the stage of gestation, there is a selection against aneuploid cells and those with chromosomal aberrations or micronuclei. The cell losses that result from cytogenetic alterations, rather than the defects *per se*, seem to be the determining factor in many developmental effects; however, genetic alterations may be involved in carcinogenesis and other late effects.

Progenitor cells of the gametic and haematopoietic lines are formed in blood islands of the yolk sac during early organogenesis and migrate into the embryo. These early cells are susceptible to apoptotic or reproductive death and to induction of latent effects expressed in subsequent cell lineages. Inactivation has been detected after acute irradiation during developmental phases ranging from early primordial cell formation through the fetal period of spermatogonial and oogonial precursors. This

effect is of particular relevance with regard to exposure to radionuclides that localize in these cells.

The central nervous system is formed through complex interactions between cell proliferation and migration, so that interference with either process affects its development. Defects induced by low doses of radiation are believed to involve the migratory processes and/or subsequent differentiation of the neural cells. The capacity for compensation decreases progressively during histogenesis. More damage will manifest because it is more likely that affected fetuses will survive than after exposure at earlier stages. Thus, deficits tend to progress and become apparent as delayed or late effects during the postnatal period.

Mammalian species generally have similar teratological characteristics in response to exposure to radiation, including short, stage-specific sensitive periods during early development and a relatively high capacity for restoration. The effects of radiation on the central nervous system may be exacerbated by progressive loss of neuronal reproductive capacity, which can lead to functional deficits in the absence of gross anatomical brain malformations. As has been noted, scaling is required when susceptibility to specific effects is related to developmental stage at exposure. Phylogenetic differences must also be considered when comparing interactions in humans with those that are important in rodents.

4.3.2 *Malformations in human populations after the Chernobyl accident*

Several research groups have examined the incidence of mutations, chromosomal abnormalities and congenital anomalies in the areas surrounding the 1986 reactor accident in Chernobyl (see section 2.7.2(*d*)). No clear consensus has been reached with regard to the incidence of malformations, and its attribution to exposure to radiation, either directly or indirectly, poses numerous difficulties.

A well-documented health consequence of the Chernobyl disaster was a dramatic increase in the number of pregnancy terminations in regions nearby and far from the accident site, as anxiety about possible prenatal exposure led to an increased demand for abortions and delays in planned conception. Reductions in birth rates over the 5-year period after the accident were seen not only in the Russian Federation but also in Denmark, Hungary, Italy and Norway (Castronovo, 1999).

Congenital malformations were studied in 16 590 5–12-week-old embryos and fetuses obtained from pregnant women during legal medical abortions in Minsk (control area) and from 2578 women in the Gomel and Mogilev regions where the soil was contaminated with ^{137}Cs at a rate of > 0.6 MBq/m^2. The malformation frequency during the period 1986–94 was 7.41 per 100 abortuses in the contaminated areas and 4.66 per 100 in the control regions. No information was given on malformations in abortuses obtained before 1986 (Lazjuk *et al.*, 1997).

In the same study, congenital malformations among neonates were also analysed. The frequency was 7.00 per 1000 live births in the contaminated areas in the period

1987–94 and 3.87 in 1982–85 ($p < 0.05$). In the control regions, the frequencies per 1000 neonates were 5.58 and 3.90 during those periods, respectively ($p < 0.05$). It was not possible to correlate the individual doses of pregnant women with the incidence of congenital malformations. No convincing data were obtained that structural changes in chromosomes are associated with the increase in malformation frequency in the contaminated area (Lazjuk *et al.*, 1997).

A retrospective analysis of the birth archives in two large hospitals in Kiev over the period 1969–90 showed no change in the rates of miscarriage, congenital anomalies or perinatal mortality between the periods before and after 1986 (Buzhievskaya *et al.*, 1995).

Castronovo (1999) concluded that there is no evidence that exposure of pregnant women to radiation from ^{137}Cs released during the Chernobyl accident has had any harmful effects.

4.3.3 *Developmental responses to radionuclides*

(*a*) *Radon and progeny*

A group of 43 pregnant Sprague-Dawley rats was exposed to ^{222}Rn in air at a dose of 1.3×10^7 Bq/m^3 radon and its progeny adsorbed onto ore dust for 18 h/day on days 6–19 of gestation. Another 26 rats were exposed to a filtered-air atmosphere. No developmental toxicity or teratological changes were detected. The calculated dose rate on the last day was 1.5 mGy, which was estimated to have resulted in 20 mGy during the post-implantation period, with a protracted dose equivalent of 0.4 Sv (Sikov *et al.*, 1992).

(*b*) *Radium*

Seventeen children of 10 mothers who had been employed as radium-dial painters were evaluated. One child was born while the mother was still employed, and the others were born 2–15 years after the mother had stopped dial painting. At the time of the study, seven of the 10 mothers had died from radium poisoning, but no health problems were detected in any of the children. Whole-body measurements of γ-radiation (detection limit, 0.2 μg radium) showed none in 14 of the children, with inconclusive results for the three others. No radon was found in the breath of these three children (detection limit, 0.1 pCi/L [0.0037 Bq/L]) (Martland & Martland, 1950).

The fertility of women who had been employed as radium-dial painters was investigated in epidemiological studies. The study population consisted of 199 women who had been employed in the dial-painting industry in Illinois, USA, between 1916 and 1929. The doses of α- and γ-radiation were calculated on the basis of the physical characteristics of the luminous paint used in Illinois during that period (essentially all ^{226}Ra) and the number of days that the women worked as dial painters. In most of the analyses, the estimates of total dose to the ovaries from internal radiation (α-particles from ingested radium) and of external radiation (γ-rays emitted by the luminous paint)

were combined, with a quality factor of 20 for α-particles. Internal comparisons by dose to the ovary were conducted because suitable cohorts could not be established before the analysis. There was no significant difference in the proportion of childless women in the different groups, so that differences in live-birth rates (the number of reported live births divided by the number of years of marriage until age 45) were examined only in women who had had at least one live infant. The mean of the natural logarithm of the live-birth rate decreased with increasing ovarian dose. Multiple linear regression analyses showed that the body burden, but not duration of employment, was a significant predictor of the live-birth rate (Polednak, 1980).

The study was expanded to include women who had been employed as dial painters in Connecticut and New Jersey, USA. Their exposure involved not only ^{226}Ra but also ^{228}Ra and larger doses to the ovary; however, the general approach was similar to that of the previous study. The mean numbers of pregnancies (1.2) and live-births (1.1) were significantly reduced in women in categories of internal dose to the ovary ≥ 5 Sv. Measures of health status and confounding factors that could have affected fertility, at least indirectly, were evaluated but did not appear to be important. There was no indication of an increased fetal death rate, suggesting that the findings for the live-birth rate did not involve post-implantation dominant lethal mutations, although losses before implantation could not be evaluated (Schieve *et al.*, 1997).

Most of the data on prenatal effects of exposure of animals to radium are derived from a study reported by Bagg (l922), who administered an isotonic saline solution containing dissolved radium by subcutaneous or intravenous injection to pregnant rats [strain not stated] at various stages of gestation or at times before mating. Controls were injected with the same solution after time had been allowed for decay. For comparison, other rats were exposed to external γ-rays from the same preparation of radium. The rats were killed at weekly intervals after treatment for detailed evaluation of embryos and offspring or allowed to bear their litters. Three experimental groups were considered. Sixty-five rats were mated and injected subcutaneously on days 7, 10–14, 15–17 or 18–21 of gestation. Preimplantation loss and early resorption were common, and embryonic death with continued placental growth was seen. The effects included fetal death with macroscopic haemorrhages of the placentas or fetuses, but the within-litter responses were variable so that newborn litters contained both normal and affected offspring. Another 77 rats were injected 5–7, 10–14 or 20 days before mating. Eleven died before mating, and some of the others produced either fetuses that were normal at evaluation or normal full-term young. Some females killed after mating had haemorrhagic or cystic ovaries, with either fertilization failure or early embryonic death. In order to verify the early effects seen after subcutaneous injection, a third group of pregnant rats was injected intravenously with the same preparation. Deaths with extensive haemorrhage occurred within 24 h after intravenous injection of higher doses during late gestation. The litters from rats that were exposed to γ-rays during late pregnancy showed effects that are now considered characteristic of the stage and dose.

(*c*) *Uranium*

The effects of prenatal and neonatal exposures to uranium on the development of Sprague-Dawley rats was studied in a series of experiments. Pregnant rats were injected intravenously with 0, 1.8, 3.33, 5.75 or 10 μCi/kg bw of ^{233}U [0, 66.6, 123, 213 or 370 kBq/kg bw] in citrate on day 9 or 15 of gestation and were killed at 20 days. The sizes of the groups were about 20 and 13 at the two times. The highest dose was toxic to the adults, and a statistically significant trend towards increased prenatal mortality was seen with dose. Exposure reduced the fetal and placental weights. Cleft palate was detected in nine fetuses from three litters after the highest dose at nine days (but not 15 days), and exposure at this time led to a dose-related increase in the numbers of litters and fetuses with rib anomalies. Several fetuses at the two highest doses were oedematous at 15 days (Sikov, 1987a).

Calculations of the radiation doses from parallel radioanalyses indicated that these effects were attributable to chemical toxicity rather than to radiation. Other results suggested that some of the fetal effects were mediated through alterations of maternal fluid balance, which is consistent with the known nephrotoxicity of uranium. In order to examine postnatal toxicity, groups of 10–14 newborn, 12-day-old and weanling rats of each sex from each age and dose group received an intraperitoneal injection of 0, 2, 5 or 10 μCi/kg bw of ^{233}U [0, 74, 185 or 370 kBq/kg bw]. The lowest dose did not affect the growth of weanlings, whereas 185 kBq/kg tended to decrease growth and the highest dose had a statistically significant growth-reducing effect. Only the highest dose significantly decreased the growth of the female juveniles, but not the male juveniles, and there was no effect on the growth of the neonatal rats (Sikov, 1987a).

(*d*) *Neptunium, plutonium and americium*

Numerous investigators have examined the placental transfer, fetoplacental distribution and neonatal absorption and metabolism of plutonium and americium (National Council on Radiation Protection and Measurements, 1998; see section 4.1). There are quantitative differences in the effects of these nuclides at various stages of gestation. They can be transferred to offspring via lactation, and their gastrointestinal absorption by neonatal animals is greater than that by adults.

Autoradiographic studies in several species during various periods of gestation showed that the highest fetoplacental concentrations of plutonium and americium are found in fetal membranes, especially in the developing yolk sac; the placenta contains lower concentrations and the embryo or fetus even less. The villous yolk sac is a functional nutritive structure present in early development, which contains blood islands from which stem cells of the haematopoietic system and gametes originate. Autoradiographic studies in rodents and other mammalian species, including non-human primates, have shown consistently that most of the radioactivity in embryonic membranes is contained within this structure.

Studies have shown stage-dependent changes in the deposition and localization of radionuclides in developing liver and skeleton during both the prenatal and postnatal periods. Plutonium is deposited primarily on the bone surfaces of adult animals, but there is progressive, relatively rapid burial in the bone matrix in the fetus and during the perinatal period as a result of bone remodelling.

The doses of α-radiation to embryos tend to be relatively low and homogeneous; they represent a small fraction of the average whole-body dose received by the pregnant woman and an even smaller fraction of the dose to the tissues in which the radionuclide is deposited. The localized concentrations in placental structures may, however, result in radiation doses that are as large as or larger than the doses to any maternal tissue. Because of their short path length, α-particles from radioactive decay in these extraembryonic volumes would not reach the embryo, but β-particles could irradiate embryonic tissue.

(i) *Neptunium*

Intravenous injection of rats with 0.3–5 μCi/kg [11.1–185 kBq/kg] ^{237}Np as the oxalate increased the incidence of preimplantation mortality (Ovcharenko & Fomina, 1982).

(ii) *Plutonium*

Wistar rats at day 9 of gestation were injected with graded doses of ^{239}Pu prepared with sufficient excess citrate so that it was predominantly in the monomeric form. The rats were killed for radioanalysis and for evaluation of toxicity in their litters at various times between days 10 and 15 of gestation. In the rats injected with doses < 1.5 μCi [55.5 kBq], there was no measurable increase in the mortality rate of fetuses; at doses of 3–12 μCi [111–444 kBq], there was 60% mortality, and at 25 or 50 μCi [925 or 1850 kBq] all fetuses died. None of the surviving fetuses showed gross morphological defects. When the highest dose was given by injection to pregnant rats on day 15 or 19 of gestation, no prenatal mortality was seen during the remainder of the prenatal period, although there was some microscopic damage to the fetal liver (Sikov & Mahlum, 1972).

A series of studies was conducted to examine age-related differences in the biological behaviour and effect of ^{239}Pu in relation to the physicochemical form in which it was injected, either monomeric or predominantly polymeric. In most cases, intravascular injection was used in weanling and adult rats, whereas newborn animals received injections directly into the heart. Prenatal exposure was ensured by intravenous injection of their dams.

A dose of 30, 60 or 90 μCi/kg [1.1, 2.2 or 3.3 MBq/kg] of each of the two ^{239}Pu preparations was injected intravenously into groups of 12 newborn, weanling and young adult Sprague-Dawley-derived rats. The LD_{50} and relative sensitivities were calculated on the basis of deaths that occurred over the subsequent 60 days. The polymer was about twice as toxic as the monomer to weanlings and adults, but there

was little difference between the two forms in the newborns soon after administration. Especially in weanlings and adults, a much higher percentage of the injected activity of the polymeric form than of the monomeric form was present in the liver. The difference between the physicochemical forms with respect to initial tissue distribution was less prominent in the newborns but developed as they matured (Mahlum & Sikov, 1974).

Another experiment was performed to examine differences in the effects of the monomeric and polymeric forms of plutonium on liver function in male and female Sprague-Dawley rats. Newborn and seven-day-old rats received injections into the ventricle of the heart, and 21- and 110-day-old animals received injections into the tail vein. The doses were chosen to produce minimal mortality over a 21-day period, and were 60 μCi/kg bw [2.2 MBq/kg bw] of the monomer and 30 μCi/kg bw [1.1 MBq/kg bw] of the polymer. Some of the animals were killed at sequential times for macroautoradiographs. At 21 days after injection, six rats from each age group were injected intravenously with ^{198}Au-labelled colloid and killed 10 min later to determine the reticuloendothelial function of the liver from hepatic incorporation of the radiolabelled colloid. Phagocyte function was unaffected by either form in the adults and weanlings, but in the seven-day-old animals the monomer produced a marked decrease and the polymer had only a slight effect. The polymer reduced the colloid uptake to less than half of the control value in the animals exposed at birth, and the monomer inhibited the uptake almost completely. Another six rats from each age group were injected intravenously with [^{131}I]sodium tetraiodotetrachlorofluorescein (rose bengal) to evaluate the function of the liver parenchyma, i.e. the blood clearance of radioiodine. This function was decreased in the livers of animals of the two younger age groups, the monomer being more effective than the polymer. Little effect was detected in the older animals (Kashima *et al.*, 1972).

In a series of studies to evaluate the effects of plutonium on bone strength, weanling and adult Sprague-Dawley rats were injected intravenously and newborn animals were injected intracardially with ^{239}Pu citrate at doses ranging from 0.006 to 0.09 μCi/g bw [222–3330 Bq/g bw] [group sizes not reported]. The animals were radiographed at intervals, and some from each group were killed at intervals for radioanalysis and histological examination. Subjective observations at one month after exposure indicated that the long bones of rats injected as weanlings with 0.06 or 0.09 μCi/g bw were extremely fragile, and the radiographic examinations revealed many spontaneous fractures in these animals. The frequency of fractures, which were accompanied by abnormal healing, was even greater three months after injection; histological examination showed abnormal callus at the break points in the bones, consisting of dense connective tissue. Rats in the three groups were killed and necropsied nine months after exposure for various analyses, including measurement of the mechanical breaking strength of the femur. The highest doses resulted in high doses of radiation to the femurs of adults but had little effect on their strength; there was also no effect on the strength of this bone in the newborn animals, which received only small doses to the femur. In contrast, there was a marked, dose-dependent decrease in the breaking strength of femurs from the animals injected as

weanlings, although the radiation doses were similar to those of the adults. The calcium and phosphorus contents of these femurs were not appreciably altered, but the water content was greatly increased (Mahlum & Sikov, 1969).

In experiments to investigate the late effects of plutonium, three-month-old adult and 21-day-old weanling Wistar rats were injected intravenously with 0.3, 1 or 3 μCi/kg bw [11.1, 37 or 111 kBq/kg bw]. Pregnant rats were injected intravenously on day 19 of gestation with 6, 20 or 60 μCi/kg bw [222, 740 or 2220 kBq/kg bw] of the same solutions for exposure of the fetuses, and newborns were injected intracardially with 3, 10 or 30 μCi/kg bw [111, 370, 1110 kBq/kg bw]. Other rats were injected with citrate solutions at the same concentration to serve as controls. Groups of about 25 rats of each sex from each group were maintained. Longevity decreased with increasing dose, and the effect was statistically significant in the three groups exposed postnatally. Although no significant effect on longevity was found in the group exposed prenatally in this experiment, subsequent experiments found significantly decreased survival of similarly exposed rats (see below). The incidence of bone tumours is described in section 3.3 (Sikov *et al*., 1978).

In experiments to examine the effect of gestational stage on the delayed effects of plutonium, pregnant rats were injected intravenously with ^{239}Pu citrate preparations at representative stages (day 9, 15 or 19 of gestation) at a dose of 0.011, 0.11 or 1.1 kBq/g bw. The cumulative radiation dose rates and doses to the embryo or fetus and offspring increased with prenatal age at injection. Prenatal exposure resulted in a dose-related decrease in postnatal growth that was more severe among offspring from litters injected on day 19 of gestation than in those treated on day 9; animals exposed on day 15 of gestation showed damage of intermediate severity. The exposure also shortened the lifespan (Sikov, 1989).

In studies on the influence of foster–rearing of rats on the postnatal effects of prenatal exposure to plutonium, pregnant rats were injected intravenously with 2.2 kBq/g bw ^{239}Pu citrate or with a citrate (control) solution on day 19 of gestation. At one day of age, the offspring of some control and exposed litters were kept with their own dams, while others were fostered to lactating females that had received the same (or the opposite) exposure as had their dams. The growth curves and body masses of prenatally exposed offspring reared by control dams were similar to those of control offspring reared by their own or control foster dams, but the growth curves of control offspring that were nursed by exposed dams were depressed. Offspring exposed prenatally lived significantly less long than control groups, but fostering had no consistent effect on longevity. The incidences of several histopathological lesions of soft tissues, including tumours of the liver and adrenal gland, were elevated in the three groups exposed to plutonium prenatally, but the incidences were not affected by fostering or by the exposure history of the dams that reared the offspring. These observations are in accord with measurements that showed that most of the lifetime ^{239}Pu burden was derived from placental transfer after prenatal exposure, and that milk made little contribution (Sikov, 1989).

Pregnant C57BL6 mice were injected intravenously on day 13 of gestation with 30 kBq/kg bw ^{239}Pu nitrate. The fetuses were evaluated on day 17 of gestation and the offspring at two and seven days and four, eight, 22 and 55 weeks of age. The numbers of colony-forming units in spleen and bone marrow increased rapidly after birth but at lower rates in exposed than in control mice. The quality of the haematopoietic microenvironment in femoral marrow was adversely affected in the exposed offspring (Mason *et al.*, 1992).

In experiments to investigate the possibility that transgenerational effects from preconceptional paternal irradiation might render offspring more vulnerable to secondary exposure to an unrelated carcinogen, ^{239}Pu citrate (at 0, 128 or 256 Bq/g) was administered by intravenous injection to male mice 12 weeks before mating with normal females. Two strains of mouse were used — CBA/H and BDF1. Haematopoietic spleen colony-forming units and fibroblastoid colony-forming units, a component of the regulatory microenvironment, were assayed independently in individual offspring at six, 12 and 19 weeks of age. Female offspring of BDF1 mice were injected with *N*-methyl-*N*-nitrosourea (MNU) as a secondary carcinogen at 10 weeks of age and monitored for the onset of leukaemia or lymphoma. The mean values of colony-forming units were unaffected by preconceptional paternal injection with ^{239}Pu, although there was an apparent increase in variation in fibroblastoid colony-forming units between individual animals. By 250 days, 68% of MNU-treated control animals (no preconceptional paternal injection) had developed thymic lymphoma (62%) or leukaemia (38%). The first case arose 89 days after MNU administration. In the groups in which the male parent had been treated preconceptionally, leukaemia or lymphoma developed 28 days earlier, the incidence rising to 90% by 250 days, so that leukaemia (65%) predominated over lymphoma (35%). This second-generation excess of leukaemia appears to be the result of preconceptional paternal injection with ^{239}Pu and may be related to inherited changes that affect the development of haematopoietic stem cells (Lord *et al.*, 1998c).

The transmission of chromosomal instability to the haematopoietic stem cells of offspring after exposure *in utero* to X- or ^{239}Pu radiation was investigated after pregnant CBA/Ca mice were injected with 80 kBq/kg bw ^{239}Pu nitrate in sodium-citrate solution or X-irradiated with 1 Gy on day 13 or 14 of gestation. Colony-forming units were grown from haematopoietic stem cells from fetal liver and from bone marrow from the offspring and from the dam. Non-clonal, unstable chromosomal aberrations were scored in metaphases from individual stem-cell colonies. It was concluded that irradiation *in utero* was not more efficient in inducing chromosomal instability in the offspring than in the fetus or the dam. All three cell populations showed a similar degree of unstable aberrations, in terms of both absolute numbers of non-clonal aberrations and relative excess (Rosemann *et al.*, 1999).

The effect of combined exposure to external γ-radiation and α-radiation from intratracheal injection of ^{239}Pu on the reproductive function of female rats and their progeny was studied in 609 female Wistar rats, 998 young rats of the first generation

and 80 young rats of the second generation. Female rats were exposed to γ-radiation at a dose of 12.9, 25.8, 51.6 or 103.2 mC/kg. Half of the irradiated rats received an intratracheal injection of ^{239}Pu nitrate (37 kBq/kg) immediately after γ-irradiation. The absorbed dose of α-radiation from ^{239}Pu to the ovary was 0.026 Gy 30 days after the beginning of the experiment, 0.23 Gy at the time of mating (90 days after injection of ^{239}Pu) and 0.70 Gy at the end of the experiment. No radioactivity was detected after radiometry of the progeny. No disorders of the oestrus cycle or fertility were detected in the treated rats, and no difference between the treated and control groups was observed with regard to the number of young rats or their survival, body mass or physical development. The number of erythrocytes in young rats born to females exposed to both γ-radiation (12.9 and 25.8 mC/kg) and α-radiation was higher than in young rats born to intact controls or to rats exposed to γ-radiation only or ^{239}Pu only. The ratio of brain volume to body mass in young rats of the second generation did not differ from that in the control group after combined exposure to γ- and α-radiation or exposure to γ-radiation or α-radiation only (Ovcharenko & Fomina, 1983).

In studies on the effects on the germ cells of male mice of exposure to ^{238}Pu, groups of 20–60 male hybrid mice (CBA × C57BL)F_1 aged 2.5 months received a single intraperitoneal injection of ^{238}Pu nitrate (pH 2; dose range, 7–1850 Bq/g bw). The plutonium content in the testis represented 0.02–0.04% of the amount injected. The average absorbed doses of α-radiation in the testis were 0.02–0.96 Gy, and the dose rates from α-radiation were 0.004–1 cGy/day. In order to evaluate the relative biological effectiveness of α-radiation from ^{238}Pu, the mice were exposed continuously to γ-radiation from ^{137}Cs at doses of 0.92–4.5 Gy. Exposure to α-radiation from ^{238}Pu was shown to induce dominant lethal mutations, reciprocal translocations, fragmentation of chromosomes and abnormal sperm-head morphology. No association with the average dose of α-radiation to the testis was observed for any of the end-points. The biological effectiveness of α-radiation relative to continuous exposure to γ-rays for the end-points studied was reported to be 10–20 (Pomerantseva *et al.*, 1987a,b, 1988).

(iii) *Americium*

In a study of fetal toxicity, rats were injected intravenously at various stages of gestation with high doses of ^{241}Am citrate (3–15 μCi/g bw; 111–555 kBq/g bw) and killed two days later. The amount of ^{241}Am retained in the placenta was 9–15 times higher than that in the fetuses at all times tested. The smaller the quantity of injected ^{241}Am, the larger the fraction of this radionuclide that was retained in the placenta. More ^{241}Am was transferred to the fetus towards the end of pregnancy. No malformations were noted, but injections at early stages of gestation led to lower fertility and higher intrauterine lethality (Moskalev *et al.*, 1969).

These and later studies have shown consistently that a smaller fraction of injected americium than plutonium enters the conceptus or fetoplacental unit. Proportionately less americium was selectively deposited in the placenta and membranes than that observed with plutonium. It is not clear if this difference in distribution is responsible

for the prenatal effects, but it is consistent with the higher incidence of embryolethality and malformation after administration of ^{239}Pu than of ^{241}Am at the same activities (Sikov *et al.*, 1986).

A group of 59 male BALB/c mice, 11 weeks old, were injected intraperitoneally with 103 Bq/g bw of ^{241}Am citrate, and groups of 15–62 14-week-old females received 45, 90 or 213 Bq/g bw. There were about 30 male and female controls. In a second experiment, pregnant mice were injected intravenously with 100, 500 or 1500 Bq/g bw of ^{241}Am citrate on day 14 of gestation, and the offspring were reared by untreated dams. The controls were sham-injected pregnant mice whose litters were raised by other dams. The longevity was slightly but significantly shortened by exposure of adult mice to all doses of americium; the response was non-linear. The longevity of the offspring exposed *in utero* was not reduced (Van den Heuvel *et al.*, 1995).

(*e*) *Hydrogen*

Experiments were performed to investigate the prenatal effects of ^{3}H in mice. Superovulated $BC3F_1$ (C57BL/C3H) female mice, 10–12 weeks old, were caged overnight with ICR males; the day after mating, as detected by a plug, was designated day 0. Two-cell embryos in the late G_2 phase and early S phase were isolated and exposed to $^{3}H_2O$ at 100–2000 μCi/mL [3.7–74 MBq/mL] or external γ-rays. In another experiment, the fallopian tubes of superovulated virgin $B6C3F_1$ mice were isolated and inseminated *in vitro* with sperm from ICR male mice, and the early pronuclear stage was exposed to $^{3}H_2O$ or γ-rays. More than 95% of the control embryos developed to the blastocyst stage. The immediate effect of irradiation was a delay in cleavage among embryos, which was severe in pronuclear embryos exposed to γ-radiation. Although a few embryos died during the cleavage period, most continued through several divisions before arrest at the morula stage, after which they degenerated. The LD_{50} values (in MBq/mL) were 15.8 for late G_2 phase two-cell embryos, 8.5 for early S phase two-cell stage embryos and 4.4 for the pronuclear stage; the differences were statistically significant. Similar LD_{50} values were obtained with γ-rays. The biological effectiveness of β-radiation from $^{3}H_2O$ relative to γ-radiation did not differ significantly from 1, and was < 2 (Yamada *et al.*, 1982).

In similar studies with mice (strain: Radiologisches Institut, Freiburg), an average of 92% of 178 control embryos was reported to develop to the blastocyst stage within 66 h. Development was not significantly inhibited by exposure to $^{3}H_2O$ at a concentration < 370 kBq/mL. The percentage that reached the blastocyst stage declined progressively, and the incidence of degeneration at the morula stage, or earlier, increased as the concentration of $^{3}H_2O$ increased. No blastocysts developed at the highest concentration (18.5 MBq/mL). In experiments with [^{3}H]thymidine, only 83% of the 21 embryos reached the blastocyst stage when exposed to 0.74 kBq/mL, and a concentration of 18.5 kBq/mL almost completely inhibited development to the blastocyst stage. [^{3}H]Thymidine was about 1000 times more effective than $^{3}H_2O$. Further analyses indicated that $^{3}H_2O$ inhibited the late stages of blastulation, while [^{3}H]thymidine delayed

the rapid cleavage stages. This conclusion is compatible with the intracellular distribution of energy (Streffer *et al.*, 1977).

The radiotoxicity of [^{3}H]thymidine and [^{3}H]arginine in early mammalian embryo development was studied in two-cell stage mouse embryos (strain, Radiologisches Institut, Freiburg) isolated 30 h after conception and incubated *in vitro* with 370 or 925 Bq/mL of each of the radiolabelled compounds up to the formation of the inner cell mass, 192 h after conception. No difference in the radiotoxicity of the two compounds was seen with respect to cell proliferation. In contrast, the formation of blastocysts, the outgrowth of trophoblasts and the formation of inner cell mass were impaired more strongly by [^{3}H]arginine than by radiolabelled thymidine, at similar external concentrations. Increased micronucleus formation was found 96 h after conception with the higher concentration, [^{3}H]arginine again being more effective than [^{3}H]thymidine. The authors noted that arginine is taken up more rapidly, so that the intracellular dose remained longer; furthermore, histone synthesis is not restricted to the S phase during early development, and thus arginine was incorporated while thymidine incorporation was delayed until the start of DNA synthesis (Müller *et al.*, 1987).

An assay in mouse embryo chimaeras was used to determine whether the radiosensitive target for the effects of ^{3}H on embyronic cell proliferation is nuclear or extranuclear. This in-vitro assay involves aggregating an irradiated cleavage-stage embryo with an untreated embryo, culturing them for two or three cell cycles and then dissociating them to determine the number of cells contributed by each of the two embryos. With eight-cell embryos from superovulated CD1 mice cultured in ^3H_2O or [^{3}H]thymidine, the concentrations were adjusted so that both radioactive compounds would deliver comparable calculated doses to the nucleus, which resulted in about 100-fold greater extranuclear doses delivered by ^3H_2O. In a control experiment, embryos were exposed to ^{137}Cs γ-rays. Fifteen to 20 embryos were incubated at a range of concentrations for 2 h during the S phase of the eight-cell stage, aggregated with unirradiated fluorescein isothiocyanate-labelled control embryos and incubated for about 20 h. Chimaeras of two untreated embryos (one labelled with fluorescein isothiocyanate) were used as controls. Each embryo was then partially dissociated and examined to obtain the total cell number and the number of unlabelled (non-fluorescent) cells, which were expressed as a ratio. The ratios were averaged for each dose group, and differences between the three modalities were compared. At the highest nuclear doses (up to 1 Gy), a small but statistically significant decrease in proliferation ratio was seen with all three treatments. [^{3}H]Thymidine consistently produced lower mean proliferation rates than ^3H_2O over the dose range 0.14–0.43 Gy. The authors concluded that the radiosensitive target for effects on embryonic cell proliferation is nuclear (Wiley *et al.*, 1994)

In studies on the dosimetry and effects of ^{3}H on rat embryos and fetuses, rats [strain and numbers not stated] were injected subcutaneously with ^3H_2O (0.3–11.1 MBq/g bw) at several times before mating or during gestation. Effects were found at all but the lowest dose. Injection before implantation led to failure of implantation or

defects that resulted in intrauterine death. The typical disorders in dams, fetuses and placentas were vascular. Both the maternal and fetal parts of the placenta showed oedema and congestion. Oedema and subdermal haematomas were found in 21% of 17–19-day fetuses given a dose of 3.0 MBq/g bw and in 41% at 11.1 MBq/g bw, but no other histological changes were detected in the fetus (Moskalev *et al.*, 1969).

Pregnant Sprague-Dawley rats were maintained throughout pregnancy at constant activities of ^3H_2O at 0.04–37 MBq/mL of body water via the drinking-water, providing doses of 3–300 mGy/day to the embryo and fetus. The biological effects included sterility, reduced growth, reduced litter size, increased resorptions and microencephaly. The ^3H incorporated into fetal organs represented 20–30% of the average maternal ^3H_2O activity during gestation (Cahill & Yuile, 1970).

In a similar study, groups of six Sprague-Dawley rats received ^3H-labelled drinking-water from conception of the F_1 generation through delivery of the F_2 generation. The equilibrium concentrations were 0.37, 3.7, 37 and 370 kBq/mL, which gave daily dose rates of 0.03–30 Gy to the dams in each group. The offspring were weaned at 21 days, and two males and two females from each litter continued to receive ^3H_2O. At about 110 days, the females were bred to males at the same dose but from different litters, and exposure was continued through the birth of the F_2 animals. Ovaries and term fetuses were removed for evaluation, while other fetuses and F_1 males were used for radioanalysis. No morphological abnormalities were observed in offspring of either generation; the litter sizes and postnatal growth of the F_1 generation were unaffected, although the highest dose resulted in a 30% reduction in testis weight at 125 days of age. Statistically significant effects were seen in the F_2 generation, including increased resorption and decreased litter size at the highest dose, although there appeared to be no difference in the preimplantation death rate. Birth weight was decreased at 37 and 370 kBq/mL, and the relative brain weights were reduced at all doses except 0.37 kBq/mL. The maximum tissue concentrations were reached during exposure *in utero*, with concentrations in the brain and testis that were greater than the average tissue concentration (Laskey *et al.*, 1973).

In a similar study, ^3H_2O produced a dose-related reduction in brain weight in F_2 neonates, and differences in eye opening and righting reflex, startle reflex and hypoactivity in a residential maze were reported (Cahill *et al.*, 1976).

Sprague-Dawley rats were injected intraperitoneally on day 1 of gestation with ^3H_2O and given ^3H-labelled drinking-water to maintain an equilibrium level of 0, 37, 370 or 3700 kBq/mL throughout gestation, which yielded a calculated cumulative dose of 0, 0.066, 0.66 or 6.6 Gy to the conceptus over the gestation period. Dose-related reductions in body weight and brain weight were seen after exposure to 0.66 or 6.6 Gy, but the relative brain weight was reduced only at 6.6 Gy. No changes were found in a variety of neurological indicators (Bursian *et al.*, 1975).

In another series of studies, large amounts of ^3H_2O were given by a single injection to evaluate the effects on prenatal and postnatal development. NMRI mice were injected intraperitoneally with ^3H_2O at doses of 2.5–50 MBq/g bw on day 7, 9 or

11 after conception. The doses of 40 and 50 MBq/g bw were lethal to many of the dams within the 11-day period after injection on day 7, and all embryos were resorbed in the litters that were available for sacrifice and evaluation. The rate of resorption was about 50% per dam at 30 MBq/g bw (14 litters, on day 9), with a significantly elevated frequency of dead fetuses and reduced fetal and placental weights. More than half of the live fetuses had cleft palate. Injection of 5 MBq/g bw on day 7 or 9 (13 litters each) significantly increased the frequency of resorption and decreased the fetal and placental weights. The dose of 20 MBq/g bw on day 9 or 11 (12 litters each) produced even greater reductions in weights, but the rate of resorption was increased only at the earlier time. A low incidence of skeletal anomalies was found in the fetuses of dams at 20 and 30 MBq/g bw. Histological examination of some of these fetuses showed that administration of the lower dose on day 9 or 11 of gestation retarded brain histogenesis and resulted in hypoplasia of the gonads (Török *et al.*, 1979).

In a study of postnatal development, groups of nine pregnant NMRI mice were injected with ^3H_2O at a dose of 2.5, 5 or 10 MBq/g bw on day 9 after conception. Litter size and perinatal mortality were not affected, although the number of deaths before weaning was increased at the highest dose, and birth weight and growth rate were reduced at 10 MBq/g bw. Mating tests at two months of age showed that the offspring of dams given 10 MBq/g bw were not fertile (both sexes), and female but not male offspring at 5 MBq/g bw had reduced fertility. There was no effect on the rate of mortality in the interval between weaning up to 4–5 months of age, when most offspring were killed. The weights of the gonads were reduced in males and females at all doses, and the brain weight was reduced at the higher doses. The ovaries were often cystic; the number of oocytes was drastically reduced at the lowest dose, and they were virtually absent at the highest dose. The seminiferous epithelium was in a state of disintegration in the four males at the lowest dose examined histologically and was absent in most of the tubules of five males at the high dose; spermatozoa were observed only occasionally (Török *et al.*, 1979).

In a multi-generation study, 35-day-old male inbred C57BL/6M mice were given ^3H_2O in drinking-water at a concentration of 370 kBq/mL for 35 days. The mice were then mated to unexposed females. The offspring were separated after weaning, and the new generation of males was given ^{3}H-labelled drinking-water according to the same dose regimen, followed by mating with unexposed siblings. This sequence was repeated until the 18th generation. The number of offspring and the sex ratio were recorded. Some mice of each generation were maintained for life, and others were killed. At the ninth generation, 50 pairs from the two lines were entered into a separate evaluation to obtain data on parameters such as fertility in subsequent generations. In general, there was a progressive reduction in the relative fertility of the successive generations of exposed males, which became apparent as reduced litter sizes, reduced birth weights and increased perinatal mortality, and was paralleled by increased intrauterine mortality (Méwissen *et al.*, 1984).

In a study of morphological changes in the cerebral cortex after exposure to ^3H during the neonatal period, one-day-old Swiss albino mice were injected [route unstated] with ^3H_2O at a dose of 120.62 kBq/mL of body water [assumed to represent 90% of the body weight] and then maintained with their dams on ^3H-labelled drinking-water at 185 kBq/mL throughout the experimental period. The young mice [numbers not stated] were killed at intervals up to six weeks of age. The total radiation dose delivered was calculated to be about 64 mGy/week. In sections of the brain, the overall thickness and the thickness of the visual region of the cerebral cortex relative to that of controls was significantly decreased at five and six weeks *post partum*. Decreased relative thickness was also observed in other regions of the cortex. Changes were found in total cell packing density, which became consistently statistically significant at five weeks of age. Glial packing density increased during the first and second weeks (Bhatia & Sisodia, 1988).

In a study on the testicular effects in the F_1 generation, pregnant mice were given an initial intramuscular injection of ^3H_2O at a dose of 118 kBq/mL of body water (assumed to represent 62% of the body weight) on day 16 of gestation and were then maintained on ^3H-labelled drinking-water at 185 kBq/mL. F_1 mice were killed at three, four or five weeks of age, the testes were fixed and prepared as histological sections, and cells in various stages were counted. The calculated total doses delivered were 0.23, 0.29 and 0.35 Gy at the three times. At three weeks of age, pronounced vacuolization of the cytoplasm was found in the testis, with pyknotic nuclei in many tubules. Many of these showed giant cells, haemorrhage and oedema of interstitial tissues, which led to an increased tubular diameter at four weeks; a lesser degree of damage was seen at five weeks, when fibrosis was the primary feature. By three weeks of age, the numbers of type A, I and B spermatogonial cells were reduced to about 80, 70 and 60% of the control values, respectively; these levels remained approximately the same throughout the remainder of the experiment. Various stages of spermatocytes were maintained at about 70% of the level of controls, and spermatids at 45% of control levels. The usual appearance of sperm in the lumen by five weeks of age was not observed (Bhatia & Srivastava, 1982).

A similar design was used in a study of the effect of exposure to ^3H_2O at various gestational stages. Pregnant Swiss albino mice [number not stated] were divided into three groups: one group received an intramuscular injection of 74 kBq/mL of body water at day 0 (preimplantation), day 6 (organogenesis) or day 14 (fetal period) of gestation and was then maintained on a 34% higher concentration of ^3H in the drinking-water on days 0–5, 6–12 and 14–18, respectively. Further groups of animals were given H_2O by injection at a dose of 111 or 185 kBq/mL of body water and then maintained on ^3H-labelled drinking-water during similar periods of gestation. Control pregnant females were injected with distilled water. Animals in all groups were killed on day 18 of gestation for examination of the uterus, implantation sites and prenatal mortality. During the preimplantation period, but not during the other periods, the average number of implantation sites was significantly reduced and the percentage of

resorbed embryos increased at all doses. The percentage of resorbed embryos was also increased by exposure to the higher two doses during organogenesis. Only a few types of anomalies were seen, which included open eyelids in roughly one-third of the fetuses exposed during organogenesis (the actual percentage increased with dose) and a few instances of 'short tail' at the two higher doses (Sharma & Saini, 1993).

In studies on the effects of exposure to ^3H on brain development, 14 Sprague-Dawley-derived female rats were given ^3H_2O at a concentration of 111 kBq/mL, the average daily intake being 2.9 MBq. To study the effects in newborn offspring, ^3H_2O was supplied from 30 days before pregnancy until parturition. For the multigenerational study, ^3H_2O was also supplied after birth to the offspring and their lactating dam until they reached maturity. At this time, the female offspring were mated with control males, and the process was repeated for three additional generations. Animals were analysed as newborns or at 30 or 120 days of age. None of the treated animals showed indications of radiation illness. The blood cell volume and number, blood glucose and bone marrow were not significantly altered, although alkaline phosphatase activity in blood was significantly decreased in exposed when compared with control rats. The various measures of pregnancy outcome, including litter size, neonatal body weights and weights of the cerebral hemispheres, were essentially the same as in the controls. The total DNA content of the newborns' brains showed a slight decrease in all generations, but this varied in magnitude and was not statistically significant in all cases. The protein concentration was decreased in all generations except F_3, and the reductions were statistically significant; the protein:DNA ratio relative to the controls was variable across generations (Zamenhof & van Marthens, 1979, 1981).

As part of a longitudinal study to evaluate the behavioural effects of prenatal exposure to ^3H_2O, C57BL/6J pregnant mice received a single intraperitoneal injection at 12.5 days of gestation, to give a calculated total cumulative absorbed dose *in utero* of 50, 100 or 300 mGy. The pregnant control mice received saline. The litters were weaned at 21 days, and male offspring were used for behavioural tests; there was a total of 110 offspring from 59 mothers. The exposed animals, especially at the two higher doses, showed hyperactivity in the open field test at day 21, but they were hypoactive at 100 days of age. Other tests showed that the exposed animals had difficulties in both learning and memory retention for skilled performance (Wang & Zhou, 1995).

In a study on the effect of exposure to ^3H_2O in the squirrel monkey (*Saimiri sciureus*), groups of 28–43 females were assigned to one of seven dose groups on the day of insemination and given an intraperitoneal injection of ^3H_2O to produce the desired body concentration. They were then maintained on ^3H_2O for the rest of the study. The concentration of ^3H_2O was adjusted upwards twice during the experiment to achieve preselected body water concentrations. The mean radioactivity of the drinking-water during weeks 7–33 was 0, 3, 11, 27, 52, 107 and 218 kBq/mL in the seven dose groups, respectively. The animals were weighed at four-week intervals, and urine samples were collected. Blood samples were obtained from the progeny within 24 h of birth, and they were then killed and samples taken for radioanalysis and

histological evaluation. There were three to nine full-term deliveries in each group, and a total of four full-term deliveries were stillborn. The numbers varied but there were essentially no differences among the groups in terms of delivery rate, proportion of discernible abortuses or gestation time. With occasional exceptions that were considered not meaningful, the body dimensions, body weights and organ weights did not correlate with the concentration of ^3H in the drinking-water. Haematological parameters were also unaffected. All of the 46 full-term progeny and four of 10 abortuses were necropsied and examined. No correlation was found between the distribution of grossly observable lesions and ^3H_2O concentration. Except in the gonads, the few histological lesions observed did not indicate a dose–response relationship, and the lesions reported in neonatal rats (see Zamenhof & van Marthens, 1979) were not observed in these monkeys. The ovaries of the newborn animals were markedly affected by exposure to ^3H, but the testes were not. The control progeny had ovaries with many large oocytes, each surrounded by inconspicuous follicular cells and little connective tissue. Particularly at the highest dose, few oocytes were discernible in the exposed groups (Jones *et al.*, 1980).

Male and female Hale-Stoner-Brookhaven random-bred mice [numbers not stated], four weeks of age, were exposed continuously to ^3H-labelled drinking-water at 111 kBq/mL. Control groups received tap water. When the animals reached eight weeks of age, they were bred randomly within their treatment group to produce offspring, which were maintained on ^3H_2O or tap water. When the offspring reached eight weeks of age, there were divided into four groups with exposure to ^3H_2O continued for females only, for males only, for males and females or terminated. Significantly more early embryonic deaths and fewer viable embryos were found when both parents or only the female received ^3H_2O. The authors concluded that the lower sensitivity of males was the result of elimination of radiation injury during the several cell divisions that occur in spermatogenesis (Carsten & Commerford, 1976).

Pregnant rats of the Donryu strain [number not stated] received a single dose of 50, 75, 100, 125 or 150 mCi of ^3H_2O [1850, 2775, 3700, 4625 or 5550 MBq] by intraperitoneal injection on day 8 or 9 of gestation. The rats were killed on day 18, and their fetuses were examined for external and internal abnormalities. Thirteen anomalous fetuses were found among the 327 control fetuses, which included nine with defects of the ventricular septa, three with defects of the vascular ring and two cases of umbilical hernia. All the implants of dams injected with 125 mCi or 150 mCi on day 8 of gestation (and with 150 mCi on day 9) were dead. At 100 mCi, 6/14 and 13/16 fetuses of dams injected on days 8 and 9, respectively, survived; all had anomalies, particularly in the cardiovascular system. There were fewer deaths and malformations at the lower doses at either time (Satow *et al.*, 1989).

As indicated in section 3.3, [^3H]thymidine has been of interest from a radiobiological standpoint, especially relative to tumorigenesis, because part of it is incorporated into the DNA of proliferating cells while the remainder is rapidly catabolized and excreted. The incorporated [^3H]thymidine remains in the DNA until the cell divides, at

which time the radioactivity is partitioned among the daughter cells, or until the cell dies, after which it can be reused. Because of their short range, the β-particles emitted by [^{3}H]thymidine in DNA selectively irradiate the nucleus.

A system of continuous intravenous infusion by means of a small pump delivering 1 mL/day to pregnant rats was used to compare the effects of [^{3}H]thymidine and ^3H_2O. Autoradiographic evaluation showed that all cell nuclei in newborn rats are labelled with [^{3}H]thymidine after continuous exposure of the dam from day 9 of gestation through term, and that there is a linear relationship between the dose administered to the dam and the incorporation into DNA and non-DNA fractions in various organs of the developing rat. Four-month-old Wistar rats were infused continuously with [^{3}H]thymidine or ^3H_2O on days 9–21 of gestation. The concentrations of each compound (0.8 and 1.6 μCi/g bw [29.6 and 59.2 kBq/g bw] per day of [^{3}H]thymidine and 8 and 16 μCi/g bw [296 and 592 kBq/g bw] per day of ^3H_2O) had been shown previously to reduce the numbers of oocytes by approximately 50 and 95%. On the basis of the dose to the nuclei of oocytes, the biological effectiveness of [^{3}H]thymidine relative to that of ^3H_2O was calculated to be 3.7. The oocyte depletion test was used as the biological end-point, and ^{3}H incorporation at birth as the basis for the dose calculation (Schreml & Fliedner, 1977).

Delayed and late effects of exposure to ^3H_2O and [^{3}H]thymidine *in utero* were investigated in pregnant SAS/4 mice that received ^{3}H-labelled drinking-water from day 1 of gestation at a concentration of 1.8, 11, 16 or 30 μCi/mL [66.6, 407, 592 or 1110 kBq/mL]. Another group of mice received in-dwelling subcutaneous catheters to provide continuous infusion of [^{3}H]thymidine during the 12 days between day 7 of gestation through term, which resulted in total amounts of ^{3}H infused of about 10, 27, 50 and 130 kBq/g bw. The surviving fraction of oocytes of all types decreased progressively as a function of total body ^{3}H at birth after administration of ^3H_2O or [^{3}H]thymidine, the latter being two to three times more effective than ^3H_2O. Growth and survival were adversely affected at the highest doses (Lambert & Phipps, 1977, 1983).

A solution of [^{3}H]thymidine was injected intraperitoneally at a dose of 7.4 MBq/mL into two-month-old male mice [strain not stated]. The total dose per mouse (11.1 MBq) was given in six fractions over two days, which produced uniform labelling of a wide band of maturing sperm. Since the early spermatocytes are the latest cells to pick up thymidine during spermatogenesis, the first labelled sperm would appear in the fifth week after injection. From the fourth week onwards, injected males were mated with untreated females. After mating, the uterine contents of some of these females were analysed by autoradiography. The first labelled sperm appeared on day 30 after the first injection, when 34% of all sperm were labelled. By day 32, all sperm cells were labelled. The proportion of labelled sperm decreased to 40% on day 40 after the first injection. The other females were dissected on day 13 of pregnancy, and the frequency of dominant lethal mutations was scored. This frequency paralleled the degree of labelling of the sperm (Bateman & Chandley, 1962).

(*f*) *Carbon*

The genetic effects associated with exposure to [^{14}C]glucose were investigated in male (CBA × C57Bl)F_1 hybrid mice. In one experiment, the compound was administered orally as an aqueous solution to three groups of 10 mice, each at graded doses that resulted in calculated radiation doses to the gonads after three months of 0.22, 0.5 and 1 Gy, respectively. In a second experiment, the animals received curds with labelled glucose for 33 days, resulting in estimated gonadal doses of 0.74 and 1.47 Gy at the end of this period. In the third experiment, the glucose was given in drinking-water for six or 12 months. The doses to the gonads were estimated to be 0.006 and 0.031 Gy at six months and 0.013 and 0.066 Gy at 12 months. Males were mated to females at intervals after exposure, and the frequencies of dominant lethal mutations, reciprocal translocations and sperm-head abnormalities were evaluated. Pre- and post-implantation losses occurred during the first mating intervals after single exposures, and pre-implantation losses occurred during the second interval at the two higher doses, indicating dominant lethal mutation of pre-meiotic cells and also post-meiotic cells. There was a transient decrease in male fertility at the high dose, apparently due to spermatogonial death, with subsequent recovery. After the 33-day exposure, only post-meiotic exposure increased post-implantation loss at both doses. In both of these experiments, the frequency of abnormal sperm heads was not clearly different from that in controls, but translocations were more frequent than in controls although not dose-related. Exposure in the third experiment did not affect the frequency of reciprocal translocations, but it increased the frequency of sperm-head abnormalities at 12 months, although this frequency was not altered at six months. The higher dose reduced fertility at both six and 12 months, but this was apparently not related to genetic change (Pomerantseva *et al.*, 1983).

(*g*) *Phosphorus*

Pregnant Sprague-Dawley rats received ^{32}P as sodium phosphate by intraperitoneal injection at a dose of 37 or 111 kBq/g bw on day 16, 18 or 20 of gestation. Measurements of radioactivity in femur and liver indicated a total dose per fetus of 0.1 Gy, with an inhomogeneous distribution, as judged from autoradiography, that resulted in the highest doses to the skeleton. The results suggested a substantial reduction in the lifespan of offspring after exposure of the dam to 111 kBq/g bw but not to 37 kBq/g bw. The testes of male offspring of dams at the high dose were about 25% of the normal size and showed histological changes, including an absence of spermatogenesis. Castration cells were seen in the pituitary. Nine adult animals of each sex were injected with 37 kBq/g bw and mated with fertile unexposed rats to assess effects on fertility. Only three of the treated females and two of the treated males were fertile (Berry *et al.*, 1983).

Pregnant Wistar rats were injected intraperitoneally with 18.5, 37, 55.5 or 74 MBq of ^{32}P phosphate in saline solution on day 6, 8, 9 or 10 of gestation and killed and

dissected at intervals thereafter for determination of radioactivity. A second series of animals received graded doses of 11.1–74 MBq of ^{32}P at the same stages of pregnancy as the first group. These animals were killed on day 14 of gestation. A dose-related decrease in fetal weight was found in all treated animals. At the dose that killed about 50% of fetuses, their weight was about 60% of that of controls. The LD_{50} values for each day of injection differed significantly from that on all other days. Gross and detailed histological examinations of the fetuses showed consistent patterns of growth retardation and anomalous morphology. In general, the incidence and severity increased with increasing dose, and the type of malformation was somewhat dependent on the gestational day at injection. After exposure on day 6 of gestation, some of the 14-day old fetuses had the appearance normally seen at 13 days. The malformations included limb reduction, decreased size of the mandible and occasional instances of incomplete closure of the facial grooves. Histologically, some fetuses at the highest doses showed a distinct decrease in the density of the liver cords, and the sinusoids were almost completely devoid of fetal erythrocytes. The malformations after injection at day 8 or 9 were similar but more severe and frequent. They also included ocular and facial defects, with cases of anophthalmia at the latter time. Defects of the eye were most common after injection on day 10, as were facial defects and a marked reduction of limb size. Several of the fetuses in this group showed decreased density of liver cords that were similar to those described above (Sikov & Noonan, 1957, 1958).

The effects of exposure to ^{32}P later in gestation were evaluated in subsequent studies with pregnant Wistar rats receiving a dose of 22.2, 37 or 74 MBq on day 14 or 17 of gestation. Animals were killed at intervals after injection, starting after 8 h and then daily afterwards. Other animals received an injection of 7.4 or 14.8 MBq and were kept until the birth of their litters. The number of live births per litter was reduced by injection of 74 MBq at either time but was not affected at lower doses. Injection of 74 MBq at 14 days produced fetal deaths during the last two days of gestation, while neonatal deaths attributable to the trauma of parturition were also noted. No prenatal deaths were seen with injection on day 17; a few deaths occurred during the birth process. A total of 33 litters were born, and there was no delay of parturition. Birth weight was reduced at a dose of 14.8 MBq at 14 days, and injection of the higher doses at 17 days produced statistically significant decreases in birth weight (Sikov & Lofstrom, 1957).

Injection of a low dose (7.4 MBq) of ^{32}P on day 14 or 17 of gestation led to subdural haemorrhage at birth and the preceding days, with bleeding into the abdominal viscera and brain at higher doses. There was a general decrease in the size of the skeleton in late fetuses and newborns after injection on day 14 of gestation, with alterations in the relative dimensions of several bones at high doses; injection on day 17 produced less pronounced changes. Administration of the highest dose (74 MBq) on day 14 decreased the density of lymphocytes in the cortical region of the thymus; the effect was even greater with injection on day 17. The effects on the gonads were variable; the effects of 74 MBq given on day 14 of gestation ranged from relatively normal testes to large degenerated areas, depressed mitotic rate and a pronounced decrease in the number of

primordial spermatagonia. Only a moderate decrease in mitotic rate was found after injection on day 17 (Sikov *et al.*, 1958).

The effect of radiophosphorus on the development of the anterior pituitary was studied in Swiss albino mice. A dose of 37 kBq/g bw injected intramuscularly into pregnant females seven days after fertilization did not affect the pituitary of the fetuses or newborn mice. The same dose given intraperitoneally to one-day-old mice caused hypertrophy of acidophilic cells in the pituitary. After injection of this dose into seven-day-old mice, cell death and an increased number of acidophils were seen, but a decreased number was observed in 14- and 21-day-old animals. Males and females differed markedly with respect to effects on the pituitary when injected at the age of 21 and 28 days, the females showing more severe damage (Dev & Srivastava, 1981).

(*h*) *Strontium*

The effects of ^{90}Sr on the development of the ovaries in fetal mice were studied in CBA mice injected intravenously on day 11 of gestation with 185, 370 or 740 kBq of ^{90}Sr nitrate per animal. Five randomly selected female offspring from each dose group were killed at 56 days of age, and the histological structure of one ovary was examined. Starting at 70 days of age, the remaining females (19–26 per group) were tested for fertility by mating with an untreated male for 100 days, at which time they were killed and the ovaries prepared for microscopic evaluation. There were marked quantitative changes in the histological composition of oocyte and follicle types in the controls between 56 and 170 days of age, including a substantial reduction in the total number of cells per ovary. The numbers of cells at both times were reduced to about 50% of control values by the dose of 185 kBq. A progressively greater reduction was seen at the higher doses, which was more marked at 170 than at 56 days. The earliest ovarian developmental stages (oocytes I–III and primordial follicles) were most sensitive. The mating tests did not indicate effects on fertility, as judged by the fraction of females that were fertile, the mean litter size and the total number of young weaned. Thus, despite the considerable reduction in the number of oocytes, the pool of mature follicles was adequate for production of litters at normal frequency and of normal size (Rönnbäck *et al.*, 1971).

In a subsequent study of similar design, 370 kBq ^{90}Sr nitrate were injected to female rats on day 8, 11, 13, 16 or 19 of gestation. When the offspring reached the ages of 28, 56 and 84 days, five randomly selected females in each group were killed and the ovaries prepared for histological examination. The control ovaries showed the expected changes with age. Exposure to ^{90}Sr decreased the total number of cells per ovary relative to the control, and the effect was progressively more marked with exposure later in gestation. As in other studies, the oocytes and primordial follicles were the most sensitive to radiation (Rönnbäck, 1979).

In a further study of similar design, pregnant CBA mice were injected with 185 kBq of ^{90}Sr on day 19 of gestation, and some of the litters were cross-fostered with controls at birth. This provided four groups of five or six litters that received either no

^{90}Sr, prenatal exposure to ^{90}Sr but control milk, no prenatal exposure but milk with ^{90}Sr or ^{90}Sr *in utero* and in milk. The rate of postnatal mortality was increased among mice exposed to ^{90}Sr, especially those that received exposure only in milk. No malformations were observed. As in other studies, the ovaries of mice that received prenatal and postnatal exposure contained significantly fewer cells and showed retarded cell differentiation. A smaller but significant reduction in the number of ovary cells was found in the group that received only prenatal exposure to ^{90}Sr, while the group that received only ^{90}Sr in milk showed an even smaller effect, which was not statistically significant (Rönnbäck, 1981a).

In a further study, the effects of radiostrontium on fertility after exposure in late gestation were investigated, and the reproductive capacity of individual CBA female mice was correlated with changes in the histology of their ovaries after mating. Pregnant CBA mice were injected intravenously on day 19 of gestation with ^{90}Sr nitrate at a dose of 46, 92, 185, 370 or 740 kBq, and the female offspring (15–28 per group) were bred from 12 weeks of age with control CBA males throughout a seven-month period of continuous breeding. The number of litters born, the time between the litters and the numbers of live offspring were recorded; the litters were weaned at 20 days, just before the birth of the next litter. The mating period was considered to have been completed when more than 40 days had passed after the last birth for more than 50% of the females. This occurred at about 10 months of age, at which time they were killed and their ovaries prepared for microscopic examination. One control female, one at 370 kBq and 19 of the 24 at 740 kBq were infertile. The other five mice in the latter group became pregnant and delivered one litter each, with an average interval of 21.6 days between mating and delivery. All the other females produced one or more litter. The interval between the start of mating and the birth of the first litter increased with increasing dose (except for the highest dose), but the time to birth of the last litter was not correlated. Measures of the total reproductive capacity of the females were not markedly affected, except at 370 kBq and 740 kBq, where there was a significant decrease. A progressive decrease in litter size was seen with dose (other than the lowest) during most intervals; however, fertility was not affected by doses below 370 kBq per dam. Microscopic examination of the ovaries showed that even the 46-kBq dose produced a 37% reduction in the total number of oocytes and follicles. The ovaries were severely depleted of follicles and oocytes at higher doses, but there were multiple corpora lutea at lower doses (Rönnbäck, 1981b).

In an experiment performed to obtain information on gonadal effects in male offspring after prenatal exposure of the female parent to radiostrontium, pregnant CBA mice were injected intravenously on day 19 of gestation with a dose of 92.5, 185 or 370 kBq of ^{90}Sr nitrate. The male offspring of these females and of controls were killed in groups of four to six at 14, 28 or 56 days of age, and the testes were weighed and prepared for histological examination and quantification. There was no effect on relative or absolute testis weight, measured at 28 days. The two lower doses had no microscopic effect. At 28 days, the dose of 370 kBq resulted in an almost complete absence of elongating spermatids, a number of cross-sections showing spermatocytes

as the most advanced cell type. The number of round spermatids at 28 days was decreased, but only at the highest dose. The weight of the testes, the number of spermatids per cross-section and the relative proportion of the various cell types were unaffected in animals evaluated at 56 days. A second experiment was performed to determine the time course of changes in spermatogenesis at a dose of 740 kBq of ^{90}Sr. In the control animals, almost all of the tubular cross-sections showed spermatocytes at 14 days, but spermatagonia were the most advanced cell type found in 30% of the tubules of the exposed animals. The spermatocytes that were present were generally less advanced than in the controls. At 28 days, all tubular cross-sections showed spermatocytes in controls and exposed animals, although they were somewhat more advanced in the controls; no differences were observed at 56 days. The fertility of males from litters that had been exposed *in utero* to 740 kBq of ^{90}Sr was evaluated by mating each of 20 males to a control female for about 140 days. Eight untreated couples served as controls. Reproductive capacity was measured in terms of the number of litters, mean litter size and time interval between litters for each couple. None of these parameters was affected by exposure. Counts of Leydig cells relative to Sertoli cells at 28 days showed no difference between the exposed and the control animals. The authors concluded that the fetal testis is less sensitive to the effects of radiation from radiostrontium than is the ovary. Although germ cells may be killed, the results suggest that the surviving stem cells restore their numbers, even though this might result in a delay of differentiation (De Rooij & Rönnbäck, 1989).

(*i*) *Iodine*

The uptake of iodide by the fetal thyroid has been measured in several studies, but the kinetics of iodine in the fetus is not well understood. Zanzonico and Becker (1992) modified previous metabolic models and calculated fetal absorbed doses in clinically relevant situations such as in hyperthyroid pregnant women receiving radioiodine therapy. Analysis of data from 17 published and unpublished reports of cases in which pregnant women had received therapeutic radioiodine indicated that thyroid function at birth was not affected when the mother had been treated before the 10th week of pregnancy. When radioiodine was administered after that time, even at doses < 555 MBq, fetal thyroid function was at great risk.

A case report was published of radiation-induced sterility after administration of massive doses of ^{131}I to a 24-year-old man as therapy for metastatic thyroid cancer. The patient was pretreated with thiouracil. A dose of 246 mCi [9.1 GBq] of ^{131}I was administered and another 317 mCi [11.7 GBq] after seven months. The disease was apparently arrested six years after treatment. The patient, who had previously been fertile, was evaluated for fertility three years after treatment: his ejaculate was aspermic, and biopsies of the testis showed a complete lack of germ cells in tubules, with no evidence of spermatogenesis. The Sertoli and Leydig cells appeared normal, but the amounts of pituitary gonadotrophins in the patient's urine were markedly increased. The authors concluded that injury due to treatment with ^{131}I was responsible for the infertility. They

noted that a previously reported case showed similar findings, and that comparable changes in women had been noted in the literature (Kammer & Goodman, 1959).

A six-month-old conceptus from a pregnancy that was terminated when it was detected during a protracted course of external radiotherapy and repeated doses of ^{131}I for papillary thyroid cancer was studied. The woman had received 3.7 GBq of radioiodine twice during the pregnancy, during the second and 22nd weeks. It was estimated that the radiation dose to the fetal thyroid was 370 Gy; actual measurements of radioactivity allowed extrapolation to a fetal thyroid dose of 260 Gy. The fetal thyroid was undersized for its age, atrophic and sclerotic, and fibrosis and calcifications were seen microscopically. Although post-mortem changes could not be excluded, complete 'necrobioses' of follicular epithelial cells were seen, and autoradiography showed ^{131}I deposition in these areas and none in adjacent fibrotic areas (Arndt *et al.*, 1994).

The effect of exposure of pre-implantation Swiss Webster mouse embryos to [^{125}I]iododeoxyuridine *in vitro* was compared with that of irradiation with ^{137}Cs γ-rays. ^{125}I decay is characterized by localized deposition of its energy through emission of numerous low-energy Auger electrons. The dose for survival of 37% of the mouse embryos was about 15 cGy for the ^{125}I Auger electrons and 175 cGy for the γ-rays (Narra *et al.*, 1991).

It has been established that iodine does not concentrate in the fetal thyroid gland until follicles are observable. The offspring of mice injected with high doses of iodine had necrosis, fibrosis and compensatory hyperplasia of the thyroid. These and other studies showed that injection of pregnant animals with iodine after onset of fetal thyroid function leads to retarded neonatal growth of the offspring, a phenomenon that is also observed after neonatal exposure. A similar physiological dependence has been demonstrated during development of the human thyroid (Speert *et al.*, 1951).

In a study of the early and delayed effects of ^{131}I relative to age at exposure, young adult male and female Sprague-Dawley-derived rats, pregnant rats at 19 days of gestation, weanlings (21 days) and newborns were injected intraperitoneally with carrier-free radioiodine in dilute sulfite solution at a dose of 18.5, 37 or 111 kBq/g bw or with the sulfite solution alone. The rats were fed a low iodine diet for one week before and one week after injection, when they were returned to the stock diet. Three randomly selected rats from each age and dose group were killed at one, three and seven days after injection. The fraction of the ^{131}I that was incorporated into the thyroid and its retention were different for the four age groups. Proportionately less ^{131}I was retained at higher doses as a consequence of radiation damage to the gland, especially in the older animals. Four months after injection, a dose-dependent retardation of overall growth was seen, with statistically significant differences in the body weights at the highest dose. The reduction in size of the thyroid at this time was statistically significant in all age and dose groups and was most pronounced in male animals exposed *in utero* on day 19 of gestation. Four months after the initial injection, some of the remaining rats were placed on a low-iodine diet for one week and then injected with a tracer dose of 1 μCi [37 kBq]

of carrier-free ^{131}I to test thyroid function. Thyroid radiosensitivity was quantified in terms of the initial doses required to reduce incorporation or iodine-trapping capacity to 50% of that in the controls four months after exposure. The resulting values were 9.7 Gy in the fetuses, 53 Gy in the newborns, 120 Gy in the weanlings and 180 Gy in the adults (Sikov, 1969).

Microscopic evaluations of thyroid specimens from rats in the older age groups in the preceding study (exposed as young adults or weanlings) showed dose-related degeneration of the thyroid, which was followed by fibrosis; this was presumed to be responsible for the reduced thyroid function. In the two groups exposed in the perinatal period (*in utero* or as newborns), however, inhibition of thyroid growth and a failure of differentiation into definitive follicles were the primary morphological changes. Constriction of the trachea underlying the thyroid was seen, which was most pronounced in the two youngest groups, and the severity was dose-dependent. This effect was similar to changes that had been reported in sheep and, on the basis of the histological appearance, seemed to result from failure of the segments to develop (Sikov *et al.*, 1972).

(*j*) *Cerium*

Weanling and adult Sprague-Dawley rats were injected intravenously with ^{144}Ce chloride at a dose of 9.3, 18.5 or 37 kBq/g bw, and newborn animals were injected intracardially. The animals were radiographed at intervals, and some from each group were killed for radioanalysis, histological examination and assessment of bone strength. The cerium-exposed weanlings showed only a slight decrease in femur strength, in contrast to the results of exposure to plutonium (see section 4.3.3(*d*)(ii)) (Mahlum & Sikov, 1969).

4.4 Genetic and related effects

Interactions of ionizing radiation with various components of living cells induce many different types of molecular damage, which lead to diverse cellular responses. It is well established that efficiency in producing biological damage varies with radiation type. For many biological responses, DNA is believed to be the critical target. Ionizing radiation causes various types of DNA damage, ranging from isolated base damage, single-strand breaks or simple double-strand breaks to more complex DNA alterations involving clustered damage sites with multiple breaks and/or base changes within a few base pairs. The tertiary structure may lead to damage over longer distances. The more complex forms of damage are potentially unique to ionizing radiation and are not seen spontaneously or with other DNA-damaging agents. Subsequent processing by enzymes may accurately repair radiation-induced damage, re-establishing the normal sequence and structure. Alternatively, the processing may fail and lead to alterations in DNA, which may be in the form of changes in DNA sequence, deletions or genetic rearrangements, with large alterations seen as

chromosomal aberrations. These alterations may lead to the death of the cell or to viable inherited mutations (Hutchinson, 1985; Goodhead, 1994; Ward, 1994).

4.4.1 *α-Particle emitters*

(*a*) *In-vitro studies*

(i) *DNA double-strand breaks*

Measurements of DNA double-strand break induction in mammalian cells induced by high-LET, slow α-particles (3.0–3.4 MeV) from an external source (^{238}Pu, ^{241}Am) have shown a biological effectiveness relative to that of X- or γ-radiation of < 1 (Coquerelle *et al*., 1987; Prise *et al*., 1987; Fox & McNally, 1990; Jenner *et al*., 1993), although earlier studies indicated a value of 1.6 (Blöcher, 1988) or 3.5 (Kampf & Eichhorn, 1983), whereas values for cell inactivation and mutation of up to > 6 and > 10 have been found (depending on dose), respectively, in the same cell line (Thacker *et al*., 1982). Experimental studies have shown a significantly reduced ability of cells to rejoin α-particle-induced double-strand breaks when compared with those produced by low-LET X-rays and γ-rays after incubation of cells at 37 °C (Coquerelle *et al*., 1987; Jenner *et al*., 1993), with < 50% rejoining after 3 h, while most low-LET radiation-induced breaks rejoined within 1 h. Evidence for increased clustering of damage on DNA after exposure to α-particles comes from experiments in which plasmid DNA was irradiated under conditions that mimic the cellular environment with respect to scavenger capacity. In this study, a cell-free system derived from human embryo kidney cells was used to determine the rejoining of single-strand breaks produced by α-particles, which was found to be significantly less than that of breaks induced by γ-radiation. In addition, 50% of the α-particle-induced single-strand breaks were converted to double-strand breaks, compared with only ~12% of those induced by γ-radiation (Hodgkins *et al.*, 1996).

(ii) *Chromosomal and chromatid aberrations*

α-Particles have been shown to induce chromosomal aberrations (Purrott *et al*., 1980; Welleweerd *et al*., 1984; Griffin *et al*., 1995; Simmons *et al*., 1996) and micronuclei (Bilbao *et al*., 1989; Mill *et al*., 1996) in many studies of transformed and primary mammalian cells irradiated *in vitro*. In primary human fibroblasts, a large proportion (38–47%) of the exchange aberrations observed were complex, resulting from three or more breaks in two or more chromosomes. The complex aberrations most frequently observed were insertions (Griffin *et al*., 1995). Sister chromatid exchange following irradiation with α-particles has also been shown in human lymphocytes in G_0 phase (Aghamohammadi *et al*., 1988) and in V79 hamster cells in G_2 and S phases (Griffin *et al*., 1994). Significantly increased frequencies of sister chromatid exchange have been observed in both human and rodent cells exposed to doses of α-particles (from a ^{238}Pu source) as low as 0.31 mGy (Nagasawa & Little, 1992; Deshpande *et al*., 1996): 30% of the cells showed an increased frequency of sister chromatid exchange at

this dose, although < 1% of the cell nuclei were traversed (Nagasawa & Little, 1992). This implies that the cell nucleus need not be hit directly in order to produce sister chromatid exchange (Nagasawa & Little, 1999; see also section vii below).

(iii) *Mutation*

The lethal effect and the induction of reverse gene mutations by α-radiation was studied in *Salmonella typhimurium* strain TA1538, which has a mutation that increases the permeability of the cell wall. ^{239}Pu citrate (pH 7.0–7.3) was used as a source of α-radiation, admixed with the culture medium, and was given at doses of 74–18 500 kBq/mL. The control series contained bacterial culture and sodium citrate in the same concentration. The results showed dose-dependent cell killing and induction of gene mutations. The dependence was exponential. The estimated LD_{37} and LD_{50} values were 34.8 Gy and 21.8 Gy, respectively, and the estimated mutation doubling dose was 19 Gy (Gafieva & Chudin, 1988).

The hypoxanthine-guanine phosphoribosyl transferase (*Hprt*) mutation system is widely used for quantitative studies to detect mutations in mammalian cells, ranging from single-base changes to large intrachromosomal deletions (Albertini *et al.*, 1982). α-Particles typically induce a higher frequency of mutants per unit dose in rodent and human cell lines than low-LET radiation (Thacker *et al*., 1982; Chen *et al*., 1984; Metting *et al*., 1992; Griffiths *et al*., 1994; Bao *et al*., 1995), with relative biological effectiveness values as large as 7–10. Smaller values of 2–3 have been reported for *Hprt* mutation after α-particle irradiation of some hamster and mouse lines, and, after account was taken of survival, the effectiveness was similar or inferior to that of X-rays. This appears to be due to the highly effective cell killing and mutagenesis of low-LET radiation on these cells when compared with other rodent cell lines. The mutagenic effectiveness of low-LET radiation is more variable than that of high-LET radiation, presumably because cell lines have different abilities to repair damage due to low-LET radiation, while damage due to high-LET radiation is generally regarded as less repairable (Barnhart & Cox, 1979; Iliakis, 1984).

The cytotoxic and mutagenic effects of radon and its progeny in murine lymphoblast L5178Y-R16 cells were compared after exposure *in vitro* to a steady-state ratio of radon and its progeny (^{222}Rn:^{218}Po:^{214}Po = 1:3.5:4.5) under various experimental conditions. In one series of experiments, the cells were added to growth medium, through which a filtered mixture of radon and air had previously been passed for a ≥ 4-h equilibration period, giving a dose rate of 0.03–0.1 Gy/h. In a second series, a mixture of radon, CO_2 and air was passed over the medium overnight before the cells were added and continued throughout the 2–4-h incubation period, giving a dose rate of 0.1–0.6 Gy/h. In the third experiment, cells were added to growth medium containing ^{212}Bi — a decay product of ^{220}Rn — in the presence or absence of 0.1 mol/L diethylenetriaminepentaacetic acid, a nontoxic chelator for bismuth. In all cases, a dose-dependent increase in the induced frequency of mutation at the thymidine kinase locus was found. The frequency as a fraction of the surviving cell fraction was similar in the three experiments. The mutation

frequency was lower for a given dose of chelated compared with unchelated bismuth (Evans *et al.*, 1993).

In experiments with Chinese hamster ovary cells containing a single copy of human chromosome 11, direct evidence was obtained that passage of a single α-particle from a microbeam through the cell nucleus can induce mutation in surviving cells, measured as loss of all or part of the human chromosome (Hei *et al.*, 1997). In the same system, mutations were reported to be induced when α-particles traversed the cytoplasm, with little or no cell killing (Wu *et al.*, 1999).

Deletion-pattern analysis of α-particle-induced mutations at the *Hprt* locus of V79 Chinese hamster cells revealed a larger fraction of deletions than that caused by X-rays for the same level of survival. Furthermore, non-contiguous, partial deletions were present among the α-particle-induced mutants, which were not found after X-irradiation (Schmidt & Kiefer, 1998). In contrast, no difference was found in the ratio of large deletions:point mutations at doses of low- or high-LET radiation that resulted in about 20% survival, in mutations at the *HPRT* and *Hprt* loci classified by molecular analysis (Thacker, 1986; Aghamohammadi *et al.*, 1992). The average size of radon-induced deletions of the *HPRT* gene in human TK6 lymphoblasts was not as large as those produced by X-rays (Bao *et al.*, 1995; Chaundhry *et al.*, 1996).

(iv) *Mutations in tumour-related genes*

Activation of the Ki-*RAS* protooncogene and inactivation of the *TP53* tumour-suppressor gene are events common to many types of human cancers.

After exposure of rats by inhalation of a $^{239}PuO_2$ aerosol, resulting in an initial lung burden of about 100 nCi [3.7 kBq], specific Ki-*ras* point mutations were present in 46% of the radiation-induced malignant neoplasms of the lung. Spontaneous pulmonary neoplasms, which are rare in rats, contained similar activating mutations and frequencies (40%), and similar mutation frequencies were found in radiation-induced adenomas and foci of alveolar epithelial hyperplasia. No mutations were identified in normal lung tissue, and *ras* expression in hyperplastic lesions and neoplasms was similar to that observed in normal pulmonary epithelia (Stegelmeier *et al.*, 1991). Further studies indicated that *p53* gene mutations are relatively unimportant in the development of most lung tumours in rats exposed to ^{239}Pu by inhalation (Kelly *et al.*, 1995; Belinsky *et al.*, 1997).

Immunohistochemical studies of gene alterations in lung tumours from beagle dogs exposed to $^{239}PuO_2$ by inhalation and in lung tumours from unexposed dogs indicated that activation of the K-*ras* gene is not essential for the development of lung tumours in either exposed or unexposed dogs. The study also indicated that elevated expression of *p53* is infrequent in canine lung tumours (Tierney *et al.*, 1996). In a study of lung tumours from 25 beagle dogs exposed to $^{239}PuO_2$ by inhalation (Griffey *et al.*, 1998), the rate of K-*ras* mutations (8%) was higher than that described in canine plutonium-induced lung tumours (see above) but lower than that reported in spontaneous canine lung cancers (16%), spontaneous human non-small-cell lung cancer (13–36%) (Fong

et al., 1995) and spontaneous lung cancer (40%) or lung tumours in rats exposed by inhalation to $^{239}PuO_2$ (46%) (Stegelmeier *et al.*, 1991). These results suggest that there are species differences in the involvement of K-*ras* in the development of plutonium-induced lung tumours. [The Working Group noted that specific mutations in tumour tissue may not be directly attributable to radiation.]

(v) *Cell transformation*

The induction of oncogenic transformation by α-particles has been reported from a number of laboratories where different α-particle sources and different cell culture systems were used (Lloyd *et al.*, 1979; Robertson *et al.*, 1983). Although no significant increase in the induction of preneoplastic transformation of primary rat tracheal epithelial cells was observed when the cells were exposed directly on a planar ^{210}Po α-source (distance to source, 0–9 μm) (Ford & Terzaghi-Howe, 1993), up to 10-fold increases were seen when the cells were exposed to similar fluences of α-particles from remote ^{238}Pu and ^{241}Am sources (distance, 18 μm) (Terzaghi-Howe *et al.*, 1996). The results suggest that the geometry of the tracks of α-particles through the cell and the range of LETs to which the cell is exposed are important in determining the probability of cell survival and transformation.

Malignant transformation was induced in immortalized human bronchial epithelial cells in culture by a single 300-mGy dose of α-particles. The transformed cells were able to produce progressively growing subcutaneous tumours after inoculation into athymic nude mice (Hei *et al.*, 1994). Exposure of SV40-immortalized human thyroid epithelial cells *in vitro* to single doses (0.14–1.57 Gy) of 3.26-MeV α-particles also induced malignant transformation. Tumours were detected 50–160 days after subcutaneous transplantation of the irradiated cells into athymic mice. The first estimate of the relative biological effectiveness at peak tumour induction was 3.8 (Riches *et al.*, 1997). The oncogenic transformation potential of precisely known numbers of α-particles from a microbeam traversing mammalian cell nuclei has been measured. Traversal of the nucleus of a C3H10T½ cell by a single α-particle was found to be significantly less effective in inducing cell transformation than traversal by a mean (from a Poisson distribution) of one α-particle. Furthermore, the single particles were not significantly more effective than no irradiation (Miller *et al.*, 1999). α-Particle-induced C3H10T½ transformants were reported to be less tumorigenic after injection into mice than transformants induced by X-rays. This was ascribed to induction by the α-particles of genomic instability in the parent cells of the neoplastic foci. Although tumours produced by the X-ray-induced transformants appeared earlier, they grew at similar rates to those produced by α-particles (Lehane *et al.*, 1999).

(vi) *Genomic instability*

Radiation has been shown to induce genomic instability, a characteristic of which is a longer delay between exposure and the appearance of an effect, despite a number of mitotic divisions (Morgan *et al.*, 1996; Little, 2000).

Genomic instability has been observed in clones of cultured CBA/H mouse haematopoietic stem cells derived from marrow irradiated in vitro with 0.25–1 Gy of α-particles from an external ^{238}Pu source (Kadhim *et al.*, 1992). These doses correspond to the passage of an average of 0.5–2 α-particles through each cell. Aberrations were observed in approximately 50% of the clones that survived irradiation and were mostly chromatid-type aberrations, suggesting they had arisen after many generations, whereas aberrations occurred in only 2% of survivors of X-irradiation. Similarly delayed chromosomal effects were observed in α-particle-irradiated bone-marrow samples obtained from two of four normal human subjects (Kadhim *et al.*, 1994). When bone-marrow cells obtained from a male mouse were irradiated with α-particles *in vitro* and subsequently transplanted into female recipients, the repopulated haematopoietic system showed chromosomal instability that persisted for up to at least one year (Watson *et al.*, 1996).

The frequency of mutation at the *Hprt* locus was measured in clonal populations of Chinese hamster ovary cells derived from single cells that survived exposure to doses of 2–12 Gy of X-rays or 2 Gy of α-particles from an external ^{238}Pu source. Approximately 8–9% of the clonal populations showed high frequencies of late-arising mutations when examined 23 population doublings after irradiation, as indicated by mutation fractions 10^2–10^4-fold greater than the background. These results confirm that radiation can induce a type of transmissible genetic instability in some surviving cells that can lead to persistently increased frequencies of new mutations in their progeny for up to 23 population doublings after exposure (Little *et al.*, 1997). Studies of the clonal descendants of murine haematopoietic stem cells in vitro revealed a 5–10-fold increase in the frequency of non-clonal *Hprt* mutations after high- and low-LET irradiation at similarly effective killing doses (Harper *et al.*, 1997).

(vii) *'Bystander' effects*

Cellular effects, including mutations and chromosomal aberrations, can result not only from radiation tracks directly through the nucleus but also from tracks through the cytoplasm (Wu *et al.*, 1999), and some responses can be induced in nearby 'bystander' cells (Little, 2000). As mentioned above, Nagasawa and Little (1992) observed sister chromatid exchange in 30% of a population of Chinese hamster ovary cells after exposure to low doses of α-particles, in which < 1% of the cell nuclei were actually traversed. Subsequent studies of primary human fibroblasts confirmed this finding, with a threefold higher frequency of cells with an increased number of sister chromatid exchanges (Deshpande *et al.*, 1996) or a five times higher *HPRT* gene mutation frequency (Nagasawa & Little, 1999) than predicted from the actual number of nuclei traversed. In an experiment with mouse bone-marrow cells, the use of a shielding grid between the α-particle source and these cells gave the expected reduction in cell killing of approximately 50%, but no reduction in chromosomal instability was observed from that seen after irradiation without the grid. These results show that α-particles induce chromosomal instability in the progeny of unirradiated

cells due to unexpected interactions between irradiated and unirradiated cells (Lorimore *et al.*, 1998).

(*b*) *In-vivo studies*

In the study of Guilmette *et al.* (1989) in Chinese hamsters, described in section 3.1.2(*c*), the frequency of chromosomal aberrations in animals exposed to $^{232}ThO_2$ was 0.47/cell per Gy and was similar to that in animals exposed to ^{239}Pu citrate.

The effects of α-emitting radionuclides were studied *in vivo* in Chinese hamsters injected intravenously with ^{239}Pu citrate (0.6 μCi or 22.2 kBq/kg bw) or $^{239}PuO_2$ particles (diameter, 0.17, 0.30, 0.44 and 0.84 μm) with activities up to 6 μCi/kg bw [222 kBq/kg bw]. The distribution of the particles was traced by labelling them with ^{51}Cr. They were found to concentrate in the reticuloendothelial system, such that 90% of the injected activity was in the liver several days after injection, 3% in the spleen and the remainder in the bone and bone marrow. ^{239}Pu citrate produced a linear increase in chromosomal aberration frequency with increasing dose. After injection of $^{239}PuO_2$, the aberration frequency in the liver again increased with increasing average organ dose, the response plateauing at high doses, and seemed to be independent of particle size (Brooks *et al.*, 1974).

The effects of internally deposited radionuclides in the testis of male mice and their offspring have been studied after intravenous injection of α-particle-emitting radionuclides. No significant difference from age-matched controls was found in the frequency of reciprocal translocations in primary spermatocytes of (C57BL/Cne × C3H/Cne)F_1 mice 724 days after a single intravenous injection of 185 Bq (7.5 kBq/kg bw) of monomeric ^{239}Pu citrate (Pacchierotti *et al.*, 1983). With a higher level of injected activity, there was again no significant increase over that in controls in the translocation frequency in spermatocytes of (C3H/HeH × 101/H)F_1 mice (at 21, 28 and 34 weeks) after intravenous injections of 4 μCi/kg bw [148 kBq/kg bw] ^{239}Pu citrate (Searle *et al.*, 1976).

Although initial experiments indicated no significant excess in the rate of intra-uterine death among offspring of male CBA mice injected intravenously with up to 0.5 μCi [18.5 kBq] per animal of ^{239}Pu nitrate solution, significant differences were found in subsequent experiments in males after intravenous injections of 0.05–0.5 μCi [1.85–18.5 kBq] ^{239}Pu citrate. The animals at the higher doses became sterile between 12 and 20 weeks. At the lower doses, there was a significant excess of intra-uterine deaths in matings from week 4 onwards and an increasing proportion of late deaths in offspring. The lower doses seemed to have as severe a genetic effect as the higher doses. Among the offspring of F_1 males, a general increase was seen in the rate of intra-uterine death and an excess proportion of late deaths as compared with the controls (Lüning *et al.*, 1976).

In a study of the frequency and spectrum of chromosomal aberrations in somatic cells after exposure to ^{239}Pu, male Wistar rats were given a single intravenous injection of 23.2, 46.3 or 92.5 kBq/kg bw of $^{239}PuO_2$ (particle size, 1–2 μm). Metaphase spreads

were prepared from a bone-marrow cell suspension at 8, 32, 128, 256 and 412 days after the injection. The frequency of chromosomal aberrations in myelokaryocytes during the period of observation was increased by a factor of 1.7, 2.3 or 3.7, corresponding to the three doses of $^{239}PuO_2$ injected (Nikolaevskaya *et al.*, 1988).

The dynamics of the frequency and spectrum of chromosomal aberrations was studied in hepatocytes of rats after exposure to polymeric ^{239}Pu nitrate. Male Wistar rats were given a single intravenous injection of 18.5, 55.5 or 166.5 kBq/kg bw of ^{239}Pu polymer in nitric acid (pH 1.5). In previous experiments, it had been shown that these doses of ^{239}Pu resulted in liver cirrhosis. Metaphase spreads were prepared from homogenates of the regenerating liver (after partial hepatectomy) and analysed 16–365 days after the injection of the radionuclide. Two-phase changes in the frequency of chromosomal aberrations were observed. The frequency of aberrations increased significantly 16 days after exposure, decreased considerably during the following 1.5 months and increased again 256–365 days after exposure. The increase in the frequency of structural damage to chromosomes 16 days after exposure was due mainly to aberrations of the chromatid type, while the contribution of chromosome-type aberrations increased for longer after exposure, and the frequency was dose-dependent. No dose-dependence was observed for the early increase (Zakharova *et al.*, 1988).

Increased frequencies of chromosomal aberrations were detected in cells removed from the lungs of Syrian hamsters 24 h after exposure to $^{238}PuO_2/ZrO_2$ microspheres, giving an initial lung burden of approximately 140 nCi [5.18 kBq] (Stroud, 1977), and the induction of micronuclei in a range of cell types (deep lung fibroblasts and epithelial cells, tracheal and nasal epithelial cells) was increased in male Wistar rats exposed to radon and its progeny (up to 564 working-level months) (Brooks *et al.*, 1997). A similar effect was reported in mouse lung macrophages after exposure of female CBA/Ca mice to $^{238}PuO_2$ by inhalation (initial alveolar deposit, 67 and 424 Bq) (Kellington *et al.*, 1992).

Rhesus monkeys were exposed by inhalation to a $^{239}PuO_2$ aerosol, to achieve initial lung burdens of 2–1800 nCi [0.07–66.6 kBq]. The inhaled $^{239}PuO_2$ was retained in the body with an effective half-life of 1000 days, with some translocation from the lungs to pulmonary lymph nodes. Cytogenetic damage to blood lymphocytes was assayed at various times during the 43-month period of the study. Only animals with a cumulative lung dose > 10 Gy showed a significant increase in the frequency of rings and dicentrics when compared with controls (La Bauve *et al.*, 1980). Studies on specific-locus mutations in $(101 \times C3H)F_1$ mouse spermatogonial stem cells after injection with 0.37 MBq/kg bw of ^{239}Pu suggest that plutonium is two to three times more effective in producing mutations than protracted γ-radiation but much less effective than neutrons. Furthermore, the genetic damage induced by ^{239}Pu appeared to be more severe than that induced by low-LET radiation (National Council for Radiation Protection and Measurements, 1987b).

(*c*) *Human studies*

(i) *Workers exposed to radionuclides and residents of neighbouring areas*

Plutonium: Under industrial operating conditions, the most likely route of intake of plutonium is by inhalation of contaminated dust or droplets, although occasionally other exposure routes may be important (see section 1). If the material is insoluble, the principal region of deposition is the lungs and their associated lymph nodes. Soluble material is quickly transferred to the blood and then deposited preferentially in the bones and the liver, some being excreted.

Chromosomal aberrations in human peripheral blood lymphocytes are a recognized indicator of exposure to ionizing radiation *in vivo*. An increase in the frequency of chromosomal aberrations above the background level reflects direct exposure of circulating lymphocytes and also exposure of haematopoietic precursor cells in the bone marrow — either stem cells or cells during proliferation and maturation. Irradiated mature lymphocytes show a variety of symmetrical exchanges (translocations, inversions and insertions) and asymmetrical exchanges (dicentrics, centric rings and interstitial deletions); however, lymphocytes derived from irradiated haemopoietic precursor cells generally contain mainly symmetrical aberrations owing to selection during repeated divisions.

A banding technique that allows recognition of many symmetrical aberrations which would be missed with conventional staining was used to analyse peripheral blood lymphocytes from 54 plutonium workers from the British Nuclear Fuels facility at Sellafield, United Kingdom. These workers had body burdens in excess of 296 Bq and were divided into three groups by urine analysis of plutonium; all had been exposed at least 10 years before the analysis. These workers had also been exposed to significant levels of external γ-radiation. The controls were 39 newly hired workers with no known exposure to radiation or known clastogenic chemicals. The control group included more non-smokers and consisted of younger (average age, 33.7 years) persons than the exposed groups (average ages, 51–52 years). All groups of plutonium workers showed increased frequencies of both symmetrical and asymmetrical chromosomal aberrations over those in controls. The frequency of symmetrical exchanges exceeded that of asymmetrical exchanges in all groups, including the controls. The formation and survival of radiation-induced aberrations was randomly distributed among the chromosomes according to length. The distribution of the break-points within the cells showed an excess in the centromeres and telomeres (Tawn *et al.*, 1985).

Twenty-four of the workers in the above study were still employed at Sellafield and therefore available for resampling 10 years later. Analysis of chromosomes in G-banded peripheral blood lymphocytes was performed on two groups of workers who had 20–50% and > 50% of the maximum permissible body burden of plutonium. A significant increase was found in the frequencies of symmetrical aberrations in both

groups when compared with workers with similar histories of exposure to mainly external γ-radiation but with little or no intake of plutonium and with controls with negligible exposure, estimated to be < 50 mSv. In contrast, no significant differences in asymmetrical aberrations were found. As the latter are short-lived, this suggests that the recent exposure of mature lymphocytes was minimal. The frequencies of symmetrical aberrations had increased significantly since the earlier sampling time. Additional external exposure was negligible over this period. The results indicate that haematopoietic precursor cells are irradiated by internally deposited plutonium, and that subsequent selection results in only cells with symmetrical aberrations reaching the peripheral lymphocyte pool (Whitehouse *et al.*, 1998).

Peripheral blood from 22 workers at the Rocky Flats plutonium facility, Colorado, USA, was analysed for the presence of sister chromatid exchange and chromosomal aberrations. These workers were exposed to radiation from internal deposits of plutonium, continuous external irradiation and single or multiple chemicals. Sister chromatid exchange is sensitive to some chemical mutagens, while chromosomal aberrations are induced by moderate to high doses of ionizing radiation. The workers were grouped according to their internal burdens of plutonium (< 148, 148–740 and > 740 Bq). A significant increase in the frequency of chromosomal aberrations when compared with the control frequency was observed only in the cells of workers with > 740 Bq of internalized plutonium. There was no significant increase in the mean frequencies of sister chromatid exchange when analysed by estimated internal plutonium burden (Brandom *et al.*, 1990).

The frequency of symmetrical chromosomal translocations was measured in peripheral lymphocytes from 75 workers (40 men, 35 women, aged 53–80 years; mean, 66 ± 4) at the Mayak nuclear industrial complex (southern Urals, Russian Federation; see section 2.4.3). The workers received their main exposure between 1948 and 1963, approximately 35–40 years before blood sampling. Cumulative external γ-ray doses of 0.02–9.91 Gy and plutonium burdens of 0.26–18.5 kBq were reported. The controls consisted of 33 unexposed persons from uncontaminated areas of the southern Urals, aged 45–74 years (mean, 59 ± 8). Exchange aberrations (translocations) were scored by fluorescence in-situ hybridization with probes for chromosomes 1, 4 and 12, simultaneously with a pancentromeric probe. When compared with the control group, a significantly elevated translocation frequency was found for the total study group and for 48 subjects with and 27 without plutonium incorporation. The frequency of dicentrics did not significantly differ from that in the controls. The translocation frequency showed a significant dependence on external γ-ray dose, plutonium uptake having no substantial effect (Salassidis *et al.*, 1998).

Human T lymphocytes were used to determine the frequency and molecular spectrum of somatic gene mutations induced by ionizing radiation *in vivo* and *in vitro*. Blood lymphocytes from 17 former plutonium workers (mean age, 71.2 years) with a history of protracted exposure showed a 2.5-fold increase in *HPRT* mutation frequency when compared with unexposed adults of similar age (66–80 years). No increase in the

frequency of total gene deletions was found, which was consistent with the results for lymphocytes exposed to ^{222}Rn *in vitro*, but in contrast to the data obtained for humans exposed to ^{131}I (Albertini *et al*., 1997).

Uranium: Blood samples from 115 smokers (23–52 years of age) working in a nuclear fuel manufacturing facility who had been exposed to uranyl compounds over 1–25 years (mean lung dose, ~ 90 mSv) were analysed for various types of chromosomal aberrations. The control group comprised 94 smokers and 118 non-smokers who had not been exposed to uranyl compounds or any other known mutagens and belonged to the same age group. A significant increase in the frequency of chromosomal aberrations was found in the exposed smokers when compared with the control smokers. Smokers in the control group had a higher frequency of chromosomal aberrations than non-smokers, suggesting a clastogenic effect of smoking. The chromosomal aberrations observed in the exposed smokers were attributed to the cumulative effect of smoking and exposure to uranyl compounds (Prabhavathi *et al.*, 2000).

Cultured peripheral blood lymphocytes from 116 smokers and 80 non-smokers who were occupationally exposed to uranyl compounds were analysed for sister chromatid exchange. Blood samples were also collected from 59 control non-smokers and 47 control smokers who were not exposed to uranium. A significant increase in sister chromatid exchange frequency was observed among both smokers and non-smokers exposed to uranyl compounds when compared with their respective controls. In controls, a significant increase in the frequency of sister chromatid exchange was observed in smokers when compared with non-smokers (Prabhavathi *et al.*, 1995).

A cohort study was conducted with a group of miners from the Radium Hill uranium mine in South Australia, which was in operation from 1952 to 1961. Exposure to radiation underground in the mine was estimated from past measurements of radon gas. Persons who worked exclusively above ground according to the mine records were selected as controls. In 1991–92, the miners were interviewed, and blood was taken for measurement of somatic mutations. The mutation rates in *HPRT* and glycophorin A (*GPA)* were estimated with standard assay techniques. The frequency of homozygous mutations (NN) of *GPA* was increased in underground miners when compared with controls, and the mutation rate tended to rise with increasing exposure, except at the highest exposure (> 10 working-level months). However, there was no association between place of work and hemizygous (N0) mutations of *GPA* or the *HPRT* mutation. The authors concluded that there may be an association between *GPA* mutations and previous occupational exposure to ionizing radiation (Shanahan *et al.*, 1996).

A cross–sectional exploratory analysis of a possible relationship between environmental exposure to uranium and genetic effects included 56 volunteer residents from within a five-mile [9 km] radius around an uranium processing plant and 56 ‘control’ subjects from a geographically separate area who were not known to be exposed to uranium emissions. The groups were matched for age, sex and smoking habits. Three assays for human somatic gene mutations were carried out: the HPRT T-lymphocyte cloning assay to measure 6-thioguanine-resistant lymphocytes; the glycophorin A assay

to detect loss of expression of the M or N allele; and the micronucleus assay as a marker of chromosomal damage. The results showed no statistically significant difference between the groups. In both groups, age was significantly related to the *HPRT* mutant frequency (Wones *et al.*, 1995).

These studies of populations exposed to radiation from internally deposited radionuclides provide little consistent evidence for the induction of chromosomal or other cellular defects. The inconsistency may be related to the presence of other factors that affect aberration rates, such as external γ-rays, smoking, age and other chemical exposures, which were not adequately controlled for. Furthermore, several of the studies involved small numbers of subjects, and the findings are difficult to interpret. Because most radionuclides of plutonium or uranium are unlikely to be deposited in body sites from which there would be meaningful exposure of bone-marrow stem cells, it is not entirely clear that aberration frequencies should in fact be expected to be increased in the small numbers evaluated. The assessment of exposure was weak in many of the studies. As ^{238}U has a very low specific activity, it is unlikely that inhalation of even high concentrations would result in appreciable exposure of the bone marrow. Thus, these human studies provide little information on cellular damage induced by exposure to radiation from internally deposited radionuclides.

Radium: Chromosomes were studied in blood cultures from 62 women who had been radium-dial painters mainly in 1936–45 but also up to the middle of the 1950s. A whole-body counter was used to estimate the body burdens, which ranged from undetectable to as much as 0.56 μCi [20.7 kBq]; the women were allocated to one of three groups: 0–0.04 μCi [0–1.5 kBq] (nine women), 0.05–0.09 μCi [1.9–3.3 kBq] (20 women) and 0.10–0.56 μCi [3.7–20.7 kBq] (33 women). A control group of 57 women was chosen randomly from a general, representative population aged 35–64 years, a range similar to that of the luminizers. The proportion of cells with structurally abnormal chromosomes was higher in the luminizer population than among the sample of women without luminizing experience. The study also showed a consistent gradient of increasing structural abnormality with increasing body burden of radium (Boyd *et al.*, 1966). [The Working Group noted that the exposure during the painting of dials with radium also involved direct exposure to γ-radiation from the pots containing the paint and that the body burdens of radium would also be directly correlated to γ-ray exposure. Therefore, the association might be partly or entirely explained by occupational exposure to γ-rays.]

(ii) *Patients exposed to Thorotrast*

As Thorotrast is a colloidal solution, bone-marrow cells are exposed directly to α-radiation, and chromosomal aberrations can be detected in peripheral lymphocytes.

A 72-year-old man who had been given a 32-mL bolus dose of Thorotrast [not specified] during cerebral angiography performed in 1950 underwent whole-body radioactivity counts in 1993, which showed an estimated body burden of 4.65 g of thorium. This estimate may be in error by up to 50% owing to variation in counting

efficiency resulting from the distribution of thorium in various organs and in the weights of individuals. Peripheral T lymphocytes were cultured to quantify the frequencies and cellular distributions of asymmetrical and symmetrical types of chromosome aberrations in first-division metaphases and of micronuclei. Aberrations were scored by classic chromosome group analysis and chromosome painting techniques. *GPA* mutations in red blood cells were also analysed to obtain a relative measure of the damage sustained by the erythroid stem-cell population. About 30% of the lymphocytes in this patient contained one or more chromosomal aberrations, most of which were 'stable'. In addition, the frequency of unstable aberrations was significantly increased. Since any lymphocyte progenitor that sustained an asymmetrical aberration would not be expected to survive clonal expansion, mitogen-responsive T lymphocytes that bear dicentrics, rings or acentric fragments must be mature cells that were probably exposed to radiation in the recent past. Thus, radionuclides with long half-lives to which bone-marrow stem cells may be exposed would develop symmetrical and asymmetric aberrations. If the initial exposure occurred many years previously, the aberrations would be mainly symmetrical. Increased frequencies of *GPA* mutations were also observed, showing that genomic damage is induced in erythroid progenitors. The numbers of micronuclei in lymphocytes were only moderately increased when compared with the expected values for persons of comparable age (Littlefield *et al.*, 1997).

For a study of somatic mutation frequencies at the *GPA* and lymphocytic T-cell receptor (*TCR*) loci in erythrocytes from Thorotrast patients, peripheral blood samples were obtained from 18 Japanese men aged 67–83 (mean, 74 ± 4) years who had been treated with an unknown dose of Thorotrast 40–50 years previously. The control group consisted of male atomic bomb survivors aged 67–83 years, whose estimated dose of radiation had been < 0.005 Gy. Samples from 23 men were used for the assay of erythrocyte GPA and from 19 men for the assay of lymphocytic TCR. The men treated with Thorotrast had a significantly higher frequency of mutations at the lymphocytic *TCR* loci but not at the erythrocyte *GPA* loci (Umeki *et al.*, 1991).

Chromosomes in haematopoietic stem cells from the bone marrow of 50 Japanese veterans who had been injected with Thorotrast to evaluate injuries from war wounds and from two women who had been admitted to military hospitals (combined mean age, 65 years) were analysed. The frequency of cells with stable chromosomal abnormalities (4.35%) was significantly higher than that in the control group (0.48%), which consisted of 21 war-wounded veterans who had no record of Thorotrast administration (mean age, 66 years). Fourteen cases of clonal expansion of cells were found, with chromosomal aberrations in 11 patients. Clones observed in the cells of two of these patients had high frequencies of abnormalities (Tanosaki *et al.*, 1999).

The frequencies of chromosomal aberrations were measured 30–40 years after injection of Thorotrast in peripheral blood lymphocytes from 63 patients aged 49–77 years (average, 64.5 years). Of the 63 patients, 58 showed high frequencies of chromosomal aberrations (Sasaki *et al*., 1987).

(iii) *Residential exposure to radon*

DNA damage was measured in the alkaline single-cell gel electrophoresis ('Comet') assay in circulating lymphocytes in coded blood samples from 125 residents in 45 households in Sweden with various levels of ^{222}Rn in the drinking-water (10–2410 Bq/L) and indoor air (35–1025 Bq/m^3). Levels of radon in indoor air > 200 Bq/m^3 were found to be significantly associated with increased DNA damage in peripheral lymphocytes. No such correlation was detected for radon concentrations in the drinking-water, and there was no obvious relationship between the radon levels in drinking-water and in indoor air (Hellman *et al.*, 1999).

Chromosome analysis was performed on blood lymphocytes from 25 persons (14 female, 11 male aged 6–75 years (mean, 42 ± 21)) who had lived continuously in nine houses with indoor radon concentrations of 210–3000 Bq/m^3 (4–60 times the German average of 50 Bq/m^3). The mean frequency of cells containing dicentrics plus ring chromosomes and the incidence per cell of dicentrics plus ring chromosomes were significantly increased when compared with control levels. The mean frequency of symmetrical translocations, detected by means of fluorescence in-situ hybridization (target chromosomes 1, 4 and 12), in the group exposed to radon was slightly but not significantly increased. A similar tendency became apparent upon comparison of two groups of subjects exposed to above and below 2800 Bq/m^3-years (Bauchinger *et al.*, 1994, 1996).

The relationship between domestic exposure to radon and the occurrence of chromosomal aberrations, especially stable translocations, in peripheral blood lymphocytes was investigated by use of fluorescence in-situ hybridization with probes for chromosomes 1, 2 and 4. The study comprised a total of 84 non-smoking persons, divided into three groups according to indoor radon concentration: low (< 100 Bq/m^3; mean, 67 Bq/m^3), medium (200–400 Bq/m^3; mean, 293 Bq/m^3) and high (> 800 Bq/m^3; mean, 1737 Bq/m^3). The participants had lived for a minimum of 10 years in their present home. The groups were matched with regard to age, sex and medical exposure to radiation. Equal frequencies of translocations and other aberrations, e.g. dicentrics and complex rearrangements, were obtained in each group. As a significant correlation was found between translocations and age and the mean age was high (50 years), the genome-corrected frequency of translocations was high (about one in 100 metaphases). The study showed that continuous domestic exposure to high concentrations of radon did not increase the frequency of stable or unstable chromosomal aberrations (Lindholm *et al.*, 1999).

An apparent association ($p = 0.01$) was found between the log frequency of mutants at the *HPRT* locus in T lymphocytes from 19 non-smokers and indoor radon concentrations of 40–660 Bq/m^3 in their homes in England (Bridges *et al*., 1991). However, in a follow-up study by the same authors, no significant correlation was found between the *HPRT* mutant frequency or *BCL-2* translocation frequency and radon levels among 65 people in 41 houses in the same town (Cole *et al*., 1996).

(iv) *Mutations in tumour-related genes*

Two of five (40%) Thorotrast-induced hepatic angiosarcomas and five of 19 (26%) sporadic induced hepatic angiosarcomas contained K-*RAS*-2 gene mutations (Przygodzki *et al.*, 1997).

In nine cholangiocarcinomas and nine hepatic angiosarcomas from Thorotrast-exposed patients, only one *TP53* point mutation was found. This appeared to be a lower incidence than that in hepatocellular carcinomas in Europe as a whole (Andersson *et al.*, 1995c). In four hepatic angiosarcomas from Thorotrast patients, no *TP53* mutations (exons 5–8) were found (Soini *et al.*, 1995).

The *TP53* genes in lung tumours from 50 uranium miners in Germany and those in 13 liver cancers from Thorotrast-exposed patients were analysed. There was no evidence of a mutation hotspot at codon 249 of the *TP53* gene in either group, and no additional mutations were found in exons 5–8 in the Thorotrast-exposed patients (Hollstein *et al.*, 1997).

The association between residential exposure to radon and *TP53* mutations was investigated in samples of lung tumours from 83 non-smokers and 250 smokers obtained in a nationwide investigation in Sweden. The *TP53* status (exons 5–8) of a total of 243 tumours was determined. An increased prevalence of mutation was suggested among persons with heavy residential exposure to radon, but it was not significant. No specific mutational pattern was observed (Yngveson *et al.*, 1999).

In a study of *TP53* mutations (exons 5–7) in lung cancers from 16 former German uranium miners and 13 lung cancer patients without a mining history, no evidence was found for a mutational hot spot. Four of the tumours from miners contained mutations, two of which were double mutations. One G → T transversion was found in the only non-smoker (Popp *et al.*, 1999).

Mutations of the *TP53* gene were analysed in tumour and non-tumour tissues from 20 Thorotrast recipients who developed cancer, mainly of the hepatic bile duct and blood vessels. Of these patients, 19 were found to harbour *TP53* point mutations in their tumour tissue. Interestingly, *TP53* mutations were found even in non-tumorous tissues of the liver and small intestines, but at a lower frequency. The distribution pattern of the point mutations was significantly different in non-tumour and tumour tissues, most of the mutations in malignant tissues being located in the highly conserved domains of the *TP53* gene. It was noted that the predominant DNA damage expected as a result of exposure to α-radiation is deletion. The results support the idea that *TP53* alterations are important in the genesis of Thorotrast-induced tumours, but the point mutations may be the consequence of genomic instability induced by α-irradiation (Iwamoto *et al.*, 1999).

Genetic changes in the *TP53* gene were investigated in malignant liver tumours obtained at autopsy from Japanese patients with a history of Thorotrast treatment. These archival tissues were analysed for loss of heterozygosity at the 17p13 locus, followed by single-strand conformation polymorphism analysis and sequencing to detect mutations in exons 5–8 of the *TP53* gene. Fifteen cases were considered to be informative in terms

of polymorphism, and four cases showed loss of heterozygosity. Eight cases showed nine mutations in exons and two in introns, comprising seven transitions, two transversions and two deletions. It was suggested that the relatively large deletions, such as those indicated by loss of heterozygosity, could be attributed to the direct action of α-particles (Wada *et al.*, 1999).

Mutations of the K-*RAS* and the *TP53* genes were analysed in archival sections of intrahepatic cholangiocarcinomas from 22 Japanese patients, who had been injected with Thorotrast 33–49 years previously; 21 men had been injected between the ages of 20 and 30 years, and one woman had received treatment at the age of 14. The estimated total dose to the liver ranged from 2.7 to 22.1 Gy. For the analysis of *K-RAS* mutations, tumour tissues from four other Thorotrast-treated patients were included. The mutations in these two genes were compared with the spectrum in intrahepatic cholangiocarcinomas not associated with Thorotrast. The frequency of mutation of the K-*RAS* gene was lower (only one mutation found in 22 cases) while that of the *TP53* gene was more than two times higher (12 mutations in six of 22 samples) than in the non-Thorotrast-treated cases. The commonest mutation of the *TP53* gene was A → G transitions. *TP53* mutations were also found in non-cancerous areas of the livers in which Thorotrast had been deposited (Kamikawa *et al.*, 1999). [The Working Group noted that specific mutations in tumour tissue may not be directly attributable to radiation.]

4.4.2 *β-Particle emitters*

(*a*) *In-vitro studies*

(i) *Low-energy electrons*

Ultrasoft characteristic X-rays (0.1–5 keV) interact within cells, producing low-energy electrons similar not only to low-energy β-particles but also to the abundant low-energy secondary electrons produced by virtually all ionizing radiations (α-, β-, γ-, X-radiation and Auger emissions). Generally, the biological effectiveness relative to that of γ-rays and high-energy X-rays was seen to increase substantially with decreasing photon energy (and therefore electron energy) in a variety of cell lines for biological end-points such as DNA double-strand break induction (Prise *et al*., 1989; Botchway *et al*., 1997), cell inactivation (e.g. Goodhead & Thacker, 1977; Raju *et al*., 1987), chromosomal aberrations (Virsik *et al*., 1980; Griffin *et al*., 1998), mutations (Cox *et al*., 1977; Goodhead *et al*., 1979) and cell transformation (Frankenberg *et al*., 1995). In recent experiments, fluorescence in-situ hybridization was used with probes for chromosomes 1 and 2 to analyse chromosome exchanges in untransformed human fibroblasts exposed to 0.28-keV carbon K ultrasoft X-rays, which produce a single electron with a track length of < 7 nm. Despite the low energy and short range of these electrons, exchanges were produced with high efficiency. For simple exchanges between the target chromosomes, a linear dose–response relationship was observed, providing further support for the hypothesis that a single DNA lesion may form an exchange with undamaged DNA.

This suggests that the passage of a single electron may lead to genetic rearrangement (Griffin *et al.*, 1998).

(ii) *DNA strand breaks*

Methyl-labelled [^{3}H]- and [^{14}C]thymidine incorporated into DNA result in DNA single- and double-strand breaks, which are repaired rapidly (Cleaver *et al*., 1972; Cleaver & Burki, 1974; Burki *et al*., 1975; Sundell-Bergman & Johanson, 1980; Jorgensen *et al*., 1987). Incorporation of [5-^{3}H]uridine into RNA was found to be 80% less effective in causing single-strand breaks in DNA than incorporation of [^{3}H]thymidine in DNA, an intermediate result being obtained with cells irradiated by ^{3}H decays from $^{3}H_2O$ added to the medium before freezing (Burki *et al*., 1975). The Auger electron-emitter ^{125}I incorporated into DNA as iodo-2′-deoxyuridine was found to be significantly more efficient than [^{3}H]thymidine in introducing unrepairable DNA strand breaks in mammalian cells. The observed lack of repair may be due in part to the large number of ^{125}I decays per cell, which may interfere with enzymatic repair processes (Feinendegen *et al*., 1977; Sundell-Bergman & Johanson, 1980).

(iii) *Chromosomal aberrations*

Exposure of human lymphocytes *in vitro* to β-radiation from a ^{90}Sr/^{90}Y source (maximum β energy, 2.27 MeV) resulted in a biological effectiveness for micronucleus induction of 0.5 relative to 250-kVp X-rays (Mill *et al*., 1996). A dramatic increase in the frequency of chromosomal aberrations was observed after use of an Auger electron-emitting indium-111-labelled bleomycin complex, which binds to DNA in mouse glioma and human small-cell lung cancer cells, when compared with control incubations with bleomycin or $^{111}InCl_3$ (Hou *et al*., 1992). A number of studies in various test systems have shown an increased yield of chromosomal aberrations in cells exposed to β-radiation from $^{3}H_2O$, with a reported biological effectiveness relative to γ- and X-rays of 1.6–2.6 (Vulpis, 1984; Matsuda *et al*., 1986). The Auger electron-emitter ^{125}I incorporated into DNA in the form of [5-^{125}I]iodo-2′-deoxyuridine was considerably more effective than incorporated ^{131}I or [^{3}H]thymidine in cell killing and induction of chromosomal aberrations (Chan *et al*., 1976). Studies of chromosomal damage induced by the decay of [^{3}H]thymidine and [^{125}I]iodo-2′-deoxyuridine incorporated into the DNA of Chinese hamster cells indicated significantly greater effectiveness of ^{125}I than ^{3}H for induction of chromatid breaks (RBE, 17 ± 6), the sum of isochromatid breaks and chromatid exchanges (RBE, 21 ± 9) and the total number of chromatid aberrations (RBE, 18 ± 5) (Sundell-Bergman *et al*., 1985). An adaptive response *in vitro* in human lymphocytes after prior exposure to low-level irradiation from radioisotopes ([^{3}H]thymidine, [^{14}C]thymidine, $^{3}H_2O$ and [^{32}P]orthophosphate) was reported (Sankaranarayanan *et al*., 1989). The chromosomal aberration frequency observed after a challenge dose of 0.5 Gy of X-rays was lower than that expected on the basis of additivity of the effects of the individual treatments, although the response varied between samples from different donors.

(iv) *Mutation*

Cell killing and mutation to 6-thioguanine resistance were studied in growing mouse leukaemia cells in culture after exposure to ^{3}H-labelled amino acids and [^{3}H]thymidine. The greatest effect was seen with [^{3}H]thymidine, followed by [^{3}H]arginine and [^{3}H]lysine for a given concentration of ^{3}H (in kBq per mL medium). The differences between the ^{3}H-labelled amino acids disappeared almost completely when the effects were compared on the basis of the absorbed dose to the cells. The effects of [^{3}H]thymidine, however, remained more than twofold greater than those of the other ^{3}H-labelled compounds (Furuno-Fukushi *et al.*, 1987).

Incorporation of [^{125}I]iodo-2′-deoxyuridine into DNA was found to be more effective than that of the ^{131}I-labelled compound at inducing cell killing and mutations in human cells, both being more effective than unincorporated radioiodines or X-rays (Whaley & Little, 1990). Incorporated [^{125}I]iodo-2′-deoxyuridine was also more effective at inducing cell killing and mutations than the DNA-intercalating agent [^{125}I]acetylproflavine, probably because of the reduced energy deposition by the latter (Whaley *et al.*, 1990). Although [^{125}I]iodo-2′-deoxyuridine incorporated into cellular DNA was effective at producing both toxic and mutagenic effects in cells proficient in incorporating a thymidine analogue into DNA, virtually no effect was seen in cells that were deficient in this respect (Whaley & Little, 1990).

(v) *Cell transformation*

The biological effectiveness for the induction of malignant transformation in cultured mouse (C3H10T½) cells after exposure to 1–6 Gy of $^{3}H_2O$ at calculated dose rates of 51–307 mGy/h relative to γ-rays at 4 °C and 37 °C, respectively, was 1.6 and 1.7 (Yamaguchi *et al.*, 1989). A high efficiency for neoplastic transformation of BALB/3T3 mouse embryo cells was observed for ^{125}I incorporated into DNA: per radioactive decay, ^{125}I was about 25 times as effective as ^{3}H from incorporated [^{3}H]thymidine (LeMotte *et al.*, 1982).

(*b*) *In-vivo studies*

Chinese hamsters were injected with ^{144}Ce citrate (0.85 kBq/g bw), resulting in a low dose rate, estimated to be 7.3 mGy/day, of low-LET radiation to bone marrow. Although no significant increase in the total aberration frequency was observed, the treatment increased by more than twofold the number of chromatid exchanges in bone-marrow cells after a subsequent external exposure to ^{60}Co γ-rays when compared with controls exposed to γ-rays only (Brooks *et al.*, 1993).

No increase in lymphocyte aberration yields was found in hamsters injected with ^{137}Cs chloride to deliver a low committed effective dose of about 0.4 mGy (Lloyd *et al.*, 1997c).

The potential of vitamin C, an antioxidant, to protect spermatogonial cells in mouse testis against the effects of chronic irradiation from internally deposited radionuclides was investigated. A small, non-toxic amount of vitamin C (1.5 μg in 3 μL saline) injected

intratesticularly protected the spermatogonia against damage caused by Auger electrons from similarly administered [5-^{125}I]iodo-2′-deoxyuridine, as judged 29 days later by longer survival of treated spermatogonial cells than control cells without vitamin C. A dose modification factor of 2.3 was obtained. In contrast, no protection was observed when ^{210}Po citrate, an α-particle emitter, was administered (Narra *et al.*, 1994)

Ultrastructural modifications of pulmonary cells were investigated in rats after intravenous injection of ^{99m}Tc-labelled microspheres (2×10^5; radioactivity, 20 MBq), and nuclear expression of p53 protein was assessed by immunohistochemistry. Despite very high previously calculated doses [not specified] delivered to pulmonary cells, no morphological cell damage and no significant increase in nuclear expression of p53 were noted (Jacquet *et al.*, 1999).

(*c*) *Human studies*

(i) *Radioiodine therapy*

Chromosomal abnormalities in peripheral leukocytes were studied in groups of patients treated with ^{131}I for hyperthyroidism or thyroid cancer. The groups consisted of 48 patients (24–79 years of age) studied 3–14 years after treatment for hyperthyroidism with a total dose 8–54 mCi [0.3–2.0 GBq] of ^{131}I; 11 hyperthyroid patients (27–61 years of age) studied before and 0.5 h after administration of 8.3–12.7 mCi [0.31–0.47 GBq] of ^{131}I; and 11 thyroid cancer patients (16–49 years of age) studied before and 0.5, 2, 24 and 48 h after treatment with 150–200 mCi [5.6–7.4 GBq] of ^{131}I. The 21 controls (18–78 years of age) were matched for age and sex with the first group of 48 patients and had no history of irradiation or thyroid disease. Statistically significant increases in the frequency and severity of chromosomal abnormalities were observed after radioiodine therapy for hyperthyroidism. These abnormalities were detected as early as 0.5 h after administration and persisted for at least 14 years after treatment. The incidence and severity of abnormalities were greater after the larger doses of ^{131}I for thyroid carcinoma and in the period shortly after treatment (Nofal & Beierwaltes, 1964).

The presence of micronuclei was studied in binucleated peripheral blood lymphocytes from 22 women (aged 20–53 years; mean, 36.2 ± 2.1 years) with thyroid cancer who had received [^{131}I]sodium iodide orally as an adjuvant after total thyroidectomy (total dose, 3.4–37.5 GBq) 1–5 years before the study. The results showed no significant difference in the frequency of micronuclei between the patients and the control group, the latter being composed of 19 unexposed women (Gutiérrez *et al.*, 1995).

The micronucleus assay was used to investigate effects on chromosomes in peripheral blood lymphocytes from 47 patients with hyperthyroidism and 39 patients with thyroid cancer who were treated with ^{131}I. In the patients treated for hyperthyroidism, the micronucleus frequency was determined before ^{131}I therapy and one week, one month and three months afterwards; an additional sample was taken from a

subgroup of 17 patients six months after treatment. In the patients treated for thyroid cancer, samples were taken before treatment and one week, six months and one year later. At the same time, a cross–sectional study was performed with 70 control subjects and 54 thyroid cancer patients who had received the last therapeutic dose 1–6 years before the study. The patients treated for hyperthyroidism had a significantly increased average number of micronuclei over time. In the sample obtained six months after therapy, the mean micronucleus frequency was virtually the same as that in the sample taken three months earlier. In the patients treated for thyroid cancer, a twofold increase in the frequency of micronuclei was seen one week after therapy. Although this value decreased with time, the frequency of micronuclei one year after ^{131}I therapy remained higher than the value before therapy. In the cross-sectional study, a significant increase in the frequency of micronuclei was detected in the subgroup of thyroid cancer patients treated 1–3 years before the study. These results indicate that exposure to ^{131}I therapy induces chromosomal damage in peripheral lymphocytes (Gutiérrez *et al.*, 1999a).

No significant increase in the frequency of sister chromatid exchange or in the number of cells with unusually high sister chromatid exchange counts was found after ^{131}I therapy for hyperthyroidism or thyroid cancer. The study population was 46 patients treated for hyperthroidism (38 women, eight men) and 39 for thyroid cancer (27 women, 12 men), who received doses of 0.15–1.3 GBq and 3.7–5.6 GBq, respectively. In the follow-up analysis, four blood samples were drawn from each patient: the first before the radioiodine treatment and the remaining three taken sequentially over the year after therapy. In addition, a cross-sectional study was carried out with 78 control persons and 51 thyroid cancer patients who had completed radioiodine therapy (mean dose, 7.8 GBq) 1–6 years before the investigation. No statistically significant increase in the frequency of sister chromatid exchange or in the number of high-frequency cells was observed in the hyperthyroid patients or the thyroid cancer group when compared with controls (Gutiérrez *et al.*, 1999b).

Ten patients with thyroid cancer were treated with two doses of 1.85 GBq of ^{131}I given 24 h apart. Blood samples were taken from these patients before and at various times after exposure and analysed for the presence of chromosomal aberrations (dicentrics). The increase in the yield of aberrations after exposure to radioiodine was small but statistically significant. When compared with published values for whole-body doses after such treatment, the increase appeared to be somewhat smaller than expected after acute exposure of lymphocytes *in vitro* or *in vivo*. It was suggested that this was due to the low dose rate of ^{131}I (Baugnet-Mahieu *et al.*, 1994).

A significant increase in the mean number of micronuclei was measured in binucleated peripheral blood lymphocytes from patients with thyroid cancer after radio-iodine therapy, when compared with control subjects. Twenty-five patients (19 women, six men; age range, 36–72 years; mean age, 58.4 years) with differentiated thyroid carcinoma were treated with 3.7 GBq of ^{131}I after total thyroidectomy. Lymphocytes were collected from the patients before therapy and one week afterwards. The patients were classified into three groups: no prior ^{131}I treatment before the current therapy, one

prior administration of 3.7 GBq of ^{131}I and two prior administrations of 3.7 GBq of ^{131}I with at least six months between each. The mean number of micronuclei after treatment was significantly higher than that before treatment, but there was no effect on micronucleus frequency with cumulative exposure to radiation (Watanabe *et al.*, 1998).

Cytogenetic responses were investigated in 19 patients with differentiated thyroid cancer (11 papillary carcinomas and eight follicular carcinomas). After total or near-total thyroidectomy, seven patients were irradiated externally with daily fractions of 2 Gy of γ- and X-radiation (total, 50 Gy), and 12 patients underwent thyroid ablation and then received oral doses of 1734–2600 MBq of [^{131}I]sodium iodide. A further eight patients with intact thyroid glands were treated with ^{131}I at activities of 185–595 MBq for thyrotoxic diseases. For the determination of control aberration levels, 14 patients with thyroid cancer treated by surgery only and 14 healthy, age- and sex-matched controls were included in the study. Blood samples were taken 24 h after treatment in each case of external irradiation and five days after oral intake of radioiodine. The frequency of aberrant lymphocytes in the surgically treated cancer controls was significantly higher than that in matched healthy controls, and the radiation-treated patients had distinctly more chromosomal aberrations than either of the controls. External irradiation caused 10 times more aberrant cells than ^{131}I therapy. The doses of radioiodine given for ablation to the cancer patients were almost seven times higher than the doses given to the patients with thyrotoxic disease (185–595 MBq), who had intact glands. Nevertheless, the frequency of chromosomal aberrations was significantly lower among the cancer patients (Gundy *et al.*, 1996; Katz *et al.*, 1998).

Chromosomal aberrations were scored in the peripheral blood of 18 patients (14 women, four men) aged 25–79 years (mean, 48 years) with differentiated thyroid carcinoma who had received therapy with radioiodine. All the patients had undergone total thyroidectomy before the first ^{131}I treatment. Blood samples were obtained before and four days after each administration of 3.7 GBq of ^{131}I and were analysed according to conventional cytogenetics or by fluorescence in-situ hybridization with probes for chromosome 4. Repeated administration resulted in a cumulative dose of 1–3.5 Gy (two to seven treatments). An increase in the frequency of symmetrical and asymmetrical aberrations was observed with each treatment, but the number of chromosomal aberrations from the third treatment onwards was considerably lower than that expected from the calculated dose, perhaps due to killing of lymphocytes with multiple chromosomal anomalies (M'Kacher *et al.*, 1998).

Chromosomal aberrations and micronuclei were also analysed in peripheral blood lymphocytes from 19 patients with thyroid cancer who received therapeutic doses of 2.6 GBq (70 mCi) of ^{131}I. Oxidative stress was assessed by determining thiobarbituric acid-reactive substances in blood, total plasma antioxidant status and serum uric acid concentrations. All these parameters were assessed before treatment and one and six months afterwards. A significant increase in the frequency of micronucleated cells was observed at both one and six months after treatment when compared with controls before treatment. The frequency of cells with chromosomal aberrations, excluding gaps,

was also significantly higher one and six months after treatment than before treatment. Parameters of oxidative stress were slightly modified over the period studied, but the differences were not significant, except for a decrease in thiobarbituric acid-reactive products six months after therapy and in serum uric acid concentration one and six months after therapy. The overall results showed a slight but significant induction in persistent cytogenetic damage after ^{131}I therapy but no clear correlation between the cytogenetic findings and oxidative stress parameters (Monteiro Gil *et al.*, 2000).

Human T lymphocytes from 13 patients were used to determine the frequency and molecular spectrum of somatic gene mutations induced by radioimmunoglobulin therapy with ^{131}I-labelled antibody. The exposure induced *HPRT* mutations and a predominant molecular spectrum of partial deletions, rearrangements and total gene deletions. The mutation frequencies decreased with time after exposure (Albertini *et al.*, 1997).

A significant increase in *GPA* and lymphocytic *TCR* gene mutation frequencies was found in the peripheral blood of patients after ^{131}I therapy (Akiyama *et al.*, 1995).

(ii) *Technetium-99m*

Cytogenetic effects were assessed in blood samples from five patients with various arthrosic and periarthrosic diseases, obtained after bone scintigraphy with 925 MBq of [^{99m}Tc]hydroxymethylene diphosphonate. No cytogenetic effects were detected 3.6 and 24 h after administration of the radionuclide (Jacquet *et al.*, 1999).

Mutant frequencies were measured in T lymphocytes of patients undergoing radionuclide angiography with erythrocytes labelled *in vivo* with ^{99m}Tc. Blood from 13 patients was sampled before and 8–120 days after an injection of 750 MBq of ^{99m}Tc. The frequencies of *HPRT* mutants were measured by the T-cell cloning method. The mean frequency of mutants after treatment was significantly lower than that measured before exposure. Further analysis indicated that the decrease in mutant frequency after exposure could be accounted for by an effect on cloning efficiency (Van Dam *et al.*, 1991).

(iii) *Other medical treatment*

The induction of chromosomal aberrations after radiophosphorus treatment was studied in 48 patients with various forms of polycythaemia, 11 of whom received ^{32}P for polycythaemia vera. Patients without polycythaemia vera and seven regular blood donors served as controls. Peripheral blood was analysed for chromosomal aberrations on first referral to a hospital ward or clinic and was repeated once a year. A variety of non-specific chromosomal aberrations were found in polycythaemia vera patients who had had no previous treatment with radiation. Among radiophosphorus-treated patients, the frequency of these aberrations was moderately higher. Dicentric chromosomes were the aberration typical of ^{32}P-treated patients. Only recent injections of ^{32}P had an effect on the number of dicentric chromosomal aberrations detected (Modan *et al.*, 1970).

Forty-eight patients with rheumatoid arthritis who had received intra-articular injections of ^{198}Au and 22 who had been given intra-articular injections of ^{90}Y were investigated for the presence of chromosomal damage. Blood samples from some patients were not taken until several months or years after the injections. In nine cases, the blood samples were scanned before and at intervals after treatment to determine the distribution of the isotopes. ^{198}Au was administered in the form of a colloidal suspension of metallic gold stabilized with gelatine at particle sizes up to 20 μm, most of the activity being in the 10–13-μm particles. The ^{90}Y preparation was ionic yttrium bound to a colloidal ion-exchange resin with a particle size of 20–50 μm. The distribution of the radionuclides was scanned in 20 patients, and some leakage from the joint to the regional lymph nodes was detected, occasionally constituting up to 20% of the administered activity, which may account for the lack of correlation between the amount of either radionuclide and the percentage of cells with chromosomal damage. Damage was detected in many patients after 24 h; on average, there was an increase in detectable damage up to the last sampling time, 28 days after injection (Stevenson *et al.*, 1973).

The frequency of chromosomal aberrations was measured in 30 patients after ^{90}Y synovectomy. The patients (all > 45 years old) had chronic synovitis of the knee and received a dose of 5 mCi [185 MBq] of ^{90}Y silicate. Chromosomes from cultured peripheral blood lymphocytes were studied before and approximately three months after therapy. The frequency of cells with chromosomal aberrations increased significantly, from 0.33% before treatment to 0.87% after treatment (Doyle *et al.*, 1977).

^{165}Dy (dysprosium) hydroxide macroaggregates were developed for the treatment of arthritis in clinical trials, as dysprosium provides a better spectrum of decay energies and a shorter half-life than the conventionally used yttrium, permitting quicker and more efficient treatment. The micronucleus frequencies in peripheral blood lymphocytes were examined in 42 patients before and two weeks after radiation synovectomy, in which 21 patients received ^{165}Dy hydroxide macroaggregates (10 GBq) and the others received ^{90}Y silicate (185 MBq). In most patients in each group, no significant change in micronucleus frequency was observed, but ^{165}Dy and ^{90}Y treatment caused significant increases in four and six patients, respectively, and a significant decrease in two and one patient, respectively. The results indicate that, in most patients, the materials and methods of administration used currently do not result in leakage of radioactive material from the injection site (Prosser *et al.*, 1993).

(iv) *Hydrogen-3*

Chromosomal translocations were analysed by fluorescence in-situ hybridization in the blood lymphocytes of a person who, 11 years previously, had accidentally inhaled a substantial amount of $^{3}H_2O$. A comparison was made between previous estimates of radiation dose and contemporary dosimetry by urine analysis and scoring of dicentric chromosomes. The blood lymphocytes were analysed by two laboratories with different chromosome probe combinations, and good agreement in translocation

yields was found. Comparison of these values with the dicentric frequency obtained shortly after the accident and with a translocation frequency measured six years after exposure showed good agreement between all measurements. Thus, the translocations were completely stable for 11 years (Lloyd *et al.*, 1986, 1998).

(v) *Chernobyl accident*

A cytogenetic study was carried out with lymphocytes from children in Belarus, the Russian Federation and the Ukraine who had been exposed to fall-out consisting mainly of ^{137}Cs from the Chernobyl reactor accident in 1986. A total of 41 children, all aged 8–10 years, were selected for the study. The first group, five girls and four boys, was from the countryside of Navrovl'a (Belarus), 70 km from Chernobyl, where the ^{137}Cs contamination was 15–50 Ci/km^2 [555–1850 GBq/km^2]. The second group, eight girls and 16 boys, came from the area of Belarus surrounding Chernobyl; they had been evacuated soon after the accident and transferred to Gomel or Drujri 200–300 km from Chernobyl, where the ^{137}Cs ground contamination was 1–10 Ci/km^2 [37–370 GBq/km^2]. The third group, three girls and five boys, was from Stolin (Belarus), 250 km from Chernobyl, with ^{137}Cs contamination of 1–5 Ci/km^2 [37–185 GBq/km^2] and 5–15 Ci/km^2 [185–555 GBq/km^2] in part of the surrounding area. Blood samples were collected from all the children during 1991–92, and internal contamination was evaluated by whole-body counter analysis of ^{137}Cs, which gave values for the three groups of 460–2795 Bq, 44–397 Bq and 7714–32 343 Bq, respectively. Remarkably, the third group had the highest values in spite of the fact that the first group was from an area with higher ground contamination. The control group consisted of 10 healthy Italian children (five girls and five boys) selected on the basis of age. The overall frequency of acentric fragments, dicentrics and translocations in the three exposed groups and of acentric fragments in the first two groups were significantly higher than those in the controls (Padovani *et al.*, 1993).

DNA from 129 paired thyroid tumours and non-tumorous tissue samples from 102 Belarussian children (age at surgery, ≤ 18 years) and 27 adults (age at surgery, 19–35 years), who had been exposed to radioactive fall-out from the Chernobyl reactor accident, was examined for microsatellite instability and loss of heterozygosity. Twenty-eight microsatellite markers were chosen because of their vicinity to DNA repair genes or genes involved in tumorigenesis and to regions of chromosomal breakpoints in thyroid tumours. In 40 patients (31% of 129), a total of 73 alterations were observed, 80% of which were classified as loss of heterozygosity and only 20% as microsatellite instability. A subgroup of 11 patients was identified, mainly girls (8.5% of 129), who had alterations in at least two microsatellite markers. Comparisons were made with samples of spontaneous thyroid carcinomas without exposure to radiation from 20 adult patients in Munich, Germany (mean age at surgery, 56 ± 13 years). None of the tumour samples from this group showed alterations in the 28 microsatellite markers tested. The results indicate greater instability of microsatellite markers in thyroid cancers from Belarussian patients. It remains uncertain whether the increased genomic instability is

the result of exposure to radioactive iodine from the Chernobyl reactor accident or to the young age of the patients (Richter *et al.*, 1999).

(vi) *Techa River, southern Urals*

About 28 000 inhabitants of settlements on the banks of the Techa River were exposed internally (predominantly to ^{90}Sr), mainly due to the use of the River as a source of drinking-water, and externally due to ^{137}Cs γ-rays from contaminated sediments in the River (see section 2.9.2). Forty-three years after the beginning of the exposure, stable chromosomal aberrations were analysed in peripheral blood lymphocytes, and somatic mutations were measured in erythrocytes (*GPA*) and lymphocytes (*TCR*). Stable chromosomal aberrations including translocations, inversions and deletions were analysed by fluorescence in-situ hybridization. Mutant lymphocytes and erythrocytes were registered according to *TCR* and *GPA* mutation frequencies by flow cytometry. The study was carried out on 80 subjects whose individual accumulated doses and dose-rate dynamics, from ^{90}Sr and ^{137}Cs, in the red bone marrow were reconstructed on the basis of the findings of measurements with a whole-body counter *in vivo*. There was no significant difference in the incidence of chromosomal translocations between people exposed at various levels and the controls. The frequency of mutant lymphocytes defective in *TCR* gene expression increased with cumulative doses to the red bone marrow, and, at doses > 2 Gy, the difference from the control group was statistically significant. The frequency of mutations within the *GPA* system in individuals with long-term exposure did not differ from that in the comparison group, and the frequency of mutant erythrocytes of different types did not depend on accumulated dose to the red bone marrow (Akleyev *et al.*, 1995).

Symmetrical translocations were measured by fluorescence in-situ hybridization with probes for chromosomes 1, 4 and 12 in peripheral lymphocytes from residents of settlements along the Techa River. The study group consisted of 73 individuals born between 1911 and 1953 and residing in 13 villages along the River, 7–148 km downstream of the site of release of radioactive waste. Blood was sampled between 1994 and 1996. Data for dose reconstruction based on physical measurements and calculations for the population in settlements along the River were obtained from Degteva *et al*. (1994). External doses were calculated on the basis of long-term area measurements of γ-radiation at relevant sites in each village. The external exposure ranged from < 0.01 Gy/year in the lower regions of the River (> 150 km downstream) to an overall average dose for the year 1951 of 0.5–1.0 Gy, as was estimated for the inhabitants of Metlino, a village located only 7 km downstream from the site of release. Internal dosimetry was achieved by large-scale measurements of ^{90}Sr and β-irradiation on the surface of teeth in 1960 and by whole-body measurements started in 1974. The control group consisted of 39 healthy unexposed persons of a comparable age range and living in uncontaminated areas of the southern Urals. A significantly elevated mean translocation frequency was found when compared with controls for the total study group and for both groups of inhabitants of the villages in the upper reaches of the Techa

River (7–60 km) during 1950–51 (the time of maximum release of radioactive waste) and in villages in the lower reaches (78–148 km) until the time of blood sampling. The latter group was further divided into a subgroup comprising 14 individuals who had left the riverside settlements before 1965 and a subgroup consisting of 19 people who continued to live in the settlements until the time of blood sampling. While the translocation frequency of the first subgroup was not significantly elevated above background, a threefold higher value was found for the second. In the lower reaches of the Techa River, the influence of external exposure can be excluded. The reported difference in the response of these two subgroups may be attributable to internal exposure, since the members of the second subgroup had a further 30 years in which to incorporate the long-lived radionuclides, particularly bone-seeking ^{90}Sr (Bauchinger *et al.*, 1998).

(vii) *Mutations in tumour-related genes*

The identification of a genomic fingerprint that would provide proof of the interaction between a specific exposure and a target cell would be highly desirable for molecular epidemiology. However, a specific molecular lesion is almost always missing, probably because of the large number of factors that act on tumour induction and progression. Signalling via protein tyrosine kinases has been identified as one of the most important events in cellular regulation, and rearrangements of the tyrosine kinase domain of the *RET* proto-oncogene have been found in thyroid cancers thought to be associated with ionizing radiation (Ito *et al.*, 1993; Fugazzola *et al.*, 1995; Klugbauer *et al.*, 1995). However, the biological and clinical significance of *RET* activation remains controversial, and further studies of the molecular biology of radiation-induced thyroid cancers are needed before the carcinogenic pathway can be fully understood.

RET oncogene rearrangements were studied in papillary thyroid carcinomas of children exposed to radioactive fall-out in Belarus after the Chernobyl accident. Small tissue samples from thyroidectomy specimens were analysed, comprising 12 papillary thyroid carcinomas from children, two papillary thyroid carcinomas and one follicular carcinoma from adults and non-tumourous thyroid tissue from four children and four adults as controls. Two-thirds of the papillary thyroid carcinomas in children had a *RET* rearrangement, and all the tumours with *RET* rearrangements had lymph-node metastases. Intra-chromosomal rearrangement involving *RET* and the adjacent *H4* or *ELE* gene on chromosome 10 was a frequent event in the thyroid cancers of children in the zone of Belarus contaminated by the accident (Klugbauer *et al.*, 1995).

Mutations in the *TP53* tumour-suppressor gene (exons 5–8) were investigated in 31 thyroid tumours from children in Belarus (24 cases of papillary thyroid carcinoma, three benign tumours and two cases each of thyroiditis and goitre) and 33 thyroid tumours from adolescents and adults with no exposure to radiation (25 carcinomas of various histological types, including 11 papillary carcinomas and eight adenomas); six tumours from adults (four papillary carcinomas, one adenoma and one goitre) served as controls. The mutational spectrum of *TP53* in the thyroid carcinomas from Belarussian children differed greatly from those in the other groups. In the 29 malignant tumours in the

control groups, seven different mutations were detected on exons 5–8, none of which occurred among the 15 papillary carcinomas in this group. Five mutations were found in tissue samples from the 24 childhood papillary carcinomas, and they were all the same *TP53* point mutation (CGA → CGG) on codon 213 of exon 6 (Smida *et al.*, 1997).

Molecular biological studies showed that the proportion of cases of papillary carcinoma of the thyroid that expressed the *RET* gene was not significantly different in tumours from exposed and unexposed persons (mainly in other countries, such as France, Italy and the United Kingdom). Studies of the type of translocation leading to *RET* gene expression are inconclusive (UNSCEAR, 2000). *RAS* gene mutations were found (as expected) in follicular carcinomas but were absent from papillary carcinomas from either exposed or unexposed areas. Thyroid-stimulating hormone (*TSH*) receptor mutations, which are normally found in follicular tumours, were not found in any papillary carcinoma, nor were any *TP53* mutations identified. These results are consistent with the hypothesis that papillary carcinomas are associated only with *RET* translocation, and that *RAS* and *TSH* receptor mutations occur in follicular tumours and *TP53* mutations in undifferentiated carcinomas.

[The Working Group noted that specific mutations in tumour tissue may not be directly attributable to radiation.]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The radionuclides considered in this monograph belong to two broad categories, those that emit α-particles (helium nuclei) and those that emit β-particles (electrons) during their primary radioactive decay. The α- and β-emitting radionuclides can be further characterized as 'pure' and 'mixed' emitters, primarily on the basis of the emissions of their decay products. Pure emitters in the strict sense, i.e. radionuclides that emit one type of radiation and have a stable isotope as their decay products, are rare, and they are seldom encountered as such in practical situations of human exposure. The predominant type of radiation released by mixed emitters during long-term internal exposure is calculated from the energy contributed by the various types of emission throughout the decay chain, integrated over an assumed period of 50 years after initial exposure. For all practical purposes, a decay product with a very long half-life may be considered to be the end of the decay chain, because its energy contribution and that of the decay products beyond it will be negligible. The overall biological consequences of exposure to mixed emitters result from the combined effects of their emissions and those of their decay products. Apart from α- and β-particles, these emissions may involve γ-radiation, X-rays and secondary electrons. In some cases, however, the overall mixture of emissions from a radionuclide and its decay products may be dominated, in terms of energy contribution, by one type of radiation, so that the radiobiological effect may be considered to be caused by this radiation alone.

Radionuclides that undergo radioactive decay processes which do not primarily involve emission of α- or β-particles are not considered in detail in this monograph. Examples are iron-55 and gallium-67, both of which decay through electron capture.

For the purposes of this monograph, 'internally deposited' refers to radionuclides in dispersed forms, e.g., dusts, suspensions, solutions or gases, that enter the body by inhalation, ingestion, some form of injection or, in some cases, by percutaneous absorption. Not considered in this monograph are radionuclides that enter tissues within removable objects, such as radioactive beads, pellets or needles, which may be implanted surgically for therapeutic purposes, or those that enter the body accidentally, in the form of other kinds of radioactive fragments.

The doses of radiation to organs and tissues in the body arising from intake of natural and man-made radionuclides are variable and depend on many factors, including geographical location and occupation. The major sources arise from the inhalation of radon-222; from the deposition of long-lived primordial isotopes of cosmic origin, namely

potassium-40, thorium-232 and uranium isotopes; from the deposition of shorter-lived decay products of primordial radionuclides, principally lead-210, polonium-210 and radium-226; and from anthropogenic radionuclides released into the environment, including strontium-90, ruthenium-106, iodine-131, caesium-137, plutonium isotopes and americium-241. Potential exposure of lesser importance may occur after accidental intake from miscellaneous radioactive devices such as thorium-232 gas-lantern mantles, americium-241-containing fire detectors and polonium-210-containing anti-static devices.

In addition, as a consequence of their employment, workers may be exposed to and absorb radionuclides that occur in the nuclear fuel cycle; in radiopharmaceuticals such as technetium-99m, iodine-131, phosphorus-32 and strontium-90; in radiolabelled compounds (mostly hydrogen-3 and carbon-14-labelled organic compounds); and a variety of miscellaneous sources. Patients may also take in radionuclides during diagnostic medical procedures or for the treatment of severe diseases — principally cancer and diseases of the skeletal system — such as with iodine-131 and radium-224. Finally, tobacco smoking may result in intakes of the volatile radionuclides lead-210 and polonium-210.

For most members of the public, the dose of ionizing radiation received from inhaled and tissue-deposited radionuclides is predominantly from inhalation of naturally occurring radon-222. This accounts for about one-half of the 2.4 mSv/year which is the average total background effective dose of radiation received from all sources, including external ionizing electromagnetic radiation. However, in some geological areas, the fraction of the total effective dose received from radon-222 may easily exceed 80% of the annual average background effective dose.

Similarly, exposure to thorium-232, uranium isotopes and their shorter-lived decay products is variable and depends principally upon their concentration in soils. Such radionuclides may enter the body as the result of inhalation of resuspended soil particles containing these elements and/or their presence in food and water. However, the effective dose received from these sources is smaller than that received from radon-222. In contrast, the body content of the radioisotope potassium-40, which comprises 0.2% of total potassium, is maintained at a constant level as a result of the metabolic processes that control the tissue concentration of this element in the body. Again, the contribution to the total effective dose from potassium-40 is small, averaging 0.175 mSv/year.

Nuclear explosions, nuclear fuel reprocessing, nuclear-generated electricity and accidents at nuclear facilities all result in increased exposure of workers and of the general population to radionuclides. For the general population, the body content of anthropogenic nuclides from such sources is usually small. The effective radiation dose received from global fall-out, i.e. from nuclear fission products and fuel components (principally plutonium-239, -240 and -241 and americium-241) released into the atmosphere by the explosion of nuclear devices, accounts for only 0.01 mSv of the contemporary annual background effective dose of 2.4 mSv. This dose is uniform

within populations in the two hemispheres — a result of the dispersion of most fall-out throughout the atmosphere of the northern hemisphere and its subsequent but significantly delayed transfer at a lower level to the southern hemisphere or *vice versa*.

Intakes of radionuclides originating from the nuclear industry, released either accidentally or deliberately, e.g. krypton-85, are also normally low but can be high under some circumstances. For instance, intake that is much higher than normal may occur among persons living close to the sites of releases of nuclear fuel reprocessing effluents, e.g. in West Cumbria, United Kingdom, or the Techa River in the Russian Federation, since the wastes may contain fission products such as caesium-137 and strontium-90 and fuel-derived components such as plutonium-239, plutonium-241 and americium-241. Reactor accidents such as those at Chernobyl and Windscale resulted in the release of more volatile fission products into the environment, including iodine and caesium isotopes, and the exposed populations had much higher than normal intakes of these radionuclides.

Similarly, some local populations have been exposed non-occupationally to radionuclides released during nuclear weapons testing, for example, in St George, Utah (USA), on Pacific islands within the fall-out plume from testing at Bikini atoll and in Sarzhal, Kazakhstan, close to the Semipalatinsk nuclear test site of the former USSR. Under these conditions, the intake of radionuclides reflects the spectrum of fission products released by the device, except that the delay between detonation of the device and exposure must be very short if the intake of short-lived isotopes, such as those of iodine, is to be significant. Radionuclides originating from nuclear fuel wastes may be taken in after deliberate releases and accidents at fuel reprocessing facilities, such as occurred at Mayak in the southern Urals. Normal operation of nuclear energy power plants results in little radionuclide intake by members of the public, but they may be exposed to radionuclides of primordial origin in the fly ash released by conventional thermal power plants.

Workers involved in the manufacture and application of radionuclides, including those for medical purposes, are also exposed. Such exposure is usually regulated by local procedures designed to limit occupational exposure of classified workers to a maximum of 20 mSv in any one year or of unclassified workers to the lower limit of 1 mSv/year. These are internationally recognized standards recommended by the International Commission on Radiological Protection. However, in the past, other national and international standards have applied that have resulted in higher permitted intake of radionuclides, and, in addition, accidents have resulted in intakes that exceed these limits.

In the uranium–plutonium fuel cycle, the most significant radionuclides with respect to occupational exposure are strontium-90, caesium-134, caesium-137, curium-242, americium-241 and plutonium isotopes. With other fuel types, e.g. thorium fuels, other radionuclides are also important, particularly thorium-238, protactinium-231 and uranium-239. Currently, however, use of this type of fuel cycle is low. In western Europe and the USA, studies have shown that the plutonium body burdens seldom

exceed 1 kBq; in the countries of the former USSR, e.g. in the Mayak nuclear complex, however, many workers have plutonium body burdens that exceed this amount.

5.2 Human carcinogenicity data

Radon

Twelve cohort studies of underground miners exposed to high concentrations of radon-222 and its short-lived decay products in air have been carried out in several countries. Additionally, the data from 11 of these studies were pooled and analysed. Each individual study and the pooled analysis showed clear evidence of an increased risk for lung cancer associated with exposure to radon. In none of the studies was convincing evidence found for an increase in the risk for death from cancer other than lung cancer.

Thirteen case–control studies addressed the association between lung cancer and residential exposure to radon. A meta-analysis of eight of these studies and subsequent studies found an association between exposure to radon and lung cancer. The risk estimates from studies of residential exposure are consistent with those predicted from the studies of underground miners.

Radium

The studies of cancer risk among radium watch-dial painters in the USA, some of whom ingested radium-226, often in combination with radium-228, by the practice of 'pointing' their paintbrush tips with their lips, showed consistent increases in the risk for bone sarcoma related to exposure to α-particles. Both isotopes of radium contributed significantly and independently to the rate of mortality from bone sarcomas in multivariate analyses of dose–response relationships in which the two isotopes were included as separate variables. It is also clear that excess risk for carcinomas of the paranasal sinuses and mastoid process is associated with internally deposited radium-226, but probably not radium-228. An association between exposure to α-particles from internally deposited radium-226 and radium-228 and other cancers has not been well established.

Bone sarcomas were the major late effect among patients with tuberculosis, ankylosing spondylitis and other diseases who were treated with high doses of radium-224 (mean bone surface dose, 30 Gy). Significant increases in the incidences of cancers of the breast, kidney, liver, urinary system, thyroid and soft tissues were also observed. The number of cases of leukaemia was greater than expected, but, after allowance for a minimum delay of two years after exposure, the increase was not statistically significant. Among ankylosing spondylitis patients treated with lower doses of radium-224 (mean bone surface dose, 5 Gy), several tumours originating in the bone were observed, and there was an excess risk for leukaemia. There is no reason to doubt the

radiogenic origin of the bone tumours in patients treated with radium-224. The reasons for the increased incidences of other cancers are at present unclear.

Thorium

Occupational exposure to thorium by inhalation of fine particles containing thorium and its decay products occurred in thorium refineries and in mines of monazite and rare-earth ores. Two epidemiological studies, in China and the USA, cover more than 6000 exposed workers. Although a high radiation burden could be demonstrated, especially in lung tissue, the results of the studies are not conclusive in showing an elevated risk for lung cancer due exclusively to the inhaled radioactive substances. Large differences in smoking habits and the effects of dust on the broncho-epithelial system must also be considered.

Stabilized thorium-232 dioxide (Thorotrast) was used extensively in medical practice between the 1930s and the 1950s as a radiographic contrast agent. Owing to its colloidal nature, Thorotrast is retained mostly in the reticuloendothelial system (liver, spleen and bone marrow) after intravenous injection. Cohort studies of almost 10 000 patients given Thorotrast and 10 000 controls in Denmark, Germany, Japan, Portugal and Sweden have demonstrated significantly increased risks (by 36–129 times) for primary liver cancer (approximately one-third being haemangiosarcomas), which are significantly correlated with the volume of Thorotrast injected. The incidence of and mortality from liver cirrhosis were also significantly increased in all studies (by 6–13 times). These studies have also shown a significantly increased risk (by 11–20 times) for leukaemia excluding chronic lymphocytic leukaemia. Increased risks for cancers at other sites were reported in some studies but not consistently. Consistent increases have not been found for lung cancer, although patients given Thorotrast exhale high concentrations of radon-220 (thoron).

Plutonium

At the Mayak plutonium production plant in the Russian Federation, exposure to plutonium (chiefly plutonium-239) was substantial, large numbers of workers having estimated body burdens greater than 3 kBq. Some workers had such heavy exposure to plutonium that they developed pulmonary sclerosis, a condition reported previously only in animals given very large doses of this element. Increased risks for cancers of the lung, liver (including haemangiosarcoma) and bone (predominantly osteosarcoma) have been observed among these workers. Dose–response relationships have been demonstrated for cancers of the lung, liver and bone in both men and women exposed to a broad range of doses. Cancers at other sites have not been studied. Very few workers in the United Kingdom and the USA were estimated to have plutonium body burdens greater than 1 kBq, and no health risks were convincingly linked to this low exposure.

Uranium

Some studies of workers in uranium processing have shown an increased mortality rate from lung cancer, although the finding is not consistent. The doses to the lung were relatively low. The mortality rates from other site-specific cancers were increased in some studies, but the small numbers of cases and lack of consistency among these findings make them difficult to interpret. The studies of workers exposed to uranium are hampered by difficulty in measuring the dose of radiation, potential concomitant exposure to chemicals, possible effects of age at the time of exposure, the 'healthy worker effect' and confounding by smoking.

Polonium

The epidemiological studies of nuclear industry workers exposed to polonium-210 are inadequate to allow a conclusion about cancer risk. In only one study were data available to analyse dose–response relationships, but the cohort was small, and no significant trends were identified in the rates of death from all causes, all cancers or specific cancers.

Iodine

After the accident at the Chernobyl nuclear reactor in the Ukraine in 1986, substantial increases in the incidence of thyroid cancer were observed among persons exposed during childhood in the regions most heavily contaminated with iodine isotopes (iodine-131 and short-lived isotopes in varying combinations) in Belarus and the Ukraine and — to a lesser extent — the Russian Federation. The evidence that this increase is related to exposure to iodine isotopes is indirect, yet it is very strong.

Geographical correlation studies in Belarus, the Russian Federation and the Ukraine have shown strong correlations between the presumed dose to the thyroid and the incidence of thyroid cancer among persons exposed during childhood or *in utero*, and most of the tumours to date have appeared in children. A significant dose–response relationship was observed in a case–control study of thyroid cancer in children carried out in Belarus. Overall, the number of thyroid cancers in individuals exposed during childhood, particularly in the severely contaminated areas of the three countries, is considerably greater than that expected on the basis of previous information on the effects of iatrogenic exposure of adults to radioiodine.

In a cohort study of persons exposed to iodine isotopes in fall-out from nuclear weapons testing in southwestern USA, a significant dose-related increase in the risk for benign and malignant thyroid tumours combined was seen; the increase was not, however, significant for malignant thyroid tumours alone. In the Marshall Islands, increases in the incidences of thyroid cancer and thyroid nodules were observed among persons exposed during childhood to iodine-131, other short-lived isotopes of iodine and external radiation from nuclear weapons testing.

In contrast, no appreciable increase in the risk for radiation-related thyroid cancer was observed in several comprehensive follow-up studies of populations who had received diagnostic or therapeutic exposure to iodine-131 for thyroidal conditions. This finding does not, however, contradict the results of the follow-up of persons exposed as a result of the Chernobyl accident or in the Marshall Islands, as the published studies of diagnostic exposures included very few exposed children and therefore do not provide information about the risk of exposures during childhood. Studies of persons exposed to external radiation also suggest that the risk for thyroid cancer is restricted to exposure during childhood.

The risk for leukaemia after exposure to iodine-131 for medical purposes has been examined in a number of studies. No exposure-related increase has been seen. Furthermore, no increase in the incidence of leukaemia has been reported among persons exposed to radioiodines as a result of the Chernobyl accident.

Phosphorus

The risk for acute leukaemia is clearly increased in patients with polycythaemia vera who were treated with phosphorus-32 in comparison with those given treatments that did not involve irradiation. However, as polycythaemia vera is a clonal malignancy of the pluripotent haematological stem cells, patients with this disease may be more sensitive to the leukaemogenic effects of irradiation than the general population.

Combined exposures (external and internal)

Persons exposed during weapons testing received mainly radioactive iodine, and studies of these populations are discussed above.

In a study of a population in the Russian Federation exposed to a mixture of internally deposited radionuclides (predominantly strontium-90) and external radiation (see IARC, 2000), a dose-related increase in the rates of mortality from solid tumours and leukaemia was observed.

Other radionuclides

Humans have been exposed to a large number of other radionuclides, including caesium-134, caesium-137, hydrogen-3 and carbon-14. There are, however, few or no epidemiological data, and their effects on humans could not be quantified.

5.3 Animal carcinogenicity data

In the summaries of the studies of carcinogenicity in animals exposed to internally deposited radionuclides, a distinction was made between pure and mixed α- and β-emitters, according to the definitions given in the General Remarks. In evaluating the effects of mixed emitters in animals, it is important to discern which type of emitted

radiation predominates over the average lifespan of the animals, which — especially for rodents — is often shorter than the decay half-life of some radionuclides. Two radionuclides considered in this monograph are classified differently as effective α- or β-emitters for humans and for short-lived experimental animals. Thus, the effects of thorium-232 in two-year bioassays in rodents can be ascribed to pure α-radiation, owing to the long half-life (5.75 years) of its primary decay product radium-228. When humans are exposed to thorium-232, sometimes over several decades, the radionuclide can be considered a mixed α-emitter, exposing tissues predominantly to α-radiation and small amounts of β- and γ-radiation. In two-year bioassays in rodents, radium-228 can be considered a mixed β-emitter, exposing tissues to β- and γ-radiation, owing to the 1.9-year half-life (comparable to the animals' lifespan) of its second decay product, thorium-228. When humans are exposed to radium-228, sometimes over several decades, the cumulative energy spectrum is dominated by α-radiation from radionuclides further down the decay chain.

α-Particle-emitting radionuclides

Lifetime studies of the carcinogenicity of pure and mixed α-particle-emitting radionuclides have been conducted in experimental animals of a number of species and strains that differ greatly in features such as size, metabolic characteristics and lifespan. The locations and types of tumours observed were influenced by factors including species, the form and route of administration, the resulting metabolic and dose patterns and the age and health status of the animals. α-Particles have a short range of penetration in biological tissues, and tumours developed at the sites of radionuclide deposition.

The carcinogenicity of radon isotopes in animals was evaluated previously (IARC, 1988).

Lung tumours were observed in hamsters given polonium-210 by intratracheal instillation. Radium-224 given parenterally to mice and dogs resulted in bone tumours; haematopoietic tumours were also observed in mice. Radium-226 administered to mice, rabbits and dogs by intraperitoneal or intravenous injection caused bone cancers. Skeletal cancers occurred in mice given thorium-227 by parenteral injection and in dogs given thorium-228 by intravenous injection. Rats and mice exposed to thorium-230 and thorium-232 in a colloidal form and hamsters given colloidal thorium-232 as Thorotrast developed liver cancers.

Lung cancers were observed in hamsters exposed to plutonium-238 by inhalation. Lung, liver and bone cancers were observed in dogs exposed by inhalation to plutonium-238 or plutonium-239; the plutonium preparations used in many studies also contained small amounts of plutonium-240. In mice, hamsters and dogs exposed to plutonium-239 by parenteral administration, bone and liver cancers were observed; haematopoietic cancers were also observed in mice. Lung cancers were observed in rats exposed by inhalation to uranium ore dust. Mice injected intraperitoneally with

americium-241 developed liver, bone and haematopoietic cancers. In rats and dogs exposed to americium-241 by intravenous injection and in dogs exposed by inhalation, bone and liver cancers were observed. Skeletal cancers were observed in mice given californium-249 or californium-252 intraperitoneally and in dogs treated intravenously. Skeletal cancers were also observed in rats exposed by intravenous injection to curium-242 and curium-244 and lung and liver cancers in rats exposed by inhalation.

β-Particle-emitting radionuclides

Lifetime studies of the carcinogenic effects of pure and mixed β-particle-emitting radionuclides have been conducted in experimental animals of a number of species that differ greatly in features such as size, metabolic characteristics and lifespan. The locations and types of tumours observed were influenced by a number of factors including the form of radionuclide, the route by which it was administered, the resulting metabolic and dosimetric patterns, the age, sex and health status of the animals and the presence of other agents.

Because the penetration of β-particles is greater than that of α-particles, effects on tissues may be seen not only at the primary site of radionuclide deposition, like the skeleton, but also in nearby tissues like the nasal or oral mucosa.

The carcinogenicity of hydrogen-3 was tested in mice by intraperitoneal injection or oral administration and in rats by intraperitoneal injection, producing tumours of the haematopoietic system in mice and mammary tumours in rats. Phosphorus-32 injected intraperitoneally to mice increased the incidence of leukaemia. In rats, intraperitoneal injection of phosphorus-32 produced osteogenic sarcomas. Strontium-90 produced bone and lymphoid tumours in mice after its intraperitoneal injection. It produced bone tumours in dogs after intravenous injection or inhalation of a soluble form. Haematopoietic neoplasms and bone cancers were also found in dogs and miniature pigs fed strontium-90 in the diet. Yttrium-90 inhaled in an insoluble form produced lung cancers in dogs. Yttrium-91 produced lung, liver and bone tumours in dogs that inhaled a soluble form and lung cancers in dogs that inhaled an insoluble form. Promethium-147 caused lung tumours in Syrian hamsters injected intravenously with insoluble particles and in rats exposed by inhalation.

Iodine-131 given by intraperitoneal injection to mice and rats produced thyroid cancers. Caesium-137 produced liver, haematopoietic and other neoplasms after intravenous injection to dogs. Cerium-144 inhaled in an insoluble form produced lung tumours in mice, rats, Syrian hamsters and dogs. Dogs that inhaled a soluble form of cerium-144 developed lung, liver, bone and haematopoietic neoplasms. Radium-228 produced bone tumours in dogs after its intravenous injection.

Perinatal carcinogenesis

Some radionuclides have been tested for their carcinogenicity to offspring when given during the prenatal and/or neonatal period. The temporal distribution and spatial localization of the dose affect the response. Moreover, the dose rates and cumulative doses of radiation to the embryo or fetus are affected by the stage of development at the time of exposure.

Dose-dependent increases in tumour incidence and shorter times to tumour appearance have been found after perinatal exposure, but the tumour incidences may be decreased, especially at high doses, due to death, inhibition of development of target tissues or endocrine malfunction. Age-related differences in the predominant tumour types and/or sites of tumour development are due to the existence of radionuclide-specific target organs or tissues, dosimetric factors and different sensitivity at various stages of tissue differentiation and development.

Plutonium-238 and plutonium-239 caused bone tumours in rats exposed prenatally or neonatally. The sensitivity of these animals per unit dose of radiation was greater than that of adults. Tumours were found frequently in the skull, which received the highest dose of radiation as a result of its proportionately greater size during fetal and neonatal life.

Americium-241 also produced skeletal tumours in mice and rats exposed perinatally, and there is some evidence that it is more potent than plutonium.

Increased incidences of ovarian or reticuloendothelial tumours were found in the offspring of mice exposed to water labelled with hydrogen-3 during gestation in two separate experiments. A slight increase in the incidence of ovarian tumours and a decrease in the incidence of mammary tumours were found in the offspring of exposed rats. Prenatal or neonatal exposure of mice to thymidine labelled with hydrogen-3 caused increased incidences of miscellaneous tumours not ordinarily found in the strains of mice tested, and commonly occurring tumours were seen earlier or at increased incidence.

In one study, the offspring of rats exposed prenatally to phosphorus-32 developed neurogenic tumours. In another study, the time to appearance of bone tumours in postnatal life was reduced, although the overall incidence was not increased. In mice, the incidence of leukaemia was increased in female offspring.

Strontium-90 was carcinogenic to the offspring of mice, increasing the incidence of ovarian tumours. In the offspring of rats, increased incidences of pituitary tumours and lymphoid tumours of the thymus were observed.

Although bone tumours were produced by cerium-144 in rats exposed as weanlings, no bone tumours were seen in rats exposed at birth.

Mice and rats have shown greater sensitivity to thyroid tumour induction by iodine-131 after prenatal and neonatal exposure than after exposure as adults.

Paternal exposure

In one study, irradiation of male mice with α-particles from plutonium-239 produced genetically transmissible damage, manifested as an increased susceptibility of their offspring to subsequent exposure to known carcinogens.

5.4 Other relevant data

Absorption, distribution, metabolism and excretion

The distribution of dose from radionuclides deposited within the body depends on the amount and route of intake, the physicochemical form and types of radiation emitted, the physical half-life of the isotope, the organs and tissues in which the radionuclide is retained and the duration of retention. Internally deposited radionuclides, particularly those that emit poorly penetrating α- and low-energy β-particles, may preferentially irradiate specific tissues and specific cells within tissues. Depending on the radioactive half-life and the duration of retention in body tissues, a dose may be delivered for a very short period or over the lifetime of the individual.

Data on the behaviour of radionuclides in the body are used with information on the geometric arrangements of organs and tissues within the human body to construct models for calculating organ and tissue doses. These models take account of the dose to both those tissues that contain the radionuclide and those that do not. The location of sensitive cells within tissues is also taken into account (e.g. in bronchial airways and adjacent to bone surfaces). The reliability of dose estimates depends on the quality of the data on which the assumptions of the model are based.

The estimated doses to organs and tissues from different radionuclides, expressed as Gy/Bq, can vary by many orders of magnitude. For example, the dose received by adults exposed to hydrogen-3-labelled water, either by ingestion or inhalation of vapour, has been calculated to be 1.8×10^{-11} Gy/Bq, with uniform doses to all tissues, whereas the dose near bone surfaces after inhalation of plutonium-239 or americium-241 has been calculated to be 8×10^{-5} Gy/Bq. While the dose from hydrogen-3 is delivered over a period of weeks, plutonium-239 and americium-241, which have longer biological half-lives, continue to deliver their dose throughout the lifetime of the exposed person.

The estimated tissue doses of radionuclides can be used to predict the risk for induction of various cancers under particular conditions of exposure and to compare the effects of different radionuclides.

Toxic effects

Radiation from internally deposited α- and β-particle emitters produces dose-dependent pathological alterations in tissues over a wide range of cumulative tissue doses. Most authors have suggested that these effects are qualitatively similar to those produced by external irradiation with X-rays or γ-rays. The most important of these

changes result from deterministic effects, including cell death, vascular damage and tissue fibrosis. Information on the relative biological effectiveness of various radiation types is complicated by considerations of chemical toxicity, such as that of neptunium-237, and by differences in the deposition patterns of different radionuclides in the tissues studied. Moreover, even when radionuclides are similarly distributed, e.g. strontium-90 and radium-224, the spatial and temporal distribution of dose may differ substantially, such that any comparisons made are at best difficult and at worst meaningless. Most of the evidence suggests that α-particle emitters cause more tissue damage than external γ-radiation per unit absorbed dose.

The available evidence suggests that tissue damage occurs over a very wide range of tissue doses and probably always occurs after α-irradiation — a consequence of the cell killing by this type of radiation. Some authors have suggested that the cancer induction process is linked to the onset of deterministic effects.

Reproductive and developmental effects

A reasonably clear, quantitative picture is available of the developmental toxicity of prenatal and neonatal exposure to incorporated radionuclides. The effects include decreased prenatal or postnatal growth, reduced reproductive capacity, malformations and prenatal or postnatal death or life shortening. Some of the data allow direct or indirect comparisons with effects in adults and analysis of relationships to administered activity, radiation dose and the spatial and temporal distributions of radionuclides. Only inferential information is available on the effectiveness of particulate radiations relative to that of external photons or neutrons.

Heavy exposure of animals to radon-222 has been shown to cause prenatal haemorrhage and fetal death. Reduced fertility has been demonstrated in women with high body burdens of radium after occupational exposure, but this effect has not been demonstrated in experimental animals. Studies of americium and isotopes of plutonium in experimental animals have shown adverse effects on prenatal mortality, haematopoiesis and postnatal growth and life-span. Continuous exposure of pregnant animals to hydrogen-3-labelled water or thymidine resulted in prenatal death, decreased birth weights, retarded postnatal growth, effects on gonadal development, altered brain histogenesis and behavioural deficits. Studies in which preimplantation embryos were exposed to hydrogen-3 *in vitro* consistently showed greater effects on development when the radionuclide was incorporated into thymidine rather than into water. Exposure of animals to phosphorus-32 *in utero* led to prenatal death, reduced growth, malformations and gonadal and pituitary lesions. Exposure of animals to strontium-90 *in utero* had deleterious effects on fetal and neonatal ovaries and a lesser effect on the development of the testis. Fetal exposure to iodine-131 affected the development of the thyroid in humans and animals to a greater extent than postnatal exposure.

Genetic and related effects

All ionizing radiations can disrupt molecules and produce many types of DNA damage, ranging from isolated base damage or single-strand breaks to simple double-strand breaks and more complex DNA alterations involving clustered damage sites with multiple breaks and/or base changes. Clustered damage is produced efficiently by the low-energy electrons that are set in motion, mostly as secondary particles, by α, β, γ, X and Auger electron emissions from radionuclides as well as from external radiations. The more complex forms of damage common to these sources are potentially unique to ionizing radiation, as compared with those that occur spontaneously or are caused by other DNA-damaging agents. For increasingly complex lesions, accurate repair is believed to become progressively more unlikely, leading to increased probabilities of gene mutation, chromosomal aberration or cell death. The types of initial DNA damage produced by all forms of ionizing radiation are essentially similar, but the quantity of damage and the range of complexity depend on the type of radiation and whether the radiation is produced at sites on or near the DNA.

In vitro, various effects have been observed in a wide variety of cells, including DNA double-strand breaks, chromosomal and chromatid aberrations, gene mutation and morphological transformation, after irradiation with α-particle-emitting radionuclides, β-particle emitters, Auger electron emitters or characteristic low-energy X-rays. Cells morphologically transformed by α-particles and X-rays *in vitro* have been observed to cause tumours after their injection into mice. Similar effects have been observed directly with the pure β-particle emitters hydrogen-3 and carbon-14, the mixed β-emitter iodine-131, the Auger electron emitters indium-111 and iodine-125, pure (filtered) α-emissions from polonium-210 and plutonium-238 and other radionuclides with mixed or pure emissions.

The full range of cellular effects can be induced by any type of ionizing radiation, as is to be expected from the commonality of DNA damage, if the radiation particles or photons enter the cell nucleus to deliver a local dose.

The presence of chromosomal aberrations in human peripheral blood lymphocytes is a recognized indicator of exposure to radiation *in vivo*, an increase in the frequency of chromosomal aberrations above the background level reflecting direct exposure of circulating lymphocytes and/or haematopoietic precursor cells in the bone marrow. Increased frequencies of aberrations were observed in a number of studies after exposure of humans or experimental animals to either α- or β-particle-emitting radionuclides. Internal exposure of rodents to α- and β-particle-emitting radionuclides was shown to produce chromosomal alterations. Chromosomal aberrations and gene mutations were also observed in many studies in cells of people exposed internally to specific radionuclides, including the β-particle emitters hydrogen-3, phosphorus-32, yttrium-90 and iodine-131 and mixed α-particle emissions from Thorotrast (thorium-232 and its decay products).

5.5 Evaluation

There is *sufficient evidence* in humans that therapeutic injection of radium-224 causes bone sarcomas.

There is *sufficient evidence* in humans that ingestion of radium-226 causes bone sarcomas and carcinomas of the paranasal sinuses and mastoid process.

There is *sufficient evidence* in humans that ingestion of radium-228 causes bone sarcomas.

There is *sufficient evidence* in humans that diagnostic injection of thorium-232 as stabilized thorium-232 dioxide in colloidal form (Thorotrast) causes primary liver cancer, including haemangiosarcomas, and leukaemia, excluding chronic lymphocytic leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of thorium-232 after inhalation.

There is *inadequate evidence* in humans for the carcinogenicity of radon-220 (thoron) from internally deposited thorium-232.

There is *sufficient evidence* in humans that inhalation of plutonium-239 aerosols causes lung cancer, liver cancer and bone sarcoma. Exposure to plutonium-239 also entails exposure to plutonium-240 and other isotopes.

There is *inadequate evidence* in humans for the carcinogenicity of natural uranium.

There is *inadequate evidence* in humans for the carcinogenicity of polonium-210.

There is *sufficient evidence* in humans that exposure during childhood to short-lived radioisotopes of iodine, including iodine-131, in fall-out from reactor accidents and nuclear weapons detonations causes thyroid cancer.

There is *sufficient evidence* in humans that therapeutic ingestion or injection of phosphorus-32 administered as inorganic phosphate causes acute leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of strontium-90.

There is *inadequate evidence* in humans for the carcinogenicity of caesium-137.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the pure α-particle emitter polonium-210.

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixed α-particle emitters (radium-224, radium-226, thorium-227, thorium-228, thorium-230, thorium-232, neptunium-237, plutonium-238, plutonium-239 (together with plutonium-240), americium-241, curium-244, californium-249 and californium-252).

There is *limited evidence* in experimental animals for the carcinogenicity of natural uranium.

There is *inadequate evidence* in experimental animals for the carcinogenicity of uranium-233.

There is *sufficient evidence* in experimental animals for the carcinogenicity of pure β-particle emitters (hydrogen-3, phosphorus-32, strontium-90, yttrium-90, yttrium-91 and promethium-147).

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixed β-particle emitters (iodine-131, caesium-137, cerium-144 and radium-228).

Overall evaluation

Radium-224 (^{224}Ra) and its decay products are *carcinogenic to humans (Group 1).*

Radium-226 (^{226}Ra) and its decay products are *carcinogenic to humans (Group 1).*

Radium-228 (^{228}Ra) and its decay products are *carcinogenic to humans (Group 1).*

Thorium-232 (^{232}Th) and its decay products, administered intravenously as a colloidal dispersion of $^{232}ThO_2$, are *carcinogenic to humans (Group 1).*

Plutonium-239 (^{239}Pu) is *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group noted that human exposure to ^{239}Pu may also include exposure to ^{240}Pu.

Phosphorus-32 (^{32}P) is *carcinogenic to humans (Group 1).*

Radioiodines are *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group noted that human exposure to radionuclides of iodine from atomic reactor accidents and nuclear weapons detonations is to iodine-131 (^{131}I) and additional short-lived isotopes.

Internalized radionuclides that emit α-particles are *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group took into consideration the following:

- α-Particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations and the same pattern of localized damage to biological molecules, including DNA. These effects, observed *in vitro*, include DNA double-strand breaks, chromosomal aberrations, gene mutations and cell transformation.
- All radionuclides that emit α-particles and that have been adequately studied, including radon-222 and its decay products, have been shown to cause cancer in humans and in experimental animals.
- α-Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans *in vivo*.
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues — for example lung cells or bone surfaces — from α-particles emitted during the decay of different radionuclides produce the same types of non-neoplastic effects and cancers.

Internalized radionuclides that emit β-particles *are carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group took into consideration the following:

- β-Particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations and the same pattern of localized damage to biological molecules, including DNA. These effects, observed *in vitro*, include DNA double-strand breaks, chromosomal aberrations, gene mutations and cell transformation.

- All radionuclides that emit β-particles and that have been adequately studied, have been shown to cause cancer in humans and in experimental animals. This includes hydrogen-3, which produces β-particles of very low energy, but for which there is nonetheless *sufficient evidence* of carcinogenicity in experimental animals.
- β-Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans *in vivo.*
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues — for example lung cells or bone surfaces — from β-particles emitted during the decay of different radionuclides produce the same types of non-neoplastic effects and cancers.

SUMMARY OF FINAL EVALUATIONS

Agent	Degree of evidence of carcinogenicity		Overall evaluation of carcinogenicity to humans
	Human	Animal	
Pure α-particle emitters[1]			
Radon-222 and its decay products	S	S	1[2]
Polonium-210	I	S	
Curium-244 and its decay products		S[3]	
Mixed α-particle emitters[1]			
Radium-224 and its decay products	S	S	1
Radium-226 and its decay products	S	S	1
Radium-228 and its decay products	S		1
Thorium-232 and its decay products, administered intravenously as a colloidal dispersion of thorium-232 dioxide	S	S[3]	1
Thorium-232 and its decay products, after inhalation	I		
Radon-220, exhaled, from internally deposited thorium-232	I		
Thorium-227 and its decay products		S	
Thorium-228 and its decay products		S	
Thorium-230 and its decay products		S	
Uranium and its decay products, inhalation of ore dust containing uranium-234, uranium-235 and uranium-238	I	L	
Uranium-233 and its decay products		I	
Plutonium-238 and its decay products (may contain plutonium-240), after inhalation		S	
Plutonium-239 and its decay products (may contain plutonium-240), after injection		S	
Plutonium-239 and its decay products (may contain plutonium-240 and other isotopes), as aerosols	S	S	1
Neptunium-237 and its decay products		S	
Americium-241 and its decay products		S	
Californium-249 and its decay products		S	
Californium-252 and its decay products		S	
α-Particle-emitting radionuclides, internally deposited			**1**
Pure β-particle emitters[1]			
Hydrogen-3		S	
Phosphorus-32, as phosphate	S	S	1
Strontium-90	I	S	
Yttrium-90		S	
Yttrium-91		S	
Promethium-147		S	
Mixed β-particle emitters[1]			
Radioiodines, short-lived isotopes, including iodine-131, from atomic reactor accidents and nuclear weapons detonations (exposure during childhood)	S		1
Iodine-131		S	
Caesium-137 and its decay products	I	S	
Cerium 144 and its decay products		S	
Radium-228 and its decay products		S[4]	
β-Particle-emitting radionuclides, internally deposited			**1**

[1] See Section 3 of General Remarks for definition of pure and mixed emitters
[2] Previously evaluated (IARC, 1988)
[3] In two-year bioassays in rodents, curium-244 and thorium-232 may be considered pure α-particle emitters.
[4] In two-year bioassays in rodents, radium-228 may be considered a mixed β-particle emitter; during long-term exposure of humans to radium-228, the effects of α-radiation predominate.

6. References

Abbatt, J.D. (1979) History of the use and toxicity of Thorotrast. *Environ. Res.*, **18**, 6–12

Abelin, T., Averkin, J.I., Egger, M., Egloff, B., Furmanchuk, A.W., Gurtner, F., Korotkevich, J.A., Marx, A., Matveyenko, I.I., Okeanov, A.E., Ruchti, C. & Schaeppi, W. (1994) Thyroid cancer in Belarus post-Chernobyl: Improved detection or increased incidence? *Soz. Präventivmed.*, **39**, 189–197

Adams, E.E., Brues, A.M. & Anast, G.A. (1983) Survey of ocular cataracts in radium dial workers. Health Phys., **44** (Suppl. 1), 73–79

Adamson, J.W., Fialkow, P.J., Murphy, S., Prchal, J.F. & Steinmann, L. (1976) Polycythemia vera: Stem-cell and probable clonal origin of the disease. *New Engl. J. Med.*, **295**, 913–916

Aghamohammadi, S.Z., Goodhead, D.T. & Savage, J.R.K. (1988) Induction of sister chromatid exchanges (SCE) in G_0 lymphocytes by plutonium-238 α-particles. *Int. J. Radiat. Biol.*, **53**, 909–915

Aghamohammadi, S.Z., Morris, T., Stevens, D.L. & Thacker, J. (1992) Rapid screening for deletion mutations in the hprt gene using the polymerase chain reaction: X-ray and α-particle mutant spectra. *Mutat. Res.*, **269**, 1–7

Ahman, B. & Ahman, G. (1994) Radiocesium in Swedish reindeer after the Chernobyl fallout: Seasonal variations and long-term decline. *Health Phys.*, **66**, 503–512

Akiyama, M., Umeki, S., Kusunoki, Y., Kyoizumi, S., Nakamura, N., Mori, T., Ishikawa, Y., Yamakido, M., Ohama, K., Kodama, T., Endo, K. & Cologne, J.B. (1995) Somatic-cell mutations as a possible predictor of cancer risk. *Health Phys.*, **68**, 643–649

Akleyev, A.V. & Lyubchansky, E.R. (1994) Environmental and medical effects of nuclear weapon production in the Southern Urals. *Sci. total Environ.*, **142**, 1–8

Akleyev, A.V., Kossenko, M.M., Silkina, L.A., Degteva, M.O., Yachmenyov, V.A., Awa, A., Akiyama, M., Veremeyeva, G.A., Vozilova, A.V., Kyozumi, S., Kozheurov, V.P. & Vyushkova, O.V. (1995) Health effects of radiation incidents in the Southern Urals. *Stem Cells*, **13** (Suppl. 1), 58–68

Alavanja, M.C.R., Brownson, R.C., Lubin, J.H., Berger, E., Chang, J. & Boice, J.D., Jr (1994) Residential radon exposure and lung cancer among nonsmoking women. *J. natl Cancer Inst.*, **86**, 1829–1837

Alavanja, M.C.R., Lubin, J.H., Mahaffey, J.A. & Brownson, R.C. (1999) Residential radon exposure and risk of lung cancer in Missouri. *Am. J. public Health*, **89**, 1042–1048

Albert, R., Klevin, P., Fresco, J., Harley, J., Harris,W. & Eisenbud, M. (1955) Industrial hygiene and medical survey of a thorium refinery. *Arch. ind. Health*, **11**, 234–242

Albertini, R.J., Castle, K.L. & Borcherding, W.R. (1982) T-cell cloning to detect the mutant 6-thioguanine-resistant lymphocytes present in human peripheral blood. *Proc. natl Acad. Sci. USA*, **79**, 6617–6621

Albertini, R.J., Clark, L.S., Nicklas, J.A., O'Neill, J.P., Hui, T.E. & Jostes, R. (1997) Radiation quality affects the efficiency of induction and the molecular spectrum of *HPRT* mutations in human T cells. *Radiat. Res.*, **148**, S76–S86

Anderson, E.C., Holland, L.M., Prine, J.R. & Thomas, R.G. (1975) Lung response to localized irradiation from plutonium microspheres. *Inhaled Part.*, **4**, 615–623

Anderson, E.C., Holland, L.M., Prine, J.R. & Smith, D.M. (1979) Lung tumorigenesis in the Syrian hamster from particulate sources of ^{147}Pm β radiation. *Radiat. Res.*, **79**, 349–367

Andersson, M. (1997) Long-term effects of internally deposited α-particle emitting radionuclides. *Dan. med. Bull.*, **44**, 169–190

Andersson, M., Carstensen, B. & Visfeldt, J. (1993) Leukemia and other related hematological disorders among Danish patients exposed to Thorotrast. *Radiat. Res.*, **134**, 224–233

Andersson, M., Vyberg, M., Visfeldt, J., Carstensen, B. & Storm, H.H. (1994) Primary liver tumors among Danish patients exposed to Thorotrast. *Radiat. Res.*, **137**, 262–273

Andersson, M., Carstensen, B. & Storm, H.H. (1995a) Mortality and cancer incidence after cerebral arteriography with or without Thorotrast. *Radiat. Res.*, **142**, 305–320

Andersson, M., Wallin, H., Jönsson, M., Nielsen, L.L., Visfeldt, J., Vyberg, M., Bennett, W.P., De Benedetti, V.M.G., Travis, L.B. & Storm, H.H. (1995b) Lung cancer and malignant mesothelioma in patients exposed to Thorotrast: Incidence, histology and *p53* status. *Int. J. Cancer*, **63**, 330–336

Andersson, M., Jönsson, M., Nielsen, L.L., Vyberg, M., Visfeldt, J., Storm, H.H. & Wallin, H. (1995c) Mutations in the tumor suppressor gene *p53* in human liver cancer induced by α-particles. *Cancer Epidemiol. Biomarkers Prev.*, **4**, 765–770

Anspaugh, L.R., Ricker, Y.E., Black, S.C., Grossman, R.F., Wheeler, D.L., Church, B.W. & Quinn, V.E. (1990) Historical estimates of external γ exposure and collective external γ exposure from testing at the Nevada Test Site. II. Test series after Hardtack II, 1958, and summary. *Health Phys.*, **59**, 525–532

Archer, V.E., Magnuson, H.J., Holaday, D.A. & Lawrence, P.A. (1962) Hazards to health in uranium mining and milling. *J. occup. Med.*, **4**, 55–60

Archer, V.E., Wagoner, J.K. & Lundin, F.E., Jr (1973) Cancer mortality among uranium mill workers. *J. occup. Med.*, **15**, 11–14

Arndt, D., Mehnert, W.H., Franke, W.-G., Woller, P., Laude, G., Rockel, A. & Waller, M. (1994) Radioiodine therapy during an unknown remained pregnancy and radiation exposure of the fetus. *Strahlenther. Onkol.*, **170**, 408–414

Arnold, W. & Weber, C. (1989) Radiation effects on the bone marrow of ankylosing spondylitis patients treated with radium 224. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology, pp. 29–31

Astakhova, L.N., Anspaugh, L.R., Beebe, G.W., Bouville, A., Drozdovitch, V.V., Garber, V., Gavrilin, Y.I., Khrouch, V.T., Kuvshinnikov, A.V., Kuzmenkov, Y.N., Minenko, V.P., Moschik, K.V., Nalivko, A.S., Robbins, J., Shemiakina, E.V., Shinkarev, S., Tochitskaya, S.I. & Waclawiw, M.A. (1998) Chernobyl-related thyroid cancer in children of Belarus: A case–control study. *Radiat. Res.*, **150**, 349–356

Auvinen, A., Mäkeläinen, I., Hakama, M., Castrén, O., Pukkala, E., Reisbacka, H. & Rytömaa, T. (1996) Indoor radon exposure and risk of lung cancer: A nested case–control study in Finland. *J. natl Cancer Inst.*, **88**, 966–972

Auvinen, A., Makelainen, I., Hakama, M., Castrén, O., Pukkala, E., Reisbacka, H. & Rytömaa, T. (1998) Indoor radon exposure and risk of lung cancer: A nested case–control study in Finland. *J. natl. Cancer Inst.*, **90**, 401–402 (erratum)

Bagg, H.J. (l922) Disturbances in mammalian development produced by radium emanation. *Am. J. Anat.*, **30**, 133–161

Balonov, M.I., Muksinova, K.N. & Mushkacheva, G.S. (1993) Tritium radiobiological effects in mammals: Review of experiments of the last decade in Russia. *Health Phys.*, **65**, 713–726

Balonov, M., Jacob, P., Likhtarev, I. & Minenko, V. (1996) Pathways, levels and trends of population exposure after the Chernobyl accident. In: Karaoglou, A., Desmet, G., Kelly, G.N. & Menzel, H.G., eds, *The Radiological Consequences of the Chernobyl Accident, Proceedings of the First International Conference, Minsk, Belarus, 18 to 22 March 1996* (EUR 16544 EN), Luxembourg, Office for Official Publications of the European Communities, pp. 235–249

Bao, C.-Y., Ma, A.-H., Evans, H.H., Horng, M.F., Mencl, J., Hui, T.E. & Sedwick, W.D. (1995) Molecular analysis of hypoxanthine phosphoribosyltransferase gene deletions induced by α- and X-radiation in human lymphoblastoid cells. *Mutat. Res.*, **326**, 1–15

Barabanova, A. & Osanov, D.P. (1990) The dependence of skin lesions on the depth–dose distribution from β-irradiation of people in the Chernobyl nuclear power plant accident. *Int. J. Radiat. Biol.*, **57**, 775–782

Baranov, A., Gale, R.P., Guskova, A., Piatkin, E., Selidovkin, G., Muravyova, L., Champlin, R.E., Danilova, N., Yevseeva, L., Petrosyan, L., Pushkareva, S., Konchalovsky, M., Gordeeva, A., Protasova, T., Reisner, Y., Mickey, M.R. & Terasaki, P.I. (1989) Bone marrow transplantation after the Chernobyl nuclear accident. *New Engl. J. Med.*, **321**, 205–212

Barnhart, B.J. & Cox, S.H. (1979) Mutagenicity and cytotoxicity of 4.4-MeV α particles emitted by plutonium-238. *Radiat. Res.*, **80**, 542–548

Baserga, R., Lisco, H. & Kisieleski, W.E. (1966) Tumor induction in mice by radioactive thymidine. *Radiat. Res.*, **2**, 583–596

Bateman, A.J. & Chandley, A.C. (1962) Mutations induced in the mouse with tritiated thymidine. *Nature*, **193**, 705–706

Bauchinger, M., Schmid, E., Braselmann, H. & Kulka, U. (1994) Chromosome aberrations in peripheral lymphocytes from occupants of houses with elevated indoor radon concentrations. *Mutat. Res.*, **310**, 135–142

Bauchinger, M., Braselmann, H., Kulka, U., Huber, R. & Georgiadou-Schumacher, V. (1996) Quantification of FISH-painted chromsome aberrations after domestic radon exposure. *Int. J. Radiat. Biol.*, **70**, 657–663

Bauchinger, M., Salassidis, K., Braselmann, H., Vozilova, A., Pressl, S., Stephan, G., Snigiryova, G., Kozheurov, V.P. & Akleyev, A. (1998) FISH-based analysis of stable translocations in a Techa River population. *Int. J. Radiat. Biol.*, **73**, 605–612

Baugnet-Mahieu, L., Lemaire, M., Léonard, E.D., Léonard, A. & Gerber, G.B. (1994) Chromosome aberrations after treatment with radioactive iodine for thyroid-cancer. *Radiat. Res.*, **140**, 429–431

Bäverstam, U. & Lagarde, F. (1999) The impact of measurement errors in exposure assessment for residential radon. A stochastic approach. In: Ron, E. & Hoffman, F.O., eds, *Uncertainties in Radiation Dosimetry and Their Impact on Dose–Response Analyses* (NIH Publication No. 99-4541), Bethesda, MD, National Cancer Institute, pp. 132–138

Bäverstam, U. & Swedjemark, G.-A. (1991) Where are the errors when we estimate radon exposure in retrospect? *Radiat. Prot. Dosim.*, **36**, 107–112

Baverstock, K.F. & Papworth, D.G. (1985) The UK radium luminiser survey: Significance of a lack of excess leukaemia. *Strahlentherapie*, **80**, 22–26

Beasley, T.M., Palmer, H.E. & Nelp, W.B. (1966) Distribution and excretion of technetium in humans. *Health Phys.*, **12**, 1425–1435

Beck, A. (1922) [On the question of X-ray induced sarcoma; a contribution to the pathogenesis of sarcoma]. *Munch. Med. Wochenschr.*, **17**, 623–625 (in German)

Beling, U. & Einhorn, J. (1961) Incidence of hypothyroidism and recurrences following I^{131} treatment of hyperthyroidism. *Acta Radiol.*, **56**, 275–288

Belinsky, S.A., Swafford, D.S., Finch, G.L., Mitchell, C.E., Kelly, G., Hahn, F.F., Anderson, M.W. & Nikula, K.J. (1997) Alterations in the K-*ras* and *p53* genes in rat lung tumors. *Environ. Health Perspectives*, **105**, 901–906

Beral, V., Fraser, P., Carpenter, L., Booth, M., Brown, A. & Rose, G. (1988) Mortality of employees of the Atomic Weapons Establishment, 1951–82. *Br. med. J.*, **297**, 757–770

Berglund, S. & Zettervall, O. (1992) Incidence of polycythemia vera in a defined population. *Eur. J. Haematol.*, **48**, 20–26

Berk, P.D., Goldberg, J.D., Donovan, P.B., Fruchtman, S.M., Berlin, N.I. & Wasserman, L.R. (1986) Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. *Semin. Hematol.*, **23**, 132–143

Berkovski, V. (1999) Radioiodine biokinetics in the mother and fetus. Part 2. Fetus. In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer* (EUR 18552 EN), Singapore, World Scientific, pp. 327–332

Berrett, A. & McRae, D.L. (1958) A follow-up study after Thorotrast carotid arteriography. *Can. med. Assoc. J.*, **78**, 916–921

Berry, C.L., Amerigo, J., Nickols, C. & Swettenham, K.V. (1983) Transplacental carcinogenesis with radioactive phosphorus. *Hum. Toxicol.*, **2**, 49–62

Bertelli, L., Oliveira, C.A.N., Lipsztein, J.L. & Wrenn, M.E. (1992) A case study of the transfer of ^{137}Cs to the human fetus and nursing infant. *Radiat. Prot. Dosim.*, **41**, 131–136

Bhatia, A.L. & Sisodia, R. (1988) Neuromorphometrical changes in cerebral cortex of Swiss albino mice during postnatal development under HTO-exposure. *Radiobiol. Radiother.*, **29**, 717–727

Bhatia, A.L. & Srivastava, P.N. (1982) Tritium toxicity in mouse testis: Effect of continuous exposure during pre- and postnatal development. *Strahlentherapie*, **158**, 752–755

Biberman, R., Lusky, A., Schlesinger, T., Margaloit, M., Neeman, E. & Modan, B. (1993) Increased risk for small cell lung cancer following residential exposure to low-dose radon: A pilot study. *Arch. environ. Health*, **48**, 209–212

Bickel, A. (1913) [New contribution to thorium X therapy in anaemia, leukaemia and rheumatic diseases]. *Berl. klin. Wschr.*, **50**, 346–348 (in German)

Bilbao, A., Prosser, J.S., Edwards, A.A., Moody, J.C. & Lloyd, D.C. (1989) The induction of micronuclei in human lymphocytes by *in vitro* irradiation with alpha particles from plutonium-239. *Int. J. Radiat. Biol.*, **56**, 287–292

Birchall, A. & James, A.C. (1994) Uncertainty analysis of the effective dose per unit exposure from radon progeny and implications for ICRP risk-weighting factors. *Radiat. Prot. Dosim.*, **53**, 133–140

Blanchard, R.L. (1967) Concentrations of ^{210}Pb and ^{210}Po in human soft tissues. *Health Phys*., **13**, 625–632

Bleuer, J.P., Averkin, Y.I. & Abelin, T. (1997) Chernobyl-related thyroid cancer: What evidence for role of short-lived iodines? *Environ. Health Perspectives*, **105** (Suppl. 6), 1483–1486

Blöcher, D. (1988) DNA double-strand break repair determines the RBE of alpha-particles. *Int. J. Radiat. Biol.*, **54**, 761–771

Blomberg, R., Larsson, L.E., Lindell, B. & Lindgren, E. (1967) Late effects of Thorotrast in cerebral angiography. *Am. N.Y. Acad. Sci.*, **145**, 853–858

Blot, W.J., Xu, Z.-Y., Boice, J.D., Jr, Zhao, D.-Z., Stone, B.J., Sun, J., Jing, L.-B. & Fraumeni, J.F., Jr (1990) Indoor radon and lung cancer in China. *J. natl Cancer Inst.*, **82**, 1025–1030

Blum, T. (1924) Osteomyelitis of the mandible and maxilla. *J. Am. med. dent. Assoc*., **11**, 802–805

Boecker, B.B., Muggenburg, B.A., Miller, S.C. & Brackley, P.L., eds (1994) *Biennial Report on Long-term Dose–Response Studies of Inhaled or Injected Radionuclides 1991–1993* (US Department of Energy Report ITRI-139), Springfield, VA, National Technical Information Service, pp. 126–129, 193–195

Bogdan, G.M. & Aposhian, H.V. (1990) *N*-(2,3-Dimercaptopropyl)phthalamidic acid (DMPA) increases polonium-210 excretion. *Biol. Metals*, **3**, 232–236

Bond, V.P., Fliedner, T.M. & Archambau, J.O. (1965) *Mammalian Radiation Lethality: A Disturbance in Cellular Kinetics*, New York, Academic Press

Book, S.A. & Goldman, M. (1975) Thyroidal radioiodine exposure of the fetus. *Health Phys*., **29**, 874–877

Botchway, S.W., Stevens, D.L., Hill, M.A., Jenner, T.J. & O'Neill, P. (1997) Induction and rejoining of DNA double-strand breaks in Chinese hamster V79-4 cells irradiated with characteristic aluminum K and copper L ultrasoft X rays. *Radiat. Res*., **148**, 317–324

Boulahdour, H. & Galle, P. (1998) Ultrastructural lesions in mammalian cells after neptunium-237 intoxication: Radiological or chemical lesions? *Scanning*, **20**, 193–194

Bouville, A., Anspaugh, L., Balonov, M.I., Gordeev, K.I., Kiselev, V.I., Loborev, V.M., Luckyanov, N.K., Pauli, E., Robison, W.L., Savkin, M., Sudakov, V.V. & Zelentsov, S. (2000) Estimation of doses. In: Warner, F. & Kirchman, R.J., eds, *Nuclear Test Explosions: Environmental and Human Impacts*, New York, Wiley & Sons, pp. 115–177

Bowlt, C. & Tiplady, P. (1989) Radioiodine in human thyroid glands and incidence of thyroid cancer in Cumbria. *Br. med. J.*, **299**, 301–302

Boyd, J.T., Court Brown, W.M., Vennart, J. & Woodcock, G.E. (1966) Chromosome studies on women formerly employed as luminous-dial painters. *Br. med. J*., **i**, 377–382

Boyd, J.T., Langlands, A.O. & MacCabe, J.J. (1968) Long-term hazards of Thorotrast. *Br. med. J*., **ii**, 517–521

Brandom, W.F., McGavran, L., Bistline, R.W. & Bloom, A.D. (1990) Sister chromatid exchanges and chromosome aberration frequencies in plutonium workers. *Int. J. Radiat. Biol.*, **58**, 195–207

Breitenstein, B.D., Jr & Palmer, H.E. (1989) Lifetime follow-up of the 1976 americium accident victim. *Radiat. Protect. Dosim*., **26**, 317–322

Bremner, W.F., McDougall, I.R. & Greig, W.R. (1973) Results of treating 297 thyrotoxic patients with ^{125}I. *Lancet*, **ii**, 281–282

Brenner, D.J. (1994) The significance of dose rate in assessing the hazards of domestic radon exposure. *Health Phys.*, **67**, 76–79

Bridges, B.A., Cole, J., Arlett, C.F., Green, M.H.L., Waugh, A.P.W., Beare, D., Henshaw, D.L. & Last, R.D. (1991) Possible association between mutant frequency in peripheral lymphocytes and domestic radon concentrations. *Lancet*, **337**, 1187–1189

Brincker, H., Hansen, H.S. & Andersen, A.P. (1973) Induction of leukaemia by ^{131}I treatment of thyroid carcinoma. *Br. J. Cancer*, **28**, 232–237

Britcher, A.R. & Strong, R. (1994) Personal air sampling — A technique for the assessment of chronic low level exposure? *Radiat. Protect. Dosim.*, **53**, 59–62

Brooks, A.L., Retherford, J.C. & McClellan, R.O. (1974) Effect of $^{239}PuO_2$ particle number and size on the frequency and distribution of chromosome aberrations in the liver of the Chinese hamster. *Radiat. Res.*, **59**, 693–709

Brooks, A.L., Benjamin, S.A., Hahn, F.F., Brownstein, D.G., Griffith, W.C. & McClellan, R.O. (1983) The induction of liver tumors by ^{239}Pu citrate or $^{239}PuO_2$ particles in the Chinese hamster. *Radiat. Res.*, **96**, 135–151

Brooks, A.L., Guilmette, R.A., Hahn, F.F., Haley, P.J., Muggenburg, B.A., Mewhinney, J.A. & McClellan, R.O. (1992) Distribution and biological effects of inhaled $^{239}Pu(NO_3)_4$ in cynomolgus monkeys. *Radiat. Res.*, **130**, 79–87

Brooks, A.L., Khan, M.A., Jostes, R.F. & Cross, F.T. (1993) Metaphase chromosome aberrations as markers of radiation exposure and dose. *J. Toxicol. environ. Health*, **40**, 277–288

Brooks, A.L., Bao, S., Harwood, P.W., Wood, B.H., Chrisler, W.B., Khan, M.A., Gies, R.A. & Cross, F.T. (1997) Induction of micronuclei in respiratory tract following radon inhalation. *Int. J. Radiat. Biol.*, **72**, 485–495

Bruenger, F.W., Lloyd, R.D. & Miller S.C. (1991a) The influence of age at time of exposure to ^{226}Ra or ^{229}Pu on distribution, retention, postinjection survival and tumor induction in beagle dogs. *Radiat. Res.*, **125**, 248–256

Bruenger, F.W., Taylor, D.M., Taylor, G.N. & Lloyd, R.D. (1991b) Effectiveness of DTPA treatments following the injection of particulate plutonium. *Int. J. Radiat. Biol.*, **60**, 803–818

Bruenger, F.W., Lloyd, R.D., Miller, S.C., Taylor, G.N., Angus, W. & Huth, D.A. (1994) Occurrence of mammary tumors in beagles given radium-226. *Radiat. Res.*, **138**, 423–434

Bulman, R.A. (1990) Interaction of chelation agents with bone. In: Priest, N.D. & Van De Vyver, F.L., eds, *Trace Metals and Fluoride in Bones and Teeth*, Boca Raton, FL, CRC Press, pp. 271–306

Burch, P.R.J. (1959) Iodine-131 in human thyroids and iodine-131 and caesium-137 in milk. *Nature*, **183**, 515–517

Burkart, W. (1996) Radioepidemiology of the aftermath of the nuclear program of the former Soviet Union: Unique lessons to be learnt. *Radiat. Environ. Biophys.*, **35**, 65–73

Burki, H.J., Bunker, S., Ritter, M. & Cleaver, J.E. (1975) DNA damage from incorporated radioisotopes: Influence of the ^{3}H location in the cell. *Radiat. Res.*, **62**, 299–312

Bursian, S.J., Cahill, D.F., Laskey, J.W. & Parker, L.N. (1975) Some aspects of brain neurochemistry after intrauterine exposure to tritium. *Int. J. Radiat. Biol.*, **27**, 455–461

Butland, B.K., Muirhead, C.R. & Draper, G.J. (1990) Radon and leukaemia (Letter to the Editor). *Lancet*, **335**, 1338–1339

Buzhievskaya, T.I., Tchaikovskaya, T.L., Demidova, G.G. & Koblyanskaya, G.N. (1995) Selective monitoring for a Chernobyl effect on pregnancy outcome in Kiev, 1969–1989. *Hum. Biol.*, **67**, 657–672

Cahill, D.F. & Yuile, C.L. (1970) Tritium: Some effects of continuous exposure *in utero* on mammalian development. *Radiat. Res.*, **44**, 727–737

Cahill, D.F., Wright, J.F., Godbold, J.H., Ward, J.M., Laskey, J.W. & Tompkins, E.A. (1975a) Neoplastic and life-span effects of chronic exposure to tritium. I. Effect on adult rat exposed during pregnancy. *J. natl Cancer Inst*., **55**, 371-374

Cahill, D.F., Wright, J.F., Godbold, J.H., Ward, J.M., Laskey, J.W. & Tompkins, E.A. (1975b) Neoplastic and life-span effects of chronic exposure to tritium. II. Rats exposed in utero. *J. natl Cancer Inst*., **55,** 1165–1169

Cahill, D.F., Reiter, L.W., Santolucito, J.A., Rehnberg, G.I., Ash, M.E., Favor, M.J., Bursian, S.J., Wright, J.F. & Laskey, J.W. (1976) Biological assessment of continuous exposure to tritium and lead in the rat. In: *Biological and Environmental Effects of Low-level Radiation*, Vol. II (IAEA-SM-202/305), Vienna, International Atomic Energy Agency, pp. 65–78

Capen, C.C., Delellis, R.A. & Williams, E.D. (1999) Experimental thyroid carcinogenesis in rodents: Role of radiation and xenobiotic chemicals. In: Thomas, G., Karaoglu, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer*, Singapore, World Scientific, pp. 167–176

Cardis, E. (1996) Epidemiology of accidental radiation exposures. *Environ. Health Perspectives*, **104** (Suppl. 3), 643–649

Cardis, E., Anspaugh, L., Ivanov, V.K., Likhtarev, I.A., Mabuchi, K., Okeanov, A.E. & Prisyazhniuk, A.E. (1996) Estimated long term health effects of the Chernobyl accident. In: *One Decade after Chernobyl*, Vienna, International Atomic Energy Agency, pp. 241–279

Cardis, E., Amoros, E., Kesminiene, A., Malakhova, I.V., Poliakov, S.M., Piliptsevitch, N.N., Demidchik, E.P., Astakhova, L.N., Ivanov, V.K., Konogorov, A.P., Parshkov, E.M. & Tsyb, A.F. (1999) Observed and predicted thyroid cancer incidence following the Chernobyl accident. Evidence for factors influencing susceptibility to radiation induced thyroid cancer. In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer* (EUR 18552 EN), Singapore, World Scientific, pp. 395–405

Carlsson, S. (1995) A glance at the history of nuclear medicine. *Acta oncol.*, **34**, 1095–1102

Carnes, B.A., Groer, P.G. & Kotek, T.J. (1997) Radium dial workers: Issues concerning dose response and modeling. *Radiat. Res.*, **147**, 707–714

Carpenter, L.M., Higgins, C.D., Douglas, A.J., Maconochie, N.E.S., Omar, R.Z., Fraser, P., Beral, V. & Smith, P.G. (1998) Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. *Br. J. Cancer*, **78**, 1224–1232

Carr, T.E.F. & Nolan, J. (1979) Testis mass loss in the mouse induced by tritiated thymidine, tritiated water, and ^{60}Co gamma irradiation. *Health Phys*., **36**, 135–145

Carsten, A.L. & Commerford, S.L. (1976) Dominant lethal mutations in mice resulting from chronic tritiated water (HTO) ingestion. *Radiat. Res*., **66**, 609–614

Carsten, A.L., Commerford, S.L. & Cronkite, E.P. (1977) The genetic and late somatic effects of chronic tritium ingestion in mice. *Curr. Topics Radiat. Res. Q*., **12**, 212–224

Castle, J.N., Scott, K.G. & Reilly, W.A. (1964) The skeletal uptake of radiophosphorus (^{32}P). *Am. J. Roentgenol.*, **91**, 1128–1131

Castronovo, F.P. (1999) Teratogen update: Radiation and Chernobyl. *Teratology*, **60**, 100–106

Cayolla da Motta, L., da Silva Horta, J. & Tavares, M.H. (1979) Prospective epidemiological study of Thorotrast-exposed patients in Portugal. *Environ. Res.*, **18**, 152–172

Chamberlain, A.C. & Dunster, H.J. (1958) Deposition of radioactivity in north-west England from the accident at Windscale. *Nature*, **182**, 629–630

Chambers, D.B., Stager, R.H. & Frost, S.E. (1999) How uncertainty could affect dose–response in the Beaverlodge Canada miners studies. In: Ron, E. & Hoffman, F.O., eds, *Uncertainties in Radiation Dosimetry and their Impact on Dose–Response Analyses* (NIH Publication No. 99-4541), Bethesda, MD, National Cancer Institute

Chan, P.C., Lisco, E., Lisco, H. & Adelstein, S.J. (1976) The radiotoxicity of iodine-125 in mammalian cells. II. A comparative study on cell survival and cytogenetic responses to ^{125}IUdR, ^{131}IUdR, and ^{3}HTdR. *Radiat. Res.*, **67**, 332–343

Chaundhry, M.A., Jiang, Q., Ricanati, M., Horng, M.F. & Evans, H.H. (1996) Charaterization of multilocus lesions in human cells exposed to X radiation and radon. *Radiat. Res.*, **145**, 31–38

Checkoway, H., Pearce, N., Crawford-Brown, D.J. & Cragle, D.L. (1988) Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. *Am. J. Epidemiol.*, **127**, 255–266

Chen, D.J., Strniste, G.F. & Tokita, N. (1984) The genotoxicity of alpha particles in human embryonic skin fibroblasts. *Radiat. Res.*, **100**, 321–327

Chen, X.-A., Huo, Q., Dong, Z., Li, W., Wang, Y., Cha, Y., Tan, G., He, W., Chen, M., Feng, R., Liang, L. & Li, R. (1986) Activity concentration of exhaled ^{220}Rn and burden of ^{228}Th in workers working at the Bai Yuan iron mine in Innermongolia and in inhabitants living in the high background radiation area in China. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, München, Urban & Schwarzenberg, pp. 157–162

Chen, X.-A., Xiao, H.-J., Yang, Y.-J., Chen, L., Long, S.-C., Deng, Y.-M. & Fong, G.-D. (1989) A follow-up study (1980–87) on the relationship between thorium lung burden and health effects on miners at the Baiyan Obo mine, China. In: Taylor, D.M., Mays, C.M., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology. pp. 180–183

Chen, X.-A., Xiao, H.-J., Cheng, Y.-E., Dong, Z.-H., Yang, Y.-J., Chen, L., Hao, J.-F. & He, Q.-C. (1993) A follow-up study (1982–1991) on the relationship between thorium lung burden and health effects in miners at the Baiyan Obo rare earth and iron mine. *Radiat. Prot. Aust.*, **11**, 157–161

Chen, X.-A., Cheng, Y.-E., Rong, Z. & Yan, X.-S. (1999) Results of the follow-up study of the thorium lung burden and its health effects of thorium miners in China. *Radiat. Res.*, **152**, S163–S164

Chen, X.-A., Cheng, Y.-E. & Rong, Z. (2000) Health effects following long-term exposure to thorium dusts. A fourteen-year follow-up study in China. In: *Proceedings of the 10th International Congress of IRPA*, Hiroshima, Japan Health Physics Society (CD-ROM)

Chmelevsky, D., Mays, C.W., Spiess, H., Stefani, F.H. & Kellerer, A.M. (1988) An epidemiological assessment of lens opacifications that impaired vision in patients injected with radium-224. *Radiat. Res.*, **115**, 238–257

Clarke, W.J. & Bair, W.J. (1964) Plutonium inhalation studies. VI. Pathologic effects of inhaled plutonium particles in dogs. *Health Phys.*, **10**, 391–398

Cleaver, J.E. & Burki, H.J. (1974) Biological damage from intranuclear carbon-14 decays: DNA single-strand breaks and repair in mammalian cells. *Int. J. Radiat. Biol.*, **26**, 399–403

Cleaver, J.E., Thomas, G.H. & Burki, H.J. (1972) Biological damage from intranuclear tritium: DNA strand breaks and their repair. *Science*, **177**, 996–998

Coggle, J.E. (1983) *Biological Effects of Radiation*, London, Taylor Francis

Cohen, B.L. (1995) Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys.*, **68**, 157-174

Cohen, B.L. (1998) Response to criticisms of Smith et al. *Health Phys*., **75**, 23–28, 31–33

Cohen, B.L. (2000) Testing a BEIR-VI suggestion for explaining the lung cancer vs. radon relationship for US counties. *Health Phys.*, **78**, 522–527

Cohen, B.S., Eisenbud, M. & Harley, N.H. (1980) Alpha radioactivity in cigarette smoke. *Radiat. Res*., **83**, 190–196

Cole, J., Green, M.H.L., Bridges, B.A., Waugh, A.P.W., Beare, D.M., Henshaw, D., Last, R., Liu, Y. & Cortopassi, G. (1996) Lack of evidence for an association between the frequency of mutants or translocations in circulating lymphocytes and exposure to radon gas in the home. *Radiat. Res*., **145**, 61–69

Committee on the Biological Effects of Ionizing Radiations (BEIR IV) (1988) *Health Risks of Radon and Other Internally Deposited Alpha-Emitters*, Washington DC, National Academy Press

Committee on Health Risks of Exposure to Radon (BEIR VI) (1999) *Health Effects of Exposure to Radon*, Washington DC, National Academy Press

Conard, R.A. (1984) Late radiation effects in Marshall Islanders exposed to fall-out 28 years ago. In: Boice, J.D., Jr & Fraumeni, J.F., Jr, eds, *Radiation Carcinogenesis: Epidemiology and Biological Significance*, New York, Raven Press, pp. 57–71

Conard, R.A., Knudsen, K.D. & Dobyns, B.M. (1974) *A Twenty Year Review of Medical Findings in a Marshallese Population Accidentally Exposed to Radioactive Fallout* (BNL 50424), Upton, NY, Brookhaven National Laboratory

Conard, R.A., Paglia, D.E., Larsen, R.P., Sutow, W.W., Dobyns, B.M., Robbins, J., Krotosky, W.A., Field, J.B., Rall, J.E. & Wolff, J. (1980) *Review of Medical Findings in a Marshallese Population Twenty-six Years after Accidental Exposure to Radioactive Fallout* (Brookhaven National Laboratory Report BNL 51261), Springfield, VA, National Technical Information Service

Coquerelle, T.M., Weibezahn, K.F. & Lücke-Huhle, C. (1987) Rejoining of double strand breaks in normal human and ataxia-telangiectasia fibroblasts after exposure to ^{60}Co gamma-rays, ^{241}Am alpha-particles or bleomycin. *Int. J. Radiat. Biol.*, **51**, 209–218

Council on Pharmacy and Chemistry (1932) Thorotrast. *J. Am. med. Assoc*., **99**, 2183–2185

Cox, R., Thacker, J. & Goodhead, D.T. (1977) Inactivation and mutation of cultured mammalian cells by aluminium characteristic ultrasoft X-rays. II. Dose–responses of Chinese hamster and human diploid cells to aluminium X-rays and radiations of different LET. *Int. J. Radiat. Biol.*, **31**, 561–576

Cox, D.R., Darby, S.C., Reeves, G.K. & Whitley, E. (1999) The effects of measurement errors with particular reference to a study of exposure to residential radon. In: Ron, E. & Hoffman, F.O., eds, *Uncertainties in Radiation Dosimetry and Their Impact on Dose–Response Analyses* (Publication No. 99-4541), Bethesda, MD, National Cancer Institute, pp. 139–151

Crabtree, J. (1995) The travel and diffusion of the radioactive material emitted during the Windscale accident. *Q. J. roy. Meteo. Soc.*, **85**, 362–370

Cronkite, E.P., Bond, V.P. & Conard, R.A. (1995) Medical effects of exposure of human beings to fallout radiation from a thermonuclear explosion. *Stem Cells*, **13** (Suppl. 1), 49–57

Cross, F.T., Endres, G.W.R. & Sullivan, M.F. (1978) Dose to the GI tract from ingested insoluble beta emitters. *Radiat. Res.*, **73**, 37–50

Daghighian, F., Humm, J.L., Macapinlac, H.A., Zhang, J., Izzo, J., Finn, R., Kemeny, N. & Larson, S.M. (1995) Pharmacokinetics and dosimetry of iodine-125-IUdR in the treatment of colorectal cancer metastatic to liver. *J. nucl. Med.*, **37**, 29S–32S

Dagle, G.E., Weller, R.E., Filipy, R.E., Watson, C.R. & Buschbom, R.L. (1996) The distribution and effects of inhaled $^{239}Pu(NO_3)_4$ deposited in the liver of dogs. *Health Phys.*, **71**, 198–205

Daher, A., Varin, M., Lamontagne, Y. & Oth, D. (1998) Effect of pre-conceptional external or internal irradiation of N5 male mice and the risk of leukemia in their offspring. *Carcinogenesis*, **19**, 1553–1558

Dalheimer, A.R. & Kaul, A. (1989) Calculation of the basal cell dose in Thorotrast patients. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology, pp. 112–115

Dalheimer, A.R., Spiethoff, A. & Kaul, A. (1995) Calculation of dose to non-storing organs of Thorotrast patients. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 39–42

Darby, S.C. & Doll, R. (1990) Radiation and exposure rate (Letter to the Editor). *Nature*, **344**, 824

Darby, S.C., Radford, E.P. & Whitley, E. (1995a) Radon exposure and cancers other than lung cancer in Swedish iron miners. *Environ. Health Perspectives*, **103** (Suppl. 2), 45–47

Darby, S.C., Whitley, E., Howe, G.R., Hutchings, S.J., Kusiak, R.A., Lubin, J.A., Morrison, H.I., Tirmarche, M., Tomášek, L., Radford, E.P., Roscoe, R.J., Samet, J.M. & Yao, S.X. (1995b) Radon and cancers other than lung cancer in underground miners: A collaborative analysis of 11 studies. *J. natl Cancer Inst.*, **87**, 378–384

Darby, S.C., Whitley, E., Silcocks, P., Thakrar, B., Green, M., Lomas, P., Miles, J., Reeves, G., Fearn, T. & Doll, R. (1998) Risk of lung cancer associated with residential radon exposure in south-west England: A case–control study. *Br. J. Cancer*, **78**, 394–408

Darby, S.C., Whitley, E., Deo, H. & Doll, R. (2001) A parallel analysis of individual and ecological data on residential radon and lung cancer in south-west England. *J. R. stat. Soc.*, Series A, **164**, 193–203

Degteva, M.O., Kozheurov V.P. & Vorobiova, M.I. (1994) General approach to dose reconstruction in the population exposed as a result of the release of radioactive wastes into the Techa River. *Sci. total Environ.*, **142**, 49–61

Degteva, M.O., Kozheurov, V.P., Burmistrov, D.S., Vorobyova, M.I., Valchuk, V.V., Bougrov, N.G. & Shishkina, H.A. (1996) An approach to dose reconstruction for the Urals population. *Health Phys.*, **71**, 71–76

Degteva, M.O., Vorobiova, M.I., Kozheurov, V.P., Tolstykh, E.I., Anspaugh, L.R. & Napier, B.A. (2000a) Dose reconstruction system for the exposed population living along the Techa River. *Health Phys.*, **78**, 542–554

Degteva, M.O., Kozheurov, V.P., Tolstykh, E.I., Vorobiova, M.I., Anspaugh, L.R., Napier, B.A. & Kovtun, A.N. (2000b) The Techa River dosimetry system: Methods for the reconstruction of internal dose. *Health Phys.*, **79**, 24–35

Demidchik, E.P., Mrochek, A., Demidchik, Y., Vorontsova, T., Cherstvoy, E., Kenigsberg, J., Rebeko V. & Sugenoya, A. (1999) Thyroid cancer promoted by radiation in young people of Belarus (clinical and epidemiological features). In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer* (EUR 18552 EN), Singapore, World Scientific, pp. 51–54

De Rooij, D.G. & Rönnbäck, C. (1989) The effect of ^{90}Sr given to pregnant mice on spermatogenesis in the male offspring: A comparison with the effect on the ovaries in the female offspring. *Int. J. Radiat. Biol.*, **56**, 151–159

Desai, P., Perino, G., Present, D. & Steiner, G.C. (1996) Sarcoma in association with bone infarcts. Report of five cases. *Arch. Pathol. Lab. Med.*, **120**, 482–489

Deshpande, A., Goodwin, E.H., Bailey, S.M., Marrone, B.L. & Lehnert, B.E. (1996) Alpha-particle-induced sister chromatid exchange in normal human lung fibroblasts: Evidence for an extranuclear target. *Radiat. Res.*, **145**, 260–267

Dev, P.K. & Srivastava, P.N. (1981) Effects of radiophosphorus on the developing endocrine glands of Swiss albino mice. *Strahlentherapie*, **157**, 418–426

Diel, J.H., Guilmette, R.A., Muggenburg, B.A., Hahn, F.F. & Chang, I.–Y. (1992) Influence of dose rate on survival time for $^{239}PuO_2$-induced radiation pneumonitis or pulmonary fibrosis in dogs. *Radiat. Res.*, **129**, 53–60

Doll, R. (1998) Effects of small doses of ionising radiation. *J. radiol. Prot.*, **18**, 163–174

Dougherty, T.F. & Mays, C.W. (1969) Bone cancer induced by internally-deposited emitters in beagles. In: *Radiation-induced Cancer*, Vienna, International Atomic Energy Agency, pp. 361–367

Dougherty, T.F., Stover, B.J., Dougherty, J.H., Jee, W.S.S., Mays, C.W., Rehfeld, C.E., Christensen, W.R. & Goldthorpe, H.C. (1962) Studies of the biological effects of Ra^{226}, Pu^{239}, $Ra^{228}(MsTh_1)$, Th^{228}(RdTh), and Sr^{90} in adult beagles. *Radiat. Res.*, **17**, 625–681

Douglas, A.J., Omar, R.Z. & Smith, P.G. (1994) Cancer mortality and morbidity among workers at the Sellafield plant of British Nuclear Fuels. *Br. J. Cancer*, **70**,1232–1243

Doyle, D.V., Glass, J.S., Gow, P.J., Daker, M. & Grahame, R. (1977) A clinical and prospective chromosomal study of yttrium-90 synovectomy. *Rheumatol. Rehabil.*, **16**, 217–222

Druckrey, H. (1973) Chemical structure and action in transplacental carcinogenesis and teratogenesis. In: Tomatis, L. & Mohr, U., eds, *Transplacental Carcinogenesis* (IARC Scientific Publications No. 4), Lyon, IARC*Press*, pp. 45–55

Dubasov, U.V., Matushenko, A.M. & Pilonov, N.P. (1994) *Semi Palatinsk Test Site: Estimated Radiological Consequences (Information Bulletin)*, Moscow, Centre for Public Information on Atomic Energy

Dudoignon, N., Guézingar-Liébard, F., Guillet, K., L'Huillier, I., Rateau, G., Monchaux, G. & Fritsch, P. (1999) Lung carcinogenesis in rats after inhalation exposure to $^{237}NpO_2$. *Radiat. Res.*, **152**, S31–S33

Dunning, D.E., Jr & Schwartz, G. (1981) Variability of human thyroid characteristics and estimates of dose from ingested ^{131}I. *Health Phys.*, **40**, 661–675

Dupree, E.A., Cragle, D.L., McLain, R.W., Crawford-Brown, D.J. & Teta, M.J. (1987) Mortality among workers at a uranium processing facility, the Linde Air Products Company Ceramics Plant, 1943–1949. *Scand. J. Work Environ. Health*, **13**, 100–107

Dupree, E.A., Watkins, J.P., Ingle, J.N., Wallace, P.W., West, C.M. & Tankersley, W.G. (1995) Uranium dust exposure and lung cancer risk in four uranium processing operations. *Epidemiology*, **6**, 370–375

Durbin, P.W. (1972) Plutonium in man: A new look at the old data. In: Stover, B.J. & Jee, W.S.S., eds, *Radiobiology of Plutonium*, Salt Lake City, J.W. Press, pp. 469–530

Durbin, P.W., White, D.L., Jeung, N.L., Weitl, F.L., Uhlir, L.C., Jones, E.S., Bruenger, F.W. & Raymond, K.N. (1989) Chelation of 238Pu(IV) in vivo by 3,3,4-LICAM(C): Effects of ligand methylation and pH. *Health Phys.*, **56**, 839–855

Eatough, J.P. & Henshaw, D.L. (1992) Radon and thoron associated dose to the basal layer of the skin. *Phys. Med. Biol.*, **37**, 955–967

Eatough, J.P. & Henshaw, D.L. (1995) The theoretical risk of non-melanoma skin cancer from environmental radon exposure. *J. Radiol. Prot.*, **15**, 45–51

Edmonds, C.J. & Smith, T. (1986) The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br. J. Radiol.*, **59**, 45–51

Efurd, D.W., Perrin, R.E. & McInroy, J.F. (1986) Neptunium-237 in human tissue samples. *Health Phys.*, **51**, 665–666

Elkind, M.M. (1980) Cells, targets and molecules in radiation biology. In: Meyn, R.E. & Withers, H.R., eds, *Radiation Biology in Cancer Research*, New York, Raven Press, pp. 71–93

Ellender, M., Harrison, J.D., Pottinger, H. & Thomas, J.M. (2001) Induction of osteosarcoma and acute myeloid leukaemia in CBA/H mice by the alpha-emitting nuclides, uranium-233, plutonium-239 and americium-241. *Int. J. Radiat. Biol.*, **77**, 41–52

Etnier, E.L., Travis, C.C. & Hetrick, D.M. (1984) Metabolism of organically bound tritium in man. *Radiat. Res.*, **100**, 487–502

EURATOM (1996) Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. *Off. J. Eur. Comm.*, **39**, L159/1114

Evans, R.D. (1966) The effect of skeletally deposited alpha-ray emitters in man. *Br. J. Radiol.*, **39**, 881–895

Evans, R.D., Keane, A.T., Kolenkow, R.J., Neal, W.R. & Shanahan, M.M. (1969) Radiogenic tumors in the radium and mesothorium. Cases studied at MIT. In: Mays, C.W., Jee, W.S.S. & Lloyd, R., eds, *Delayed Effects of Bone-seeking Radionuclides*, Salt Lake City, University of Utah Press

Evans, H.H., Mencl, J., Bakale, G., Rao, P.S., Jostes, R.F., Hui, T.E., Cross, F.T. & Schwartz, J.L. (1993) Interlaboratory comparison of the effects of radon on L5178Y cells: Dose contribution of radon daughter association with cells. *Radiat. Res.*, **136**, 48–56

Fauvert, R., Boivin, P., Mallarmé, J. & Nicollo, F. (1961) [Conduct and results of polycythemia vera treatment by phosphorus-32. Study of 200 cases] *Nouv. Rev. Fr. Hématol.*, **1**, 459–468 (in French)

Feinendegen, L.E., Henneberg, P. & Tisljar-Lentulis, G. (1977) DNA strand breakage and repair in human kidney cells after exposure to incorporated iodine-125 and cobalt-60 γ-rays. *Curr. Topics Radiat. Res. Q.*, **12**, 436–452

Feith, R., Slooff, T.J., Kazem, I. & van Rens, T.J. (1976) Strontium 87mSr bone scanning for the evaluation of total hip replacement. *J. Bone Joint Surg. Br.*, **58**, 79–83

Fell, T.P., Harrison, J.D. & Leggett, R.W. (1998) A model for the transfer of calcium and strontium to the fetus. *Radiat. Prot. Dosim.*, **79**, 311–315

Ferrand, S.K., Chen, C.C., Dilsizian, V. & Neumann, R.D. (1999) What is new in nuclear medicine imaging? *Surg. Oncol. Clin. N. Am.*, **8**, 185–204

Field, S.B. & Upton, A.C. (1985) Non-stochastic effects: Compatibility with present ICRP recommendations. *Int. J. Radiat. Biol.*, **48**, 81–94

Field, R.W., Steck, D.J., Smith, B.J., Brus, C.P., Fisher, E.L., Neuberger, J.S., Platz, C.E., Robinson, R.A., Woolson, R.F. & Lynch, C.F. (2000) Residential radon gas exposure and lung cancer. The Iowa Radon Lung Cancer Study. *Am. J. Epidemiol.*, **151**, 1091–1102

Finch, G.L., March, T.H., Hahn, F.F., Barr, E.B., Belinsky, S.A., Hoover, M.D., Lechner, J.F., Nikula, K.J. & Hobbs, C.H. (1998) Carcinogenic responses of transgenic heterozygous *p53* knockout mice to inhaled $^{239}PuO_2$ or metallic beryllium. *Toxicol. Pathol.*, **26**, 484–491

Fleischer, R.L. & Raabe, O.G. (1977) Fragmentation of respirable PuO_2 particles in water by alpha decay — A mode of 'dissolution'. *Health Phys.*, **32**, 253–257

Fogelman, I., Smith, L., Mazess, R., Wilson, M.A. & Bevan, J.A. (1986) Absorption of oral diphosphate in normal subjects. *Clin. Endocrinol.*, **24**, 57–62

Fong, K.M., Zimmerman, P.V. & Smith, P.J. (1995) Lung pathology: The molecular genetics of non-small cell lung cancer. *Pathology*, **27**, 295–301

Forastiere, F., Sperati, A., Cherubini, G., Miceli, M., Biggeri, A. & Axelson, O. (1998) Adult myeloid leukaemia, geology, and domestic exposure to radon and γ radiation: A case control study in central Italy. *Occup. environ. Med.*, **55**, 106–110

Ford, J.R. & Terzaghi-Howe, M. (1993) Effects of ^{210}Po alpha particles on survival and preneoplastic transformation of primary rat tracheal epithelial cells irradiated while in suspension or in the intact tissue. *Radiat. Res.*, **136**, 89–96

Foulon, C.F., Alston, K.L. & Zalutsky, M.R. (1998) Astatine-211-labeled biotin conjugates resistant to biotinidase for use in pretargeted radioimmunotherapy. *Nucl. Med. Biol.*, **25**, 81–88

Fox, J.C. & McNally, N.J. (1990) The rejoining of DNA double-strand breaks following irradiation with ^{238}Pu alpha-particles: Evidence for a fast component of repair as measured by neutral filter elution. *Int. J. Radiat. Biol.*, **57**, 513–521

Francis, C.W., Chesters, G. & Erhardt, W.H. (1968) ^{210}Polonium entry into plants. *Environ. Sci. Technol.*, **2**, 690–695

Frankenberg, D., Kühn, H., Frankenberg-Schwager, M., Lenhard, W. & Beckonert, S. (1995) 0.3 keV carbon K ultrasoft X-rays are four times more effective than γ-rays when inducing oncogenic cell transformation at low doses. *Int. J. Radiat. Biol.*, **68**, 593–601

Franklyn, J.A., Maisonneuve, P., Sheppard, M., Betteridge, J. & Boyle, P. (1999) Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: A population-based cohort study. *Lancet*, **353**, 2111–2115

Freitas, J.E., Swanson, D.P., Gross, M.D. & Sisson, J.C. (1979) Iodine-131: Optimal therapy for hyperthyroidism in children and adolescents? *J. nucl. Med.*, **20**, 847–850

Frome, E.L., Cragle, D.L., Watkins, J.P., Wing, S., Shy, C.M., Tankersley, W.G. & West, C.M. (1997) A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. *Radiat. Res.*, **148**, 64–80, 297–298 (errata)

Fry, S.A. (1998) Studies of US radium dial workers: An epidemiological classic. *Radiat. Res.*, **150** (Suppl), S21–S29

Fry, S.A. & Sipe, A.H. (1986) The REAC/TS registries status. In: Kaul, A., Dehos, A., Bögl, W., Hinz, G., Kossel, F., Schwarz, E.-R., Stamm, A. & Stephan G., eds, *Biological Indicators for Radiation Dose Assessment*, Munich, MMV Medizin Verlag, pp. 35–56

Fugazzola, L., Pilotti, S., Pinchera, A., Vorontsova, T.V., Mondellini, P., Bongarzone, I., Greco, A., Astakhova, L., Butti, M.G., Demidchik, E.P., Pacini, F. & Pierotti, M.A. (1995) Oncogenic rearrangements of the *RET* proto-oncogene in papillary thyroid carcinomas from children exposed to the Chernobyl nuclear accident. *Cancer Res.*, **55**, 5617–5620

Furuno-Fukushi, I., Ueno, A.M. & Matsudaira, H. (1987) Cell killing and mutation to 6-thioguanine resistance after exposure to tritiated amino acids and tritiated thymidine in cultured mammalian cells (L5178Y). *Radiat. Res.*, **110**, 428–438

Gafieva, Z.A. & Chudin, V.A. (1988) [Biological action of plutonium-239 on *Salmonella typhimurium*.] *Radiobiologiia*, **28**, 563–565 (in Russian)

Galvin, J.B., Bice, D.E., Guilmette, R.A., Muggenburg, B.A. & Haley, P.J. (1989) Pulmonary immune response of dogs after exposure to $^{239}PuO_2$. *Int. J. Radiat. Biol.*, **55**, 285–296

Garg, P.K., Harrison, C.L. & Zalutsky, M.R. (1990) Comparative tissue distribution in mice of the α-emitter ^{211}At and ^{131}I as labels of a monoclonal antibody and F(ab′)$_2$ fragment. *Cancer Res.*, **50**, 3514–3520

Garg, P.K., John, C.S. & Zalutsky, M.R. (1995) Preparation and preliminary evaluation of 4-[^{211}At]astato-N-piperidinoethyl benzamide. *Nucl. Med. Biol.*, **22**, 467–473

Gaull, G.E., Räihä, N.C.R., Saarikoski, S. & Sturman, J.A. (1973) Transfer of cyst(e)ine and methionine across the human placenta. *Pediat. Res.*, **7**, 908–913

George, A.C. & Breslin, A.J. (1967) Deposition of netural radon daughters in human subjects. *Health Phys.*, **13**, 375–378

Gerasimo, P., Duserre, C. & Métivier, H. (1986) Biological behaviour of Pu administered to animals as Pu-standard LICAM(C) complex: Therapeutical attempts to decrease Pu kidney burden. *Hum. Toxicol.*, **5**, 309–318

Gerber, G.B., Wick, R.R., Watson, C.R., Gössner, W. & Kellerer, A.M. (1999) International radiobiology archives of long-term animal studies: Structure, possible uses and potential extension. *Radiat. environ. Biophys.*, **38**, 75–79

Gilbert, E.S. (1994) Smoking as an explanation for the negative relationship between exposure to radon and certain types of cancer. *Health Phys.*, **67**, 197–198

Gilbert, E.S., Park, J.F. & Buschbom, R.L. (1989) Time-related factors in the study of risks in animals and humans. *Health Phys.*, **57**, 379–385

Gilbert, E.S., Tarone, R., Bouville, A. & Ron, E. (1998a) Thyroid cancer rates and ^{131}I doses from Nevada atmospheric nuclear bomb tests. *J. natl Cancer Inst.*, **90**, 1654–1660

Gilbert, E.S., Griffith, W.C., Boecker, B.B., Dagle, G.E., Guilmette, R.A., Hahn, F.F., Muggenburg, B.A., Park, J.F. & Watson, C.R. (1998b) Statistical modeling of carcinogenic risks in dogs that inhaled $^{238}PuO_2$. *Radiat. Res.*, **150**, 66–82

Gilbert, E.S., Koshurnikova, N.A., Sokolnikov, M.E., Khokhryakov, V.F., Miller, S., Preston, D.L., Romanov, S.A., Shilnikova, N.S., Suslova, K.G. & Vostrotin, V.V. (2000) Liver cancers in Mayak workers. *Radiat. Res.*, **154**, 246–252

Gillett, N.A., Hahn, F.F., Mewhinney, J.A. & Muggenberg, B.A. (1985) Osteosarcoma development following single injection exposure to americium-241 in beagle dogs. *Radiat. Res.*, **104**, 83–93

Gillett, N.A., Muggenburg, B.A., Boecker, B.B., Griffith, W.C., Hahn, F.F. & McClellan, R.O. (1987a) Single inhalation exposure to $^{90}SrCl_2$ in the beagle dog: Late biological effects. *J. natl Cancer Inst.*, **79**, 359–376

Gillett, N.A., Muggenburg, B.A., Boecker, B.B., Hahn, F.F., Seiler, F.A., Rebar, A.H., Jones, R.K. & McClellan, R.O. (1987b) Single inhalation exposure to $^{90}SrCl_2$ in the beagle dog: Hematological effects. *Radiat. Res.*, **110**, 267–288

Gillett, N.A., Muggenburg, B.A., Mewhinney, J.A., Hahn, F.F., Seiler, F.A., Boecker, B.B. & McClellan, R.O. (1988) Primary liver tumours in beagle dogs exposed by inhalation to aerosols of plutonium-238 dioxide. *Am. J. Pathol.*, **133**, 265–276

Gillett, N.A., Pool, R.R., Taylor, G.N., Muggenburg, B.A. & Boecker, B.B. (1992) Strontium-90 induced bone tumours in beagle dogs: Effects of route of exposure and dose rate. *Int. J. Radiat. Biol.*, **61**, 821–831

Goldman, M.B., Maloof, F., Monson, R.R., Aschengrau, A., Cooper, D.S. & Ridgway, E.C. (1988) Radioactive iodine therapy and breast cancer. A follow-up study of hyperthyroid women. *Am. J. Epidemiol.*, **127**, 969–980

Goodhead, D.T. (1994) Initial events in the cellular effects of ionizing radiations: Clustered damage in DNA. *Int. J. Radiat. Biol.*, **65**, 7–17

Goodhead, D.T. & Thacker, J. (1977) Inactivation and mutation of cultured mammalian cells by aluminium characteristic ultrasoft X-rays. I. Properties of aluminium X-rays and preliminary experiments with Chinese hamster cells. *Int. J. Radiat. Biol.*, **31**, 541–559

Goodhead, D.T., Thacker, J. & Cox, R. (1979) Effectiveness of 0.3 keV carbon ultrasoft X-rays for the inactivation and mutation of cultured mammalian cells. *Int. J. Radiat. Biol.*, **36**, 101–114

Goolden, A.W. & Davey, J.B. (1963) The ablation of normal thyroid tissue with iodine 131. *Br. J. Radiol.*, **36**, 340–345

Gössner, W. (1986) Pathology of radiation-induced bone tumors. *Leukemia Res.*, **10**, 897–904

Gössner, W. (1999) Pathology of radium-induced bone tumors: New aspects of histopathology and histogenesis. *Radiat. Res.*, **152**, S12–S15

Gössner, W., Hug, O., Luz, A. & Müller, W.A. (1976) Experimental induction of bone tumours by short-lived bone-seeking radionuclides. *Recent Results Cancer Res.*, **54**, 36–49

Gössner, W., Wick, R.R. & Spiess, H. (1995) Histopathological review of radium-224 induced bone sarcomas. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 255–259

Gössner, W., Masse, R. & Stather, J.W. (2000) Cells at risk for dosimetric modelling relevant to bone tumour induction. *Radiat. Prot. Dosim.*, **92**, 209–213

Goulko, G.M., Chepurny, N.I., Jacob, P., Kairo, I.A., Likhtarev, I.A., Pröhl, G. & Sobolev, B.G. (1998) Thyroid dose and thyroid cancer incidence after the Chernobyl accident: Assessments for the Zhytomyr region (Ukraine). *Radiat. environ. Biophys.*, **36**, 261–273

Gragtmans, N.J., Myers, D.K., Johnson, J.R., Jones, A.R. & Johnson, L.D. (1984) Occurrence of mammary tumors in rats after exposure to tritium beta rays and 200-kVp X rays. *Radiat. Res.*, **99**, 636–650

Graham, S.J., Heaton, R.B., Garvin, D.F. & Cotelingam, J.D. (1992) Whole-body pathologic analysis of a patient with Thorotrast-induced myelodysplasia. *Health Phys.*, **63**, 20–26

Gray, S.A., Pearce, M.J., Stradling, G.N., Wilson, I., Hodgson, A. & Isaacs, K.R. (1995) Optimizing the removal of inhaled plutonium and americium from the rat by administration of ZnDTPA in drinking water. *Hum. exp. Toxicol.*, **14**, 902–908

Greaves, C.D. & Tindale, W.B. (1999) Dose rate measurements from radiopharmaceuticals: Implications for nuclear medicine staff and for children with radioactive parents. *Nucl. Med. Commun.*, **20**, 179–187

Greenland, S. & Robins, J. (1994) Invited commentary: Ecologic studies — Biases, misconceptions, and counterexamples. *Am. J. Epidemiol.*, **139**, 747–760

Griffey, S.M., Kraegel, S.A., Weller, R.E., Watson, C.R. & Madewell, B.R. (1998) K-*ras* mutation in $^{239}PuO_2$ canine lung neoplasms. *Cancer Lett.*, **132**, 1–5

Griffin, C.S., Harvey, A.N. & Savage, J.R.K. (1994) Chromatid damage induced by ^{238}Pu α-particles in G_2 and S phase Chinese hamster V79 cells. *Int. J. Radiat. Biol.*, **66**, 85–98

Griffin, C.S., Marsden, S.J., Stevens, D.L., Simpson, P. & Savage, J.R.K. (1995) Frequencies of complex chromosome exchange aberrations induced by ^{238}Pu alpha-particles and detected by fluorescence *in situ* hybridization using single chromosome-specific probes. *Int. J. Radiat. Biol.*, **67**, 431–439

Griffin, C.S., Hill, M.A., Papworth, D.G., Townsend, K.M.S., Savage, J.R.K. & Goodhead, D.T. (1998) Effectiveness of 0.28 keV carbon K ultrasoft X-rays at producing simple and complex chromosome exchanges in human fibroblasts *in vitro* detected using FISH. *Int. J. Radiat. Biol.*, **73**, 591–598

Griffith, W.C., Mewhinney, J.A., Muggenburg, B.A., Boecker, B.B., Cuddihy, R.G. (1983) Bioassay model for estimating body burdens of ^{241}Am from excretion analyses. *Health Phys.*, **44**, 545–554

Griffith, T.P., Pirie, A. & Vaughan, J. (1985) Possible cataractogenic effect of radionuclides deposited within the eye from the blood stream. *Br. J. Ophthalmol.*, **69**, 219–227

Griffiths, S.D., Marsden, S.J., Wright, E.G., Greaves, M.F. & Goodhead, D.T. (1994) Lethality and mutagenesis of B lymphocytes progenitor cells following exposure to α-particles and X-rays. *Int. J. Radiat. Biol.*, **66**, 197–205

Grillmaier, R. & Muth, H. (1971) Radiation dose distribution in lungs of Thorotrast patients. *Health Phys.*, **20**, 409–419

Guilmette, R.A. & Muggenburg, B.A. (1993) Decorporation therapy for inhaled plutonium nitrate using repeatedly and continuously administered DTPA. *Int. J. Radiat. Biol.*, **63**, 395–403

Guilmette, R.A., Cohen, N. & Wrenn, M.E. (1980) Distribution and retention of ^{241}Am in the baboon. *Radiat. Res.*, **81**, 100–119

Guilmette, R.A., Gillett, N.A., Eidson, A.F., Griffith, W.C. & Brooks, A.L. (1989) The influence of non-uniform α-irradiation of Chinese hamster liver on chromosome damage and the induction of cancer. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BRI Report 21), London, British Institute of Radiology, pp. 142–148

Gundy, S., Katz, N., Füzy, M. & Ésik, O. (1996) Cytogenetic study of radiation burden in thyroid disease patients treated with external irradiation or radioiodine. *Mutat. Res.*, **360**, 107–113

Gutiérrez, B.S, Carbonell, E., Galofréa, P., Creus, A. & Marcos, R. (1999a) Cytogenetic damage after 131-iodine treatment for hyperthyroidism and thyroid cancer — A study using the micronucleus test. *Eur. J. nucl. Med.*, **26**, 1589–1596

Gutiérrez, S., Carbonell, E., Galofréa, P., Creus, A. & Marcos, R. (1999b) Low sensitivity of the sister chromatid exchange assay to detect the genotoxic effects of radioiodine therapy. *Mutagenesis*, **14**, 221–226

Gutiérrez, S., Carbonell, E., Galofréa, P., Xamena, N., Creus, A. & Marcos, R. (1995) A cytogenetic follow-up study of thyroid cancer patients treated with ^{131}I. *Cancer Lett.*, **91**, 199–204

Hagerman, D.D. & Villee, C.A. (1960) Transport functions of the placenta. *Physiol. Rev.*, **40**, 313–330

Hahn, F.F. & Lundgren, D.L. (1992) Pulmonary neoplasms in rats that inhaled cerium-144 dioxide. *Toxicol. Pathol.*, **20**, 169–178

Hahn, F.F., Lundgren, D.L. & McClellan, R.O. (1980) Repeated inhalation exposure of mice to $^{144}CeO_2$. II. Biologic effects. *Radiat. Res.*, **82**, 123–137

Hahn, F.F., Muggenburg, B.A. & Boecker, B.B. (1995) Hepatic lesions induced by chronic beta irradiation from ^{144}Ce in dogs. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium*, Singapore, World Scientific, pp. 337–340

Hahn, F.F., Boecker, B.B., Griffith, W.C. & Muggenburg, B.A. (1997) Biological effects of inhaled $^{144}CeCl_3$ in beagle dogs. *Radiat. Res.*, **147**, 92–108

Hahn, F.F., Muggenburg, B.A., Guilmette, R.A. & Boecker, B.B. (1999) Comparative stochastic effects of inhaled alpha- and beta-particle-emitting radionuclides in beagle dogs. *Radiat. Res.*, **152**, S19–S22

Haines, J.W., Naylor, G.P.L., Pottinger, H. & Harrison, J.D. (1993) Gastrointestinal absorption and retention of polonium in adult and newborn rats and guinea pigs. *Int. J. Radiat. Biol.*, **64**, 127–132

Haines, J.W., Harrison, J.D., Pottinger, H.E. & Phipps, A.W. (1995) Transfer of polonium to the embryo and foetus of rat and guinea pig. *Int. J. Radiat. Biol.*, **67**, 381–390

Hall, E.J. (1978) *Radiobiology for Radiologists*, 2nd Ed., New York, Harper & Rowe

Hall, P., Holm, L.-E., Lundell, G., Bjelkengren, G., Larsson, L.-G., Lindberg, S., Tennvall, J., Wicklund, H. & Boice, J.D., Jr (1991) Cancer risks in thyroid cancer patients. *Br. J. Cancer*, **64**, 159–163

Hall, P., Berg, G., Bjelkengren, G., Boice, J.D., Jr, Ericsson, U.-B., Hallquist, A., Lidberg, M., Lundell, G., Tennvall, J., Wiklund, K. & Holm, L.-E. (1992a) Cancer mortality after iodine-131 therapy for hyperthyroidism. *Int. J. Cancer*, **50**, 886–890

Hall, P., Boice, J.D., Jr, Berg, G., Bjelkengren, G., Ericsson, U.-B., Hallquist, A., Lidberg, M., Lundell, G., Mattsson, A., Tennvall, J., Wiklund, K. & Holm, L.-E. (1992b) Leukaemia incidence after iodine-131 exposure. *Lancet*, **340**, 1–4

Hall, P., Lundell, G. & Holm, L.-E. (1993) Mortality in patients treated for hyperthyroidism with iodine-131. *Acta endocrinol.*, **128**, 230–234

Hall, P., Fürst, C.J., Mattsson, A., Holm, L.-E., Boice, J.D., Jr & Inskip, P.D. (1996a) Thyroid nodularity after diagnostic administration of iodine-131. *Radiat. Res.*, **146**, 673–682

Hall, P., Mattsson, A. & Boice, J.D., Jr (1996b) Thyroid cancer after diagnostic administration of iodine-131. *Radiat. Res.*, **145**, 86–92

Halnan, K.E. & Russell, M.H. (1965) Polycythaemia vera. Comparison of survival and causes of death in patients managed with and without radiotherapy. *Lancet*, **ii**, 760–763

Ham, G.J. & Harrison, J.D. (2000) The gastrointestinal absorption and urinary excretion of plutonium in male volunteers. *Radiat. Prot. Dosim.*, **87**, 267–272

Harduin, J.C., Royer, P. & Piechowski, J. (1994) Uptake and urinary excretion of uranium after oral administration in man. *Radiat. Prot. Dosim.*, **53**, 245–248

Harley, N.H. & Robbins, E.S. (1992) ^{222}Rn alpha dose to organs other than lung. *Radiat. Prot. Dosim.*, **45**, 619–622

Harman, J.B. & Ledlie, E.M. (1967) Survival of polycythaemia vera patients treated with radioactive phosphorus. *Br. med. J.*, **ii**, 146–148

Harper, K., Lorimore, S.A. & Wright, E.G. (1997) Delayed appearance of radiation-induced mutations at the *Hprt* locus in murine hemopoietic cells. *Exp. Hematol.*, **25**, 263–269

Harrington, H.L. & Huggins, C. (1939) Rate of removal of thorium dioxide from blood stream. *Arch. intern. Med.*, **63**, 445–452

Harrison, J.D. (1991) The gastrointestinal absorption of the actinide elements. *Sci. total Environ.*, **100**, 43–60

Harrison, J.D. & Fritsch, P. (1992) The effect of age on the absorption and intestinal retention of ingested radionuclides. *Radiat. Prot. Dosim.*, **41**, 71–76

Hassfjell, S.P., Bruland, Ø.S. & Hoff, P. (1997) ^{212}Bi-DOTMP: An alpha particle emitting bone-seeking agent for targeted radiotherapy. *Nucl. Med. Biol.*, **24**, 231–237

Hayek, A., Chapman, E.M. & Crawford, J.D. (1970) Long-term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. *New Engl. J. Med.*, **283**, 949–953

Hei, T.K., Piao, C.Q., Willey, J.C., Thomas, S. & Hall, E.J. (1994) Malignant transformation of human bronchial epithelial cells by radon-simulated α-particles. *Carcinogenesis*, **15**, 431–437

Hei, T.K., Wu, L.-J., Liu, S.-X., Vannais, D., Waldren, C.A. & Randers-Pehrson, G. (1997) Mutagenic effects of a single and an exact number of α particles in mammalian cells. *Proc. natl Acad. Sci. USA*, **94**, 3765–3770

Heid, K.R. (1983) A comparison of systemic burdens at autopsy to estimates based on health physics data for selected plutonium workers. *Health Phys.*, **44** (Suppl. 1), 477–483

Heidenreich, W.F., Kenigsberg, J., Jacob, P., Buglova, E., Goulko, G., Paretzke, H.G., Demidchik, E.P. & Golovneva, A. (1999) Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. *Radiat. Res.*, **151**, 617–625

Heller, S.L. (1996) Radiation safety in the central radiopharmacy. *Semin. nucl. Med.*, **26**, 107–118

Hellman, B., Friis, L., Vaghef, H. & Edling, C. (1999) Alkaline single cell gel electrophoresis and human biomonitoring for genotoxicity: A study on subjects with residential exposure to radon. *Mutat. Res.*, **442**, 121–132

Henrichs, K., Paretzke, H.G., Voigt, G. & Berg, D. (1989) Measurement of Cs absorption and retention in man. *Health Phys.*, **57**, 571–578

Henshaw, D.L., Eatough, J.P. & Richardson, R.B. (1990) Radon as a causative factor in induction of myeloid leukaemia and other cancers. *Lancet*, **335**, 1008–1012

Herbert, R.A., Scott, B.R., Hahn, F.F., Newton, G.J., Snipes, M.B., Damon, E.G. & Boecker, B.B. (1987) The prevalence and morphology of primary pulmonary neoplasms in rats 18 months after inhalation of ^{147}Pm in fused aluminosilicate particles. In: Sun, J.D. & Mewhinney, J.A., eds, *Inhalation Toxicology Research Institute Annual Report 1986–1987* (Report LMF-120), Albuquerque, NM, Inhalation Toxicology Research Institute, pp. 331–335

Herbert, R.A., Scott, B.R., Hahn, F.F., Newton, G.J., Snipes, M.S., Damon, E.G. & Boecker, B.B. (1988) The occurrence of primary pulmonary neoplasms in rats after inhalation of Pm-147 in fused aluminosilicate particles. In: Mewhinney, J.A., Bechtold, W.E., Sun, J.D. & Coons, T.A., eds, *Annual Report of the Inhalation Toxicology Research Institute, 1987–1988* (Report LMF-121), Albuquerque, NM, Inhalation Toxicology Research Institute, pp. 234–240

Herbert, R.A., Gillett, N.A., Rebar, A.H., Lundgren, D.L., Hoover, M.D., Chang, I.Y., Carlton, W.W. & Hahn, F.F. (1993) Sequential analysis of the pathogenesis of plutonium-induced pulmonary neoplasms in the rat: Morphology, morphometry, and cytokinetics. *Radiat. Res*., **134**, 29–42

Herbert, R.A., Stegelmeier, B.S., Gillett, N.A., Rebar, A.H., Carlton, W.W., Singh, G. & Hahn, F.F. (1994) Plutonium-induced proliferative lesions and pulmonary epithelial neoplasms in the rat: Immunohistochemical and ultrastructural evidence for their origin from type II pneumocytes. *Vet. Pathol*., **31**, 366–374

Hill, C.R. (1965) Polonium-210 in man. *Natur*e, **208**, 423–428

Hill, C.R. (1966) Polonium-210 content of human tissue in relation to dietary habits. *Science*, **152**, 1261–1262

Hill, R.L. & Johnson, J.R. (1993) Metabolism and dosimetry of tritium. *Health Phys*., **65**, 628–647

Hitchman, J.W., Taylor, G.N., Eaton, J.A., Shabestari, L.R. & Angus, W. (1978) Comparison of some skeletal effects of ^{239}Pu administered at 3 months vs. 17 months of age in beagles. In: Jee, W.S.S., ed., *Research in Radiobiology* (COO-119-253), Salt Lake City, University of Utah Press, pp. 169–185

Hobbs, C.H., Barnes, J.E., McClellan, R.O., Chiffelle, T.L., Jones, R.K., Lundgren, D.L., Mauderley, J.L., Pickrell, J.A. & Rypka, E.W. (1972) Toxicity in the dog of inhaled ^{90}Y in fused clay particles: Early biological effects. *Radiat. Res*., **49**, 430–460

Hodgkins, P.S., O'Neill, P., Stevens, D. & Fairman, M.P. (1996) The severity of alpha-particle-induced DNA damage is revealed by exposure to cell-free extracts. *Radiat. Res*., **146**, 660–667

Hodgson, J.T. & Jones, R.D. (1990) Mortality of a cohort of tin miners, 1941–86. *Br. J. ind. Med.*, **47**, 665–676

Hoefnagel, C.A. (1991) Radionuclide therapy revisited. *Eur. J. nucl. Med.*, **18**, 408–431

Hoefnagel, C.A., Clarke, S.E.M., Fischer, M., Chatal, J.F., Lewington, V.J., Nilsson, S., Troncone, L. & Vieira, M.R. (1999) Radionuclide therapy practice and facilities in Europe. *Eur. J. nucl. Med*., **26**, 277–282

Hoffmann, W. & Daschil, F. (1986) Dose distribution and lung cancer incidence in Thorotrast patients. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 143–146

Holaday, D.A., Rushing, D.E., Coleman, R.D., Woolrich, P.F. & Kusnetz, H.L. (1957) *Control of Radon and Daughters in Uranium Mines and Calculations on Biologic Effects* (PHS Publ. No. 494), Washington DC, US Government Printing Office

Hollstein, M., Bartsch, H., Wesch, H., Kure, E.H., Mustonen, R., Mühlbauer, K.-R., Spiethoff, A., Wegener, K., Wiethege, T. & Müller, K.-M. (1997) *p53* Gene mutation analysis in tumors of patients exposed to α-particles. *Carcinogenesis*, **18**, 511–516

Holm, E. & Persson, R.B. (1978) Biophysical aspects of Am-241 and Pu-241 in the environment. *Radiat. environ. Biophys.*, **15**, 261–276

Holm, L.-E., Hall, P., Wiklund, K., Lundell, G., Berg, G., Bjelkengren, G., Cederquist, E., Ericsson, U.-B., Hallquist, A., Larsson, L.-G., Lidberg, M., Lindberg, S., Tennvall, J., Wicklund, H. & Boice, J.D., Jr (1991) Cancer risk after iodine-131 therapy for hyperthyroidism. *J. natl Cancer Inst.*, **83**, 1072–1077

Holmberg, E.A.D., Dosne De Pasqualini, C., Arini, E., Pavlovsky, A. & Rabasa, S.L. (1964) Leukemogenic effect of radioactive phosphorus in adult and fetally exposed BALB mice. *Cancer Res.* **24**, 1745-1748

Holtzman, R.B. & Ilcewicz, F.H. (1966) Lead-210 and polonium-210 in tissues of cigarette smokers. *Science*, **153**, 1259–1260

Honstead, J.F. & Brady, D.N. (1967) The uptake and retention of ^{32}P and ^{65}Zn from the consumption of Columbia River fish. *Health Phys.*, **13**, 455–463

Hopewell, J.W., Coggle, J.E., Wells, J., Hamlet, R., Williams, J.P. & Charles, M.W. (1986) The acute effects of different energy beta-emitters on pig and mouse skin. *Br. J. Radiol.*, **Suppl. 19**, 47–51

Hopewell, J.W., Sieber, V.K., Heryet, J.C., Wells, J. & Charles, M.W. (1993) Dose- and source-size-related changes in the late response of pig skin to irradiation with single doses of beta radiation from sources of differing energy. *Radiat. Res.*, **133**, 303–311

Hornik, S. & Kaul, A. (1995) The calculated α-dose and lung cancer risk in Thorotrast patients. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides*, Singapore, World Scientific, pp. 43–46

Hornung, R.W. & Meinhardt, T.J. (1987) Quantitative risk assessment of lung cancer in US uranium miners. *Health Phys.*, **52**, 417–430

Hornung, R.W., Deddens, J.A. & Roscoe, R.J. (1998) Modifiers of lung cancer risk in uranium miners from the Colorado plateau. *Health Phys.*, **74**, 12–21

Hou, D.-Y., Maruyama, Y. & Drago, J.R. (1992) Chromosome aberrations of human small cell lung cancer induced by a new ^{111}In-bleomycin complex. *J. surg. Oncol.*, **51**, 236–242

Howard, J.E., Vaswani, A. & Heotis, P. (1997) Thyroid disease among the Rongelap and Utirik population — An update. *Health Phys.*, **73**, 190–198

Howe, G.R. & Stager, R.H. (1996) Risk of lung cancer mortality after exposure to radon decay products in the Beaverlodge cohort based on revised exposure estimates. *Radiat. Res.*, **146**, 37–42

Howe, G.R., Nair, R.C., Newcombe, H.B., Miller, A.B. & Abbatt, J.D. (1986) Lung cancer mortality (1950–80) in relation to radon daughter exposure in a cohort of workers at the Eldorado Beaverlodge uranium mine. *J. natl Cancer Inst.*, **77**, 357–362

Howe, G.R., Nair, R.C., Newcombe, H.B., Miller, A.B., Burch, J.D. & Abbatt, J.D. (1987) Lung cancer mortality (1950–80) in relation to radon daughter exposure in a cohort of workers at the Eldorado Port Radium uranium mine: Possible modification of risk by exposure rate. *J. natl Cancer Inst.*, **79**, 1255–1260

Hubbard, L.M. & Swedjemark, G.A. (1993) Challenges in comparing radon data sets from the same Swedish houses: 1955–1990. *Indoor Air*, **3**, 361–368

Humphreys, E.R., Robins, M.W. & Stones, V.A. (1985) Age-related and ^{224}Ra-induced abnormalities in the teeth of male mice. *Arch. oral Biol*., **30**, 55–64

Humphreys, E.R., Loutit, J.F. & Stones, V.A. (1987) The induction by ^{239}Pu of myeloid leukaemia and osteosarcoma in female CBA mice. *Int. J. Radiat. Biol*., **51**, 331–339

Humphreys, E.R., Isaacs, K.R., Raine, T.A., Saunders, J., Stones, VA. & Wood, D.L. (1993) Myeloid leukaemia and osteosarcoma in CBA/H mice given ^{224}Ra. *Int. J. Radiat. Biol*., **64**, 231–235

Hunt, G.J. (1998) Transfer across the human gut of environmental plutonium, americium, cobalt, caesium and technetium: Studies with cockles (*Cerastoderma edule*) from the Irish Sea. *J. Radiol. Prot*., **18**, 101–109

Hunt, G.J. & Allington, D.J. (1993) Absorption of environmental polonium-210 by the human gut. *J. Radiol. Prot.*, **13**, 119–126

Hunt, G.J., Leonard, D.R.P. & Lovett, M.B. (1990) Transfer of environmental plutonium and americium across the human gut: A second study. *Sci. Total Environ.*, **90**, 273–282

Hunt, G.J., Young, A.K. & Bonfield, R.A. (2001) Transfer across the human gut of environmental technetium in lobsters (*Homarus gammarus* L.) from the Irish Sea. *J. Radiol. Prot*., **21**, 21–29

Hursh, J.B., Steadman, L.T., Looney, W.B. & Colodzin, M. (1957) The excretion of thorium and thorium daughters after Thorotrast administration. *Acta radiol*., **47**, 481–498

Hursh, J.B., Neuman, W.R., Toribara, T., Wilson, H. & Waterhouse, C. (1969) Oral ingestion of uranium by man. *Health Phys.*, **17**, 619–621

Hutchinson, F. (1985) Chemical changes induced in DNA by ionizing radiation. *Prog. nucl. Acid Res. mol. Biol.*, **32**, 115–154

Huvos, A.G. (1991) *Bone Tumours: Diagnosis, Treatment and Prognosis*, 2nd Ed., Philadelphia, PA, W.B. Saunders

Huvos, A.G. & Woodard, H.Q. (1988) Postradiation sarcomas of bone. *Health Phys*., **55**, 631–636

IAEA (International Atomic Energy Agency) (1997) *IAEA Yearbook 1997* (STI/PUB/1034), Vienna

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, IARC*Press*, pp. 216–219

IARC (1988) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 43, *Man-made Mineral Fibres and Radon*, Lyon, IARC*Press*

IARC (1998) CD-ROM, Globocan 1: *Cancer Incidence and Mortality Worldwide in 1990*, Lyon, IARC*Press*

IARC (2000) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 75, *Ionizing Radiation, Part 1: X- and Gamma (γ)-Radiation, and Neutrons*, Lyon, IARC*Press*

Ibrahim, S.A., Wrenn, M.E., Singh, N.P., Cohen, N. & Saccomano, G. (1983) Thorium concentration in human tissues from two US populations. *Health Phys.*, **44**, 213–220

ICRP (International Commission on Radiological Protection) (1966) Task Group on Lung Dynamics. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys*., **12**, 173–207

ICRP (International Commission on Radiological Protection) (1968) *Report of Committee IV on Evaluation of Radiation Doses to Body Tissues from Internal Contamination Due to Occupational Exposure* (ICRP Publication 10), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1973) *Alkaline Earth Metabolism in Adult Man* (ICRP Publication 20), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1975) *Report of the Task Group on Reference Man* (ICRP Publication 23), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1979) *Limits for Intakes of Radionuclides by Workers*, Part 1 (ICRP Publication 30; Annals of the ICRP, Vol. 2, No. 3/4), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1980) *Limits for Intakes of Radionuclides by Workers*, Part 2 (ICRP Publication 30; Annals of the ICRP, Vol. 4, No. 3/4), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1981) *Limits for Intakes of Radionuclides by Workers*, Part 3 (ICRP Publication 30; Annals of the ICRP, Vol. 6, No. 2/3), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1984) *Nonstochastic Effects of Ionizing Radiation* (ICRP Publication 41; Annals of the ICRP, Vol. 14, No. 3), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1986) *The Metabolism of Plutonium and Related Elements* (ICRP Publication 48), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1989) *Age-dependent Doses to Members of the Public from Intake of Radionuclides*, Part 1 (ICRP Publication 56; Annals of the ICRP, Vol. 20, No. 2), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1991) 1990 Recommendations of the International Commission on Radiological Protection (ICRP Publication 60; Annals of the ICRP, Vol. 21), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1993a) *Protection against Radon-222 at Home and at Work* (ICRP Publication 65; Annals of the ICRP, Vol. 23, No. 2), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1993b) *Radiation Dose to Patients from Radiopharmaceuticals* (ICRP Publication No. 53), 2nd Ed., Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1993c) *Age-dependent Doses to Members of the Public from Intake of Radionuclides*, Part 2, *Ingestion Dose Coefficients* (ICRP Publication 67; Annals of the ICRP, Vol. 23, No. 3/4), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1994a) *Dose Coefficients for Intakes of Radionuclides by Workers: Replacement of ICRP Publication 61* (ICRP Publication 68; Annals of the ICRP, Vol. 24), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1994b) *Human Respiratory Tract Model for Radiological Protection* (ICRP Publication 66; Annals of the ICRP, Vol. 26, No. 1), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1995a) *Age-dependent Doses to Members of the Public from Intake of Radionuclides*, Part 3, *Ingestion Dose Coefficients* (ICRP Publication 69; Annals of the ICRP, Vol. 25, No. 1), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1995b) *Age-dependent Doses to Members of the Public from Intake of Radionuclides*, Part 4, *Inhalation Dose Coefficients* (ICRP Publication 71; Annals of the ICRP, Vol. 25, No. 3-4), Oxford, Pergamon Press

ICRP (International Commission on Radiological Protection) (1999) *The ICRP Database of Dose Coefficients: Workers and Members of the Public*, Version 1. CD-ROM, Oxford, Pergamon Press

Iliakis, G. (1984) The mutagenicity of alpha particles in Ehrilich ascites tumor cells. *Radiat. Res*., **99**, 52–58

Ilyin, L.A., Balonov, M.I., Buldakov, L.A., Bur'yak, V.N., Gordeev, K.I., Dement'ev, S.I., Zhakov, I.G., Zubovsky, G.A., Kondrusev, A.I., Konstantinov, Y.O., Linge, I.I., Likhtarev, I.A., Lyaginskaya, A.M., Maryuhin, V.A., Pavlovsky, O.A., Potapov, A.I., Prysyazhnyuk, A.E., Ramsaev, P.V., Romanenko, A.E., Savkin, M.N., Starkova, N.T., Tron'ko, N.D. & Tsyb, A.V. (1990) Radiocontamination patterns and possible health consequences of the accident at the Chernobyl nuclear power station. *J. radiol. Prot.*, **10**, 3–29

Ishikawa, Y., Kato, Y. & Hatakeyama, S. (1989) Late effects of alpha-particles on Thorotrast patients in Japan. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology, pp. 129–131

Ishikawa, Y., Kato, Y., Mori, T., Machinami, R. & Kitagawa, T. (1993a) Alpha-particle dose to the liver and spleen tissues of Japanese Thorotrast patients. *Health Phys*., **65**, 497–506

Ishikawa, Y., Mori, T., Kato, Y., Machinami, R., Priest, N.D. & Kitagawa, T. (1993b) Systemic deposits of thorium in Thorotrast patients with particular reference to sites of minor storage. *Radiat. Res*., **135**, 244–248

Ishikawa, Y., Humphreys, J.A.H., Collier, C.G., Priest, N.D., Kato, Y., Mori, T. & Machinami, R. (1999) Revised organ partition of thorium-232 in Thorotrast patients. *Radiat. Res*., **152**, S102–S106

Ishiwata, K., Ido, T., Kawashima, K., Yamada, H., Takahashi, T., Iwata, R., Matsui, A. & Sakuragawa, N. (1985) Placental transfer of positron-emitting radionuclides in metabolic substrates. *Int. J. nucl. Med. Biol.*, **12**, 33–36

Islam, A. (1985) Chronic granulocytic leukaemia: A defect in cellular interactions between stromal and haemopoietic stem cells? *Med. Hypoth*., **17**, 69–77

Ito, T., Seyama, T., Iwamoto, K.S., Hayashi, T., Mizuno, T., Tsuyama, N., Dohi, K., Nakamura, N. & Akiyama, M. (1993) *In vitro* irradiation is able to cause *RET* oncogene rearrangement. *Cancer Res.*, **53**, 2940–2943

Ivanov, V.K., Tsyb, A.F., Gorsky, A.I., Maksyutov, M.A., Rastopchin, E.M., Konogorov, A.P., Biryukov, A.P., Matyash, V.A. & Mould, R.F. (1997a) Thyroid cancer among 'liquidators' of the Chernobyl accident. *Br. J. Radiol.*, **70**, 937–941

Ivanov, V.K., Tsyb, A.F., Nilova, E.V., Efendiev, V.F., Gorsky, A.I., Pitkevich, V.A., Leshakov, S.Y. & Shiryaev, V.I. (1997b) Cancer risks in the Kaluga oblast of the Russian Federation 10 years after the Chernobyl accident. *Radiat. environ. Biophys*., **36**, 161–167

Ivanov, E.P., Tolochko, G.V., Shuvaeva, L.P., Ivanov, V.E., Iaroshevich, R.F., Becker, S., Nekolla, E. & Kellerer, A.M. (1998) Infant leukemia in Belarus after the Chernobyl accident. *Radiat. environ. Biophys.*, **37**, 53–55

Ivanov, V.K., Gorski, A.I., Pitkevitch, V.A., Tsyb, A.F., Cardis, E. & Storm, H. (1999a) Risk of radiogenic thyroid cancer in Russia following the Chernobyl accident. In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer* (EUR 18552 EN), Singapore, World Scientific, pp. 89–96

Ivanov, V.K., Gorsky, A.I., Tsyb, A.F., Maksyutov, M.A. & Rastopchin, E.M. (1999b) Dynamics of thyroid cancer incidence in Russia following the Chernobyl accident. *J. Radiol. Prot.*, **19**, 305–318

Iwamoto, K.S., Fujii, S., Kurata, A., Suzuki, M., Hayashi, T., Ohtsuki, Y., Okada, Y., Narita, M., Takahashi, M., Hosobe, S., Doishita, K., Manabe, T., Hata, S., Murakami, I., Hata, S., Itoyama, S., Akatsuka, S., Ohara, N., Iwasaki, K., Akabane, H., Fujihara, M., Seyama, T. & Mori, T. (1999) p53 Mutations in tumor and non-tumor tissues of Thorotrast recipients: A model for cellular selection during radiation carcinogenesis in the liver. *Carcinogenesis*, **20**, 1283–1291

Jackson, S. & Dolphin, G.W. (1966) The estimation of internal radiation dose from metabolic and urinary excretion data for a number of important radionuclides. *Health Phys.*, **12**, 481–500

Jacob, P., Goulko, G., Heidenreich, W.F., Likhtarev, I., Kairo, I., Tronko, N.D., Bogdanova, T.I., Kenigsberg, J., Buglova, E., Drozdovitch, V., Golovneva, A., Demidchik, E.P., Balonov, M., Zvonova, I. & Beral, V. (1998) Thyroid cancer risk to children calculated. *Nature*, **392**, 31–32

Jacob, P., Kenigsberg, Y., Zvonova, I., Goulko, G., Buglova, E., Heidenreich, W.F., Golovneva, A., Bratilova, A.A., Drozdovitch, V., Kruk, J., Pochtennaja, G.T., Balonov, M., Demidchik, E.P. & Paretzke, H.G. (1999) Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia. *Br. J. Cancer*, **80**, 1461–1469

Jacquet, N., Bourahla, K., Guiraud-Vitaux, F., Petiet, A., Voisin, P. & Colas-Linhart, N. (1999) Biological consequences of irradiation by low doses of technetium 99m: Ultrastructural studies, p53 protein expression and cytogenetic effects. *Cell. mol. Biol.*, **45**, 1139–1147

Janower, M.L., Miettinen, O.S. & Flynn, M.J. (1972) Effects of long-term Thorotrast exposure. *Radiology*, **103**, 13–20

Jee, W.S.S. (1972) Distribution and toxicity of ^{239}Pu in bone. *Health Phys.*, **22**, 583–595

Jee, W.S.S. & Arnold, J.S. (1960) Radioisotopes in the teeth of dogs. I. The distribution of plutonium, radium, radiothorium, mesothorium, and strontium and the sequence of histopathologic changes in teeth containing plutonium. *Arch. oral Biol.*, **2**, 215–238

Jee, W.S.S., Arnold, J.S., Cochran, T.H., Twente, J.A. & Mical, R.S. (1962) Relationship of microdistribution of alpha-particles to damage. In: Dougherty, T.F., Jee, W.S.S., Mays, C.W. & Stover, B.J., eds, *Some Aspects of Internal Irradiation*, Oxford, Pergamon Press, pp. 27–45

Jee, W.S.S., Bartley, M.H., Dockum, N.L., Yee, J. & Kenner, G.H. (1969) Vascular changes in bones following bone-seeking radionuclides. In: Mays, C.W., Jee, W.S.S., Lloyd, R.D., Stover, B.J., Doughterty, J.H. & Taylor, G.N., eds, *Delayed Effects of Bone-seeking Radionuclides*, Salt Lake City, University of Utah Press, pp. 437–455

Jee, W.S., Parks, N.J., Miller, S.C. & Dell, R.B. (1986) Relationship of bone composition to the location of radium-induced bone cancer. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 75–78

Jenner, T.J., deLara, C.M., O'Neill, P. & Stevens, D.L. (1993) Induction and rejoining of DNA double-strand breaks in V79-4 mammalian cells following γ- and α-irradiation. *Int. J. Radiat. Biol.*, **64**, 265–273

Johansson, L., Mattsson, S. & Nosslin, B. (1984) Effective dose equivalent from radiopharmaceuticals. *Eur. J. nucl. Med.*, **9**, 485–489

Johansson, L., Mattsson, S., Nosslin, B. & Leide-Svegborn, S. (1992) Effective dose from radiopharmaceuticals. *Eur. J. nucl. Med.*, **19**, 933–938

Johnson, J.R., Myers, D.K., Jackson, J.S., Dunfor, D.W., Gragtmans, N.J., Wyatt, H.M., Jones, A.R. & Percy, D.H. (1995) Relative biological effectiveness of tritium for induction of myeloid leukemia in CBA/H mice. *Radiat. Res.*, **144**, 82–89

Jones, D.C.L., Krebs, J.S., Sasmore, D.P. & Mitoma, C. (1980) Evaluation of neonatal squirrel monkeys receiving tritiated water throughout gestation. *Radiat. Res.*, **83**, 592–608

Jones, C.W, Mays, C.W., Taylor G.N., Lloyd, R.D. & Packer, S.M. (1986) Reducing the cancer risk of ^{239}Pu by chelation therapy. *Radiat. Res.*, **107**, 296–306

Jönsson, H. & Mattsson, S. (1998) Thyroid burdens of ^{125}I in hospital laboratory workers during a 20-y period. *Health Phys.*, **75**, 475–478

Jorgensen, T.J., Olive, P.L. & Durand, R.E. (1987) DNA strand breakage in Chinese hamster V79 cells caused by low levels of incorporated [^{3}H] and [^{14}C]thymidine. *Int. J. Radiat. Biol.*, **51**, 673–680

Kadhim, M.A., Macdonald, D.A., Goodhead, D.T., Lorimore, S.A., Marsden, S.J. & Wright, E.G. (1992) Transmission of chromosomal instability after plutonium α-particle irradiation. *Nature*, **355**, 738–740

Kadhim, M.A., Lorimore, S.A., Hepburn, M.D., Goodhead, D.T., Buckle, V.J. & Wright, E.G. (1994) Alpha-particle-induced chromosomal instability in human bone marrow cells. *Lancet*, **344**, 987–988

van Kaick, G., Muth, H. & Kaul, A., eds (1984) *The German Thorotrast Study — Results of Epidemiological, Clinical and Biophysical Examinations on Radiation-induced Late Effects in Man caused by Incorporated Colloidal Thorium Dioxide (Thorotrast)* (EUR 9504 EN), Luxembourg, Office for Offical Publications of the European Commission

van Kaick, G., Muth, H., Kaul, A., Wesch, H., Immich, H., Liebermann, D., Lorenz, D., Lorenz, W.J., Lührs, H., Scheer, K.E., Wagner, G. & Wegener, K. (1986a) Report on the German Thorotrast study. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 114–118

van Kaick, G., Wesch, H., Lührs, H. & Liebermann, D. (1986b) Radiation-induced primary liver tumors in 'Thorotrast patients'. *Recent Results Cancer Res.*, **100**, 16–22

van Kaick, G., Wesch, H., Lührs, H., Liebermann, D., Kaul, A. & Muth, H. (1989) The German Thorotrast study — Report on 20 years follow-up. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology, pp. 98–103

van Kaick, G., Wesch, H., Lührs, H., Liebermann, D. & Kaul, A. (1991) Neoplastic diseases induced by chronic alpha-irradiation — Epidemiological, biophysical and clinical results of the German Thorotrast study. *J. Radiat. Res.*, **32** (Suppl. 2), 20–33

van Kaick, G., Wesch, H., Lührs, H., Liebermann, D. & Kaul, A. (1995) Epidemiologic results and dosimetric calculations — An update of the German Thorotrast study. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 171–175

van Kaick, G., Dalheimer, A., Hornik, S., Kaul, A., Liebermann, D., Lührs, H., Spiethoff, A., Wegener, K. & Wesch H. (1999) The German Thorotrast Study: Recent results and assessment of risks. *Radiat. Res.*, **152**, S64–S71

Kaletsch, U., Kaatsch, P., Meinert, R., Schüz, J., Czarwinski, R. & Michaelis, J. (1999) Childhood cancer and residential radon exposure — Results of a population-based case–control study in Lower Saxony (Germany). *Radiat. environ. Biophys.*, **38**, 211–215

Kamikawa, T., Amenomori, M., Itoh, T., Momoi, H., Hiai, H., Machinami, R., Ishikawa, Y., Mori, T., Shimahara, Y., Yamaoka, Y. & Fukumoto, M. (1999) Analysis of genetic changes in intrahepatic cholangiocarcinoma induced by Thorotrast. *Radiat. Res.*, **152**, S118–S124

Kammer, H. & Goodman, M.J. (1959) Sterility after radioiodine therapy for metastatic thyroid carcinoma. *J. Am. med. Assoc.*, **171**, 1963–1965

Kampf, G. & Eichhorn, K. (1983) DNA strand breakage by different radiation qualities and relations to cell-killing — Further results after the influence of alpha particles and carbon-ions. *Studia biophys.*, **93**, 17–26

Kapoor, G., Sharan, R.N. & Srivastava, P.N. (1985) Histopathological changes in the ovary following acute and chronic low-level tritium exposure in mice *in vivo*. *Int. J. Radiat. Biol.*, **47**, 197–203

Kashima, M, Mahlum, D.D. & Sikov, M.R. (1972) Metabolism and effect of monomeric and polymeric plutonium in the immature rat liver. *Health Phys.*, **22**, 749–752

Kathren, R.L. & Hill, R.L. (1992) Distribution and dosimetry of Thorotrast in USUR Case 1001. *Health Phys.*, **63**, 72–88

Kathren, R.L., Heid, K.R. & Swint, M.J. (1987) Comparison of estimates of systemic Pu from urinary excretion with estimates from post-mortem tissue analysis. *Health Phys.*, **53**, 487–493

Kato, Y. & Ishikawa, Y. (1992) Portable ^{220}Rn detector used to assess Thorotrast exposure. *Health Phys.*, **63**, 119–123

Kato, Y., Mori, T. & Kumatori, T. (1983) Estimated absorbed dose in tissues and radiation effects in Japanese Thorotrast patients. *Health Phys.*, **44** (Suppl. 1), 273–279

Katz, N., Ésik, O., Füzy, M. & Gundy, S. (1998) [Cytogenetic study of thyroid patients treated with external irradiation or radioiodine.] *Orv. Hetil.*, **139**, 1521–1526 (in Hungarian)

Kaul, A. (1965) Dose in liver and spleen after injection of Thorotrast into blood. In: *The Dosimetry and Toxicity of Thorotrast* (IAEA Technical Report 1968), Vienna, International Atomic Energy Agency, pp. 30–43

Kaul, A. (1973) Mean organ dose rates in man following intravascular injection of Thorotrast. In: *Proceedings of the Third International Meeting on the Toxicity of Thorotrast* (Risö Report No. 294), Copenhagen, Danish Atomic Energy Commission, Research Establishment Risö, pp. 40–51

Kaul, A. (1995) Biokinetic models and data. In: van Kaick, H., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 53–67

Kaul, A. & Muth, H. (1978) Thorotrast kinetics and radiation dose. Results from studies in Thorotrast patients and from animal experiments. *Radiat. environ. Biophys*., **15**, 241–259

Kaul, A. & Noffz, W. (1978) Tissue dose in Thorotrast patients. *Health Phys*., **35**, 113–121

Kaul, A., Pustelnik, B., Pustelnik, C. & Riedel, W. (1986) Assessment of Thorotrast redistribution in liver tissue of the rat. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 189–196

Kawamura, H., Tanaka, G.-I. & Shiraishi, K. (1986) Distribution of Sr in the fetal skeleton. *Health Phys.*, **50**, 159–162

Keane, A.T., Lucas, H.F., Markun, F., Essling, M.A. & Holtzman, R.B. (1986) The estimation and potential radiobiological significance of the intake of ^{228}Ra by early Ra dial workers in Illinois. *Health Phys*., **51**, 313–327

Keating, F.R., Jr & Albert, A. (1949) The metabolism of iodine in man as disclosed with the use of radioiodine. *Recent Prog. Hormone Res*., **4**, 429–481

Kellington, J.P., Gibson, K., Buckle, T.M., Talbot, R.J. & Hornby, S.B. (1992) Alveolar macrophage kinetics after inhalation of $^{239}PuO_2$ by CBA/Ca mice: Changes in synthesis of DNA. *Environ. Health Perspect.*, **97**, 69–75

Kellington, J.P., Eldred, T.M., Ambrose, K., Brooks, P.N. & Priest, N.D. (1998) Effects of radiation quality on lung tumour induction in CBA/Ca mice. In: Hare, G.A., Cartweight, R.A., Chadwick, K., Charles, M.W., Fry, S.A., Goodhead, D.T. & Wade, B., eds, *Health Effects of Low Dose Radiation: Challenge of 21st Century*, London, Thomas Telford, pp. 44–51

Kelly, G., Stegelmeier, B.L. & Hahn. F.F. (1995) *p53* alterations in plutonium-induced F344 rat lung tumors. *Radiat. Res*., **142**, 263–269

Kenigsberg, J., Buglova, E., Paretzke, H.G. & Heidenreich, W. (1996) Perspectives of development of thyroid cancer in Belarus. In: Karaoglou, A., Desmet, G., Kelly, G.N. & Menzel, H.G., eds, *The Radiological Consequences of the Chernobyl Accident* (EUR 16544 EN), Luxembourg, Office for Official Publications of the European Commission, pp. 771–775

Kerber, R.A., Till, J.E., Simon, S.L., Lyon, J.L., Thomas, D.C., Preston-Martin, S., Rallison, M.L., Lloyd, R.D. & Stevens, W. (1993) A cohort study of thyroid disease in relation to fallout from nuclear weapons testing. *J. Am. med. Assoc*., **270**, 2076–2082

Khokhryakov, V.F. & Kudryavtseva, T.I. (1985) [Distribution of plutonium-239 in the body of workers at the radiochemical plant.] *Bull. Radiat. Med.*, **2**, 74–80 (in Russian)

Khokhryakov, V.F. & Romanov, S.A. (1992) [Lung cancer effect of radiation exposure.] *Sci. inform. method. Bull.*, **4**, 16–17 (in Russian)

Khokhryakov, V.F. & Romanov, S.A. (1994) Lung cancer in radiochemical industry workers. *Sci. total Environ.*, **142**, 25–28

Khokhryakov, V.F. & Romanov, S.A. (1996) Estimation of the temporal distribution and dose dependency of lung cancers among workers of nuclear fuel reprocessing plants. *Health Phys*., **71**, 83–85

Khokhryakov, V.F., Erochin, R.A. & Koshurnikova, N.A. (1988) [Forecast of frequency of arising carcinoma of lung by the staff involved into plutonium production.] *Bull. Radiat. Med.*, **1**, 23–28 (in Russian)

Khokhryakov, V.F., Kudryavtseva, T.I. & Suslova, K.G. (1990) [Effective dose equivalent of irradiation of the staff by incorporated plutonium.] *Bull. Radiat. Med.*, **2,** 77-81 (in Russian)

Khokhryakov, V.F., Kellerer, A.M., Kreisheimer, M. & Romanov, S.A. (1998) Lung cancer in nuclear workers of Mayak. A comparison of numerical procedures. *Radiat. environ. Biophys.*, **37**, 11–17

Khursheed, A. (2000) Doses to systemic tissues from radon gas. *Radiat. Prot. Dosim.*, **88**, 171–181

Kido, C., Sasaki, F., Hirota, Y., Kiyosawa, K., Hayashi, S., Mori, T. & Sobue, T. (1999) Cancer mortality of Thorotrast patients in Japan: The second series updated 1998. *Radiat. Res.*, **152**, S81–S83

Klugbauer, S., Lengfelder, E., Demidchik, E.P. & Rabes, H.M. (1995) High prevalence of *RET* rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene*, **11**, 2459–2467

Kobayashi, T., Kageyama, N. & Ohara, K. (1981) Internal irradiation for cystic craniopharyngioma. *J. Neurosurg.*, **55**, 896–903

Koletsky, S., Bonte, F.J. & Friedell, H.L. (1950) Production of malignant tumours in rats with radioactive phosphorus. *Cancer Res.*, **10**, 129–138

Komatsu, K., Okumura, Y. & Sakamoto, K. (1990) Radiation dose to mouse liver cells from ingestion of tritiated food or water. *Health Phys.*, **58**, 625–629

Koshurnikova, N.A. & Nifatov, A.P. (1978) [Carcinoma of lung by workers involved into plutonium production.] *Bull. Radiat. Med.*, **4**, 60–66 (in Russian)

Koshurnikova, N.A., Lemberg, V.K., Mamakova, O.V., Nifatov, A.P. & Surov, A.I. (1973) [Some late health effects of exposure to inhaled plutonium-239 in man.] *Bull. Radiat. Med.*. **1**, 3–17 (in Russian)

Koshurnikova, N.A., Komleva, N.S., Bysogolov, G.D., Bolotnikova, M.G., Budushchev, E.B., Buldakov, L.A., Lizlov, A.F., Menshikh, Z.S., Nifatov, A.P. & Khokhryakov, V.F. (1992) [Effect of radiation exposure in workers of the 'Mayak' PA.] *Sci. inform. method. Bull.*, **4**, 18–21 (in Russian)

Koshurnikova, N.A., Kreslov, V.V., Bolotnikova, M.G., Nifatov, A.P., Shilnikova, N.S., Okatenko, P.V., Romanov, S.A. & Khokhryakov, V.F. (1995) [Lung cancer mortality among personnel of 'Mayak' complex.] *Radiat. Risk*, **5**, 145–150 (in Russian)

Koshurnikova, N.A., Bysogolov, G.D., Bolotnikova, M.G., Khokhryakov, V.F., Kreslov, V.V., Okatenko, P.V., Romanov, S.A. & Shilnikova, N.S. (1996) Mortality among personnel who worked at the Mayak complex in the first years of its operation. *Health Phys.*, **71**, 90–93

Koshurnikova, N.A., Shilnikova, N.S., Okatenko, P.V., Kreslov, V.V., Bolotnikova, Romanov, S.A. & Sokolnikov, M.E. (1997a) The risk of cancer among nuclear workers at the 'Mayak' Production Association: Preliminary results of an epidemiological study. In: Boice, J.D., Jr, ed., *Implications of New Data on Radiation Cancer Risk* (NCRP Proceedings No. 18), Bethesda, MD, National Council on Radiation Protection and Measurements, pp. 113–122

Koshurnikova, N.A., Kreslov, V.V., Okatenko, P.V., Romanov, S.A., Shilnikova, N.S. & Sokolnikov, M.E. (1997b) Epidemiological effects and lung cancer risk due to radiation exposure. In: Kellogg, S.L. & Kirk, E.J., eds, *Assessing Health and Environmental Risks from Long-term Radiation Contamination in Chelyabinsk, Russia* (Proceedings of the 1996 AAAS Annual Meeting Symposium), Washington DC, American Association for the Advancement of Science, pp. 61–70

Koshurnikova, N.A., Bolotnikova, M.G., Ilyin, L.A., Keirim-Markus, I.B., Menshikh, Z.S., Okatenko, P.V., Romanov, S.A., Tsvetkov, V.I. & Shilnikova, N.S. (1998) Lung cancer risk due to exposure to incorporated plutonium. *Radiat. Res.*, **149**, 366–371

Koshurnikova, N.A., Shilnikova, N.S., Okatenko, P.V., Kreslov, V.V., Bolotnikova, M.G., Sokolnikov, M.E., Khokhriakov, V.F., Suslova, K.G., Vassilenko, E.K. & Romanov, S.A. (1999) Characteristics of the cohort of workers at the Mayak nuclear complex. *Radiat. Res.*, **152**, 352–363

Koshurnikova, N.A., Gilbert, E.S., Sokolnikov, M.E., Khokhryakov, V., Miller, S., Preston, D.L., Romanov, S.A., Shilnikova, N.S., Suslova, K.G. & Vostrotin, V.V. (2000) Bone tumors in Mayak workers. *Radiat. Res.*, **154**, 237–245

Kossenko, M.M. (1996) Cancer mortality in the exposed population of the Techa River area. *World Health Stat. Q.*, **49**, 17–21

Kossenko, M.M. & Degteva, M.O. (1994) Cancer mortality and radiation risk evaluation for the Techa River population. *Sci. total Environ.*, **142**, 73–89

Kossenko, M.M., Degteva, M.O., Vyushkova, O.V., Preston, D.L., Mabuchi, K. & Kozheurov, V.P. (1997) Issues in the comparison of risk estimates for the population in the Techa River region and atomic bomb survivors. *Radiat. Res.*, **148**, 54–63

Kozheurov, V.P. & Degteva, M. (1994) Dietary intake evaluation and dosimetric modelling for the Techa River residents based on in vivo measurements of strontium-90 in teeth and skeleton. *Sci. total Environ.*, **142**, 67–72

Kreienbrock, L., Kreuzer, M., Gerken, M., Dingerkus, G., Wellmann, J., Keller, G. & Wichmann, H.E. (2000) Case–control study on lung cancer and residential radon in West Germany. *Am. J. Epidemiol.* (in press)

Kreisheimer, M., Koshurnikova, N.A., Nekolla, E., Khokhryakov, V.F., Romanov, S.A., Sokolnikov, M.E., Shilnikova, N.S., Okatenko, P.V. & Kellerer, A.M. (2000) Lung cancer mortality among male nuclear workers of the Mayak facilities in the former Soviet Union. *Radiat. Res.*, **154**, 3–11

Kreuzer, M., Grosche, B., Brachner, A., Martignoni, K., Schnelzer, M., Schopka, H.-J., Brüske-Hohlfeld, I., Wichmann, H.-E. & Burkart, W. (1999) The German uranium miners cohort study: Feasibility and first results. *Radiat. Res.*, **152**, S56–S58

Kusiak, R.A., Ritchie, A.C., Muller, J. & Springer, J. (1993) Mortality from lung cancer in Ontario uranium miners. *Br. J. ind. Med.*, **50**, 920–928

Kwadow, M. & Chevalier, C. (1988) Occupational exposure to radionuclides in French nuclear power plants: Five years excretion monitoring results. *Sci. total Environ.*, **70**, 299–319

L'Abbé, K.A., Howe, G.R., Burch, J.D., Miller, A.B., Abbatt, J., Band, P., Choi, W., Du, J., Feather, J., Gallagher, R., Hill, G. & Matthews, V. (1991) Radon exposure, cigarette smoking, and other mining experience in the Beaverlodge uranium miners cohort. *Health Phys.*, **60**, 489–495

LaBauve, R.J., Brooks, A.L., Mauderly, J.L., Hahn. F.F., Redman, H.C., Macken, C., Slauson, D.O., Mewhinney, J.A. & McClellan, R.O. (1980) Cytogenetic and other biological effects of $^{239}PuO_2$ inhaled by the rhesus monkey. *Radiat. Res.*, **82**, 310–335

Ladinskaya, L.A., Parfenov, Y.D., Popov, D.K. & Fedorova, A.V. (1973) ^{210}Pb and ^{210}Po content in air, water, foodstuffs, and the human body. *Arch. environ. Health*, **27**, 254–258

Lagarde, F. & Pershagen, G. (1999) Parallel analyses of individual and ecologic data on residential radon, cofactors, and lung cancer in Sweden. *Am. J. Epidemiol.*, **149**, 268–274

Lagarde, F., Pershagen, G., Åkerblom, G., Axelson, O., Bäverstam, U., Damber, L., Enflo, A., Svartengren, M. & Swedjemark, G.A. (1997) Residential radon and lung cancer in Sweden: Risk analysis accounting for random error in the exposure assessment. *Health Phys.*, **72**, 269–276

Lagerquist, C.R., Bokowski, D.L., Hammond, S.E. & Hylton, D.B. (1969) Plutonium content of several internal organs following occupational exposure. *Am. ind. Hyg. Assoc. J.*, **30**, 417–421

Laird, N.M. (1987) Thyroid cancer risk from exposure to ionizing radiation: A case study in the comparative potency model. *Risk Anal.*, **7**, 299–309

Lambert, B.E. & M.L. Phipps (1977) Some effects of irradiation of mice in utero with tritiated compounds. *Curr. Topics Radiat. Res. Q.*, **12**, 197–211

Lambert, B.E. & M.L. Phipps (1983) The long-term effects of tritium incorporated *in utero*. In: *Effects of Prenatal Irradiation with Special Emphasis on Late Effects* (Report EUR-8076), Luxembourg, Commission of the European Communities, pp. 143–158

Landaw, S.A. (1976) Acute leukemia in polycythemia vera. *Semin. Hematol.*, **13**, 33–48

Langham, W.H. (1957) Excretion methods: The application of excretion analyses to the determination of body burden of radioactive isotopes. *Br. J. Radiol.*, **Suppl. 7**, 95–113

Larsen, P.R., Conard, R.A., Knudsen, K., Robbins, J., Wolff, J., Rall, J.E. & Dobyns, B. (1978) Thyroid hypofunction appearing as a delayed manifestation of accidental exposure to radioactive fall-out in a Marshallese population. In: *Late Biological Effects of Ionizing Radiation*, Vol. 1 (IAEA-SM-224/607), Vienna, International Atomic Energy Agency, pp. 101–115

Laskey, J.W., Parrish, J.L. & Cahill, D.F. (1973) Some effects of lifetime parental exposure to low levelsof tritium on the F2 generation. *Radiat. Res.*, **56**, 171–179

La Vecchia, C., Ron, E., Franceschi, S., Dal Maso, L., Mark, S.D., Chatenoud, L., Braga, C., Preston-Martin, S., McTiernan, A., Kolonel, L., Mabuchi, K., Jin, F., Wingren, G., Galanti, M.R., Hallquist, A., Lund, E., Levi, F. & Linos, D. (1999) A pooled analysis of case–control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control*, **10**, 157–166

Law, G.R., Kane, E.V., Roman, E., Smith, A. & Cartwright, R. (2000) Residential radon exposure and adult acute leukaemia (Letter to the Editor). *Lancet*, **355**, 1888

Lawrence, J.H. (1955) *Polycythemia. Physiology, Diagnosis and Treatment Based on 303 Cases, a Modern Medical Monograph*, New York, Grune & Stratton

Lawrence, J.H., Winchell, H.S. & Donald, W.G. (1969) Leukemia in polycythemia vera. Relationship to splenic myeloid metaplasia and therapeutic radiation dose. *Ann. intern. Med.*, **70**, 763–771

Lazjuk, G.I., Nikolaev, D.L. & Novikova, I.V. (1997) Changes in registered congenital anomalies in the Republic of Belarus after the Chernobyl accident. *Stem Cells*, **15**, (Suppl. 2), 255–260

Lee, W., Chiacchierini, R.P., Schleien, B. & Telles, N.C. (1982) Thyroid tumors following ^{131}I or localized X irradiation to the thyroid and pituitary glands in rats. *Radiat. Res.*, **92**, 307–319

Lee, P.S., Gorski, R.A., Hering, W.E. & Chan, T.L. (1987) Lung clearance of inhaled particles after exposure to carbon black generated from a resuspension system. *Environ. Res.*, **43**, 364–373

Lee, D.S., Ahn, J.Y., Kim, S.K., Oh, B.H., Seo, J.D., Chung, J.-K. & Lee, M.C. (2000) Limited performance of quantitative assessment of myocardial function by thallium-201 gated myocardial single-photon emission tomography. *Eur. J. nucl. Med.*, **27**, 185–191

Lees, R.E.M., Steele, R. & Roberts, J.H. (1987) A case–control study of lung cancer relative to domestic radon exposure. *Int. J. Epidemiol.*, **16**, 7–12

Leggett, R.W. (1985) A model of retention, translocation, and excretion of systemic plutonium. *Health Phys*., **49**, 1115–1137

Leggett, R.W. (1986) Predicting the retention of Cs in individuals. *Health Phys*., **50**, 747–759

Leggett, R.W. (1992a) A generic age-specific biokinetic model for calcium-like elements. *Radiat. Prot. Dosim.*, **41**, 183–198

Leggett, R.W. (1992b) A retention–excretion model for americium in humans. *Health Phys*., **62**, 288–310

Leggett, R.W. & Harrison, J.D. (1995) Fractional absorption of ingested uranium in humans. *Health Phys*., **68**, 484–498

Leggett, R.W., Eckerman, K.F. & Williams, L.R. (1982) Strontium-90 in bone: A case study in age-dependent dosimetric modeling. *Health Phys*., **43**, 307–322

Lehane, M.M., Bryant, P.E., Riches, A.C., Allen, L.A., Briscoe, C.V., Melville, J. & Mill, A.J. (1999) ^{238}Pu α-particle-induced C3H10T1/2 transformants are less tumorigenic than the X-ray-induced equivalent. *Carcinogenesis*, **20**, 35–40

LeMotte, P.K., Adelstein, S.J. & Little, J.B. (1982) Malignant transformation induced by incorporated radionuclides in BALB/3T3 mouse embryo fibroblasts. *Proc. natl Acad. Sci. USA*, **79**, 7763–7767

LeRoy, G.V., Rust, J.H. & Hasterlik, R.J. (1966) The consequences of ingestion by man of real and simulated fall-out. *Health Phys.*, **12**, 449–473

Lessard, E., Miltenberger, R., Conard, R., Musolino, S., Naidu, J., Moorthy, A. & Schopfer, C. (1985) *Thyroid Absorbed Dose for People at Rongelap, Utinik and Sifo on March 1, 1954* (BNL 51882), Upton, NY, Brookhaven National Laboratory

Létourneau, E.G., Krewski, D., Choi, N.W., Goddard, M.J., McGregor, R.G., Zielinski, J.M. & Du, J. (1994) Case–control study of residential radon and lung cancer in Winnipeg, Manitoba, Canada. *Am. J. Epidemiol.*, **140**, 310–322

Levack, V.M., Pottinger, H., Ham, G.J., Harrison, J.D. & Paquet, F. (1994) The fetal transfer of ruthenium, cerium, plutonium and americium. In: Nimmo-Scott, W. & Golding, D.J., eds, *Proceedings of the IRPA Regional Congress on Radiological Protection, June 1994, Portsmouth*, Ashford, Nuclear Technology Publishing, pp. 161–164

Levdik, T.I., Lemberg, V.K., Buldakov, L.A., Lyubchanskii, E.R. & Pesternikov, V.M. (1972) Biological effectiveness of ^{237}Np. *Health Phys*., **22**, 643–645

Levine, W.G. (1979) The chelation of heavy metals. In: *International Encyclopedia of Pharmacology and Therapeutics*, Oxford, Pergamon Press, Section 70

Liebermann, D., Lührs, H. & van Kaick, G. (1995) Late effects by paravascular Thorotrast deposits. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 271–274

Lindholm, C., Makelainen, I., Paile, W., Koivistoinen, A. & Salomaa, S. (1999) Domestic radon exposure and the frequency of stable or unstable chromosomal aberrations in lymphocytes. *Int. J. Radiat. Biol.* **75**, 921–928

Lindsay, S., Potter, G.D. & Chaikoff, I.L. (1957) Thyroid neoplasms in the rat: A comparison of naturally occurring and I^{131}-induced tumours. *Cancer Res.*, **17**, 183–189

Lisco, H. (1956) Bone as a critical organ for the deposition of radioactive materials. In: Wolstenholme, G.E.W. & O'Connor, C.M., eds, *Ciba Foundation Symposium on Bone Structure and Metabolism*, London, Churchill, pp. 272–283

Little, J.B. (2000) Radiation carcinogenesis. *Carcinogenesis*, **21**, 397–404

Little, J.B., Kennedy, A.R. & McGandy, R.B. (1978a) Effect of dose distribution on the induction of experimental lung cancer by alpha radiation. *Radiat. Res.*, **35**, 595–606

Little, J.B., McGandy, R.B. & Kennedy, A.R. (1978b) Interactions between polonium-210 α-radiation, benzo[*a*]pyrene, and 0.9% NaCl solution instillations in the induction of experimental lung cancer. *Cancer Res.*, **38**, 1929–1935

Little, J.B., Nagasawa, H., Pfenning, T. & Vetrovs, H. (1997) Radiation-induced genomic instability: Delayed mutagenic and cytogenetic effects of X rays and alpha particles. *Radiat. Res.*, **148**, 299–307

Littlefield, L.G., Travis, L.B., Sayer, A.M., Voelz, G.L., Jensen, R.H. & Boice, J.D., Jr (1997) Cumulative genetic damage in hematopoietic stem cells in a patient with a 40-year exposure to alpha particles emitted by thorium dioxide. *Radiat. Res.*, **148**, 135–144

Liu, Z., Lee, T.-S. & Kotek, T. J. (1992) Mortality among workers in a thorium-processing plant — A second follow-up. *Scand. J. Work Environ. Health*, **18**, 162–168

Lloyd, E.L. & Henning, C.B. (1983) Cells at risk for the production of bone tumors in radium exposed individuals: An electron microscope study. *Health Phys.*, **44** (Suppl. 1), 135–148

Lloyd, E.L., Gemmell, M.A., Henning, C.B., Gemmell, D.S. & Zabransky, B.J. (1979) Transformation of mammalian cells by alpha particles. *Int. J. Radiat. Biol.*, **36**, 467–478

Lloyd, D.C., Edwards, A.A., Prosser, J.S., Auf der Maur, A., Etzweiler, A., Weickhardt, U., Gössi, U., Geiger, L., Noelpp, U. & Rösler, H. (1986) Accidental intake of tritiated water: A report of two cases. *Radiat. Prot. Dosim.*, **15**, 191–196

Lloyd, R.D., Bruenger, F.W., Miller, S.C., Angus, W., Taylor, G.N., Jee, W.S. & Polig, E. (1991) Distribution of radium-induced bone cancers in beagles and comparison with humans. *Health Phys.*, **60**, 435–438

Lloyd, R.D., Taylor, G.N., Angus, W., Bruenger, F.W. & Miller, S.C. (1993) Bone cancer occurrence among beagles given ^{239}Pu as young adults. *Health Phys.*, **64**, 45–51

Lloyd, R.D., Taylor, G.N., Angus, W., Bruenger, F.W. & Miller, S.C. (1994a) Eye tumours and other lesions among beagles given ^{90}Sr or ^{226}Ra. *Health Phys.*, **66**, 346–349

Lloyd, R.D., Taylor, G.N., Angus, W., Miller, S.C., Bruenger, F.W. & Jee, W.S. (1994b) Distribution of skeletal malignancies in beagles given ^{239}Pu citrate. *Health Phys.*, **66**, 407–413

Lloyd, R.D., Miller, S.C., Taylor, G.N., Bruenger, F.W., Jee, W.S. & Angus W. (1994c) Relative effectiveness for bone cancer induction in beagles exposed to ^{239}Pu and some other internal emitters. *Health Phys.*, **67**, 346–353

Lloyd, R.D., Angus, W., Taylor, G.N., Bruenger, F.W. & Miller, S.C. (1995) Soft tissue tumors induced by monomeric ^{239}Pu. *Health Phys.*, **69**, 530–537

Lloyd, R.D., Miller, S.C., Taylor, G.N., Bruenger, R.W., Angus, W. & Jee, W.S.S. (1997a) Comparison of internal emitter radiobiology in animals and humans. *Health Phys.*, **72**, 100–110

Lloyd, R.D., Taylor, G.N., Miller, S.C., Bruenger, F.W. & Jee, W.S. (1997b) Bone tumor location in beagles given skeletal irradiation by ^{239}Pu or ^{226}Ra. *Health Phys.*, **73**, 684–689

Lloyd, D.C., Finnon, P., Edwards, A.A. & Haines, J.W. (1997c) Chromosome aberrations in Syrian hamsters following very low radiation doses *in vivo*. *Mutat. Res.*, **377**, 63–68

Lloyd, D.C., Moquet, J.E., Oram, S., Edwards, A.A. & Lucas, J.N. (1998) Accidental intake of tritiated water: A cytogenetic follow-up case on translocation stability and dose reconstruction. *Int. J. Radiat. Biol.*, **73**, 543–547

Lloyd, R.D., Taylor, G.N., Jee, W.S.S. & Miller, S.C. (1999a) Relative radiosensitivity of bone tumor induction among beagles as a function of age at injection of ^{239}Pu or ^{226}Ra. *Health Phys.*, **76**, 50–56

Lloyd, R.D., Miller, S.C., Taylor, G.N. & Bowman, B.M. (1999b) Is there a difference in radionuclide-induced bone tumor sensitivity between male and female beagles? *Health Phys.*, **77**, 178–182

Lomas, P.R. & Green, B.M.R. (1994) Temporal variations of radon levels in dwellings. *Radiat. Prot. Dosim.*, **56**, 323–325

Loomis, D.P. & Wolf, S.H. (1996) Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennesse, 1947–1990. *Am. J. ind. Med.*, **29**, 131–141

Lord, B.I., Molineux, G., Humphreys, E.R. & Stones, V.A. (1991) Long-term effects of plutonium-239 and radium-224 on the distribution and performance of pluripotent haemopoietic progenitor cells and their regulatory microenvironment. *Int. J. Radiat. Biol.*, **59**, 211–227

Lord, B.I., Woolford, L.B., Wang, L., Stones. V.A., McDonald, D., Lorimore, S.A., Papworth, D., Wright, E.G. & Scott, D. (1998a) Tumour induction by methyl-nitroso-urea following preconceptional paternal contamination with plutonium-239. *Br. J. Cancer*, **778**, 301–311

Lord, B.I., Woolford, L.B., Wang, L., Stones. V.A., McDonald, D., Lorimore, S.A., Papworth, D., Wright, E.G. & Scott, D. (1998b) Induction of lympho-haemopoietic malignancy: Impact of preconception paternal irradiation. *Int. J. Radiat. Biol.*, **74**, 721–728

Lord, B.I., Woolford, L.B., Wang, L., McDonald, D., Lorimore, S.A., Stones, V.A., Wright, E.G. & Scott, D. (1998c) Induction of lympho-haemopoietic malignancy: Impact of preconception paternal irradiation. *Int. J. Radiat. Biol.*, **74**, 721–728.

Lorimore, S.A., Kadhim, M.A., Pocock, D.A., Papworth, D., Stevens, D.L., Goodhead, D.T. & Wright, E.G. (1998) Chromosomal instability in the descendants of unirradiated surviving cells after α-particle irradiation. *Proc. natl Acad. Sci. USA*, **95**, 5730–5733

Lubin, J.H. (1998a) On the discrepancy between epidemiologic studies in individuals of lung cancer and residential radon and Cohen's ecologic regression. *Health Phys.*, **75**, 4–10

Lubin, J.H. (1998b) Rejoinder: Cohen's response to 'on the discrepancy between epidemiologic studies in individuals of lung cancer and residential radon and Cohen's ecologic regression'. *Health Phys.*, **75**, 29–30

Lubin, J.H. (1998c) The influence of residential radon exposure on the estimation of exposure–response trends for lung cancer in underground miners exposed to radon. *Radiat. Res.*, **150**, 259–261

Lubin, J. (1999) Discussion: Indoor radon and risk of lung cancer. *Radiat. Res.*, **151**, 105–106

Lubin, J.H. & Boice, J.D., Jr (1997) Lung cancer risk from residential radon: Meta-analysis of eight epidemiologic studies. *J. natl Cancer Inst.*, **89**, 49–57

Lubin, J.H., Boice, J.D., Jr, Edling, C., Hornung, R.W., Howe, G., Kunz, E., Kusiak, R.A., Morrison, H.I., Radford, E.P., Samet, J.M., Tirmarche, M., Woodward, A., Yao, X.S. & Pierce, D.A. (1994a) *Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Studies* (NIH Publication No. 94-3644), Bethesda, MD, National Cancer Institute

Lubin, J.H., Liang, Z.-L., Hrubec, Z., Pershagen, G., Schoenberg, J.B., Blot, W.J., Klotz, J.B., Xu, Z.-Y. & Boice, J.D., Jr (1994b) Radon exposure in residences and lung cancer among women: Combined analysis of three studies. *Cancer Causes Control*, **5**, 114–128

Lubin, J.H., Boice, J.D., Jr, Edling, C., Hornung, R.W., Howe, G.R., Kunz, E., Kusiak, R.A., Morrison, H.I., Radford, E.P., Samet, J.M., Tirmarche, M., Woodward, A., Yao, X.S. & Pierce, D.A. (1995a) Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J. natl Cancer Inst.*, **87,** 817–827

Lubin, J.H., Boice, J.D., Jr, Edling, C., Hornung, R.W., Howe, G., Kunz, E., Kusiak, R.A., Morrison, H.I., Radford, E.P., Samet, J.M., Tirmarche, M., Woodward, A. & Yao, S.X. (1995b) Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health Phys.*, **69**, 494–500

Lubin, J.H., Tomášek, L., Edling, C., Hornung, R.W., Howe, G.R., Kunz, E., Kusiak, R.A., Morrison, H.I., Radford, E.P., Samet, J.M., Tirmarche, M., Woodward, A. & Yao, X.S. (1997) Estimating lung cancer mortality from residential radon using data from low exposures of miners. *Radiat. Res.*, **147**, 126–134

Lubin, J.H., Linet, M.S., Boice, J.D., Jr, Buckley, J., Conrath, S.M., Hatch, E.E., Kleinerman, R.A., Tarone, R.E., Wacholder, S. & Robison, L.L. (1998) Case–control study of childhood acute lymphoblastic leukemia and residential radon exposure. *J. natl Cancer Inst.*, **90**, 294–300

Lucie, N.P. (1989) Radon exposure and leukaemia (Letter to the Editor). *Lancet*, **ii**, 99-100

Luebeck, E.G., Heidenreich, W.F., Hazelton, W.D., Paretzke, H.G. & Moolgavkar, S.H. (1999) Biologically based analysis of the data for the Colorado uranium miners cohort: Age, dose and dose-rate effects. *Radiat. Res.*, **152**, 339–351

Lundgren, D.L., McClellan, R.O., Thomas, R.L., Hahn, F.F. & Sanchez, A. (1974) Toxicity of inhaled $^{144}CeO_2$ in mice. *Radiat. Res.*, **58**, 448–461

Lundgren, D.L., Hahn, F.F. & McClellan, R.O. (1980a) Influence of age at the time of inhalation exposure to aerosols of $^{144}CeO_2$ on ^{144}Ce retention, dosimetry and toxicity in mice. *Health Phys.*, **38**, 643–655

Lundgren, D.L., McClellan, R.O., Hahn, F.F., Newton, G.J. & Diel, J.H. (1980b) Repeated inhalation exposure of mice to $^{144}CeO_2$. I. Retention and dosimetry. *Radiat. Res.*, **82**, 106–122

Lundgren, D.L., Hahn, F.F. & McClellan, R.O. (1982) Effects of single and repeated inhalation exposure of Syrian hamsters to aerosols of $^{144}CeO_2$. *Radiat. Res.*, **90**, 374–394

Lundgren D.L., Gillett, N.A., Hahn, F.F., Griffith, W.C. & McClellan, R.O. (1987) Effects of protraction of the alpha dose to the lungs of mice by repeated inhalation exposure to aerosols of $^{239}PuO_2$. *Radiat. Res.*, **111**, 201–224

Lundgren, D.L., Mauderly, J.L., Rebar, A.H., Gillett, N.A. & Hahn, F.F. (1991) Modifying effects of preexisting pulmonary fibrosis on biological responses of rats to inhaled $^{239}PuO_2$. *Health Phys.*, **60**, 353–363

Lundgren, D.L., Hahn, F.F., Diel, J.H. & Snipes, M.B. (1992a) Repeated inhalation exposure of rats to aerosols of $^{144}CeO_2$. I. Lung, liver, and skeletal dosimetry. *Radiat. Res.*, **132**, 312–324

Lundgren, D.L., Hahn, F.F. & Diel, J.H. (1992b) Repeated inhalation exposure of rats to aerosols of $^{144}CeO_2$. II. Effects on survival and lung, liver, and skeletal neoplasms. *Radiat. Res.*, **132**, 325–333

Lundgren, D.L., Haley, P.J., Hahn, F.F., Diel, J.H., Griffith, W.C. & Scott, B.R. (1995) Pulmonary carcinogenicity of repeated inhalation exposure of rats to aerosols of $^{239}PuO_2$. *Radiat. Res.*, **142**, 39–53

Lundgren, D.L., Hahn, F.F., Griffith, W.C., Hubbs, A.F., Nikula, K.J., Newton, G.J., Cuddihy, R.G. & Boecker, B.B. (1996) Pulmonary carcinogenicity of relatively low doses of beta-particle radiation from inhaled $^{144}CeO_2$ in rats. *Radiat. Res.*, **146**, 525–535

Lundgren, D.L., Hahn, F.F., Carlton, W.W., Griffith, W.C., Guilmette, R.A. & Gillett, N.A. (1997) Dose responses from inhaled monodisperse aerosols of $^{244}Cm_2O_3$ in the lung, liver and skeleton of F344 rats and comparison with $^{239}PuO_2$. *Radiat. Res.*, **147**, 598–612

Lüning, K.G., Frölén, H. & Nilsson, A. (1976) Genetic effects of ^{239}Pu salt injections in male mice. *Mutat. Res*., **34**, 539–542

Luz, A., Müller, W.A., Gössner, W. & Hug, O. (1979) Osteosarcoma induced by short-lived bone-seeking α emitters in mice: The role of age. *Environ. Res*., **18**, 115–119

Luz, A., Erfle, V., De Fries, E., Linzner, U., Müller, W.A., Kellerer, A.M. & Gössner, W. (1982) Comparison of osteosarcoma induction in female mice of three different strains. *Verh. Dtsch. Krebs Ges*., **3**, 483

Luz, A., Gössner, W. & Heuck, F. (1991) Bone. In: Scherer, E., Streffer, C. & Trott, K.-R., eds, *Radiopathology of Organs and Tissues*, Berlin, Springer-Verlag, pp. 67–111

Mahaffey, J.A., Parkhurst, M.A., Hui, T.E., Brownson, R.C. & Alavanja, M.C.R. (1996) Factors affecting use of CR-39 surface monitor technology to estimate past exposure to indoor radon. *J. Exposure Anal. environ. Epidemiol.*, **6**, 425–437

Mahlum, D.D. & Clarke, W.J. (1966) Neptunium-237 toxicity in the rat. I. Histopathologic and chemical observations in liver and kidney. *Health Phys*., **12**, 7–13

Mahlum, D.D. & Sikov, M.R. (1968) Distribution of cerium-144 in the fetal and newborn rat. *Health Phys.*, **14**, 127–129

Mahlum, D.D. & Sikov, M.R. (1969) Skeletal changes produced by the administrationof plutonium-239 and cerium-144 to weanling rats.. In: Sikov, M.R. & Mahlum, D.D., eds, *Radiation Biology of the Fetal and Juvenile Mammal* (CONF-690501), Springfield, VA, National Technical Information Service, pp. 567–576

Mahlum, D.D. & Sikov, M.R. (1974) Distribution and toxicity of monomeric and polymeric ^{239}Pu in immature and adult rats. *Radiat. Res.*, **60**, 75–88

Maisin, J., Maisin, J.R. & Dunjic, A. (1971) The gastrointestinal tract. In: Berdjis, C.C., ed., *Pathology of Irradiation*, Baltimore, MD, William & Wilkins, pp. 296–344

Maletskos, C.J., Keane, A.T., Telles, N.C. & Evans, R.D. (1969) Retention and absorption of ^{224}Ra and ^{234}Th and some dosimetric considerations of ^{224}Ra in human beings. In: Mays, C.W., Jee, W.S.S., Lloyd, R.D., Stover, B.J., Dougherty, J.H. & Taylor, G.N., eds, *Delayed Effects of Bone-seeking Radionuclides*, Salt Lake City, University of Utah Press, pp. 29–49

Malhotra, N. & Srivastava, P.N. (1978) Haematological effects after administration of radiophosphorus in mice: Fractionated irradiation and late effects. *Radiobiol. Radiother*., **3**, 347–352

Marsh, J.W. & Birchall, A. (2000) Sensitivity analysis of the weighted equivalent lung dose per unit exposure from radon progeny. *Radiat. Prot. Dosim.*, **87**, 167–178

Martland, H.S. (1926) Macroscopic changes in certain anemias due to radioactivity. *Arch. Pathol. Lab. Med*., **2**, 465–472

Martland, H.S. (1931) The occurrence of malignancy in radioactive persons. *Am. J. Cancer*, **15**, 2435–2516

Martland, H.S. & Martland, H.S., Jr (1950) Placental barrier in carbon monoxide, barbiturate and radium poisoning: Some original observations in humans. *Am. J. Surg.*, **80**, 270–279

Martland, H.S., Conlon, P. & Knef, J.P. (1925) Some unrecognized dangers in the use and handling of radioactive substances. *J. Am. med. Assoc*., **85**, 1769–1776

Martling, U., Mattsson, A., Travis, L.B., Holm, L.-E. & Hall, P. (1999) Mortality after long-term exposure to radioactive Thorotrast: A forty-year follow-up survey in Sweden. *Radiat. Res*., **151**, 293–299

Mason, T.M., Lord, B.I., Molineux, G. & Humphries, E.R. (1992) Alpha-irradiation of haemopoietic tissues in pre- and postnatal mice. 2. Effects of mid-term contamination with ^{239}Pu *in utero*. *Int. J. Radiat. Biol*., **61**, 393–403

Matsuda, Y., Yamada, T. & Tobari, I. (1986) Chromsome aberrations induced by tritiated water or ^{60}Co γ-rays at early pronuclear stage in mouse eggs. *Mutat. Res*., **160**, 87–93

Mauderly, J.L., Muggenburg, B.A., Hahn, F.F. & Boecker, B.B. (1980) The effects of inhaled ^{144}Ce on cardiopulmonary function and histopathology of the dog. *Radiat. Res*., **84**, 307–324

Maurer, W., Niklas, A. & Engels, A. (1950) [Permeability of the placenta for thorium ions at different stages of gestation in the rat.] *Z. ges. exp. Med*., **115**, 510–524 (in German)

Mays, C.W. (1973) Cancer induction in man from internal radioactivity. *Health Phys*., **25**, 585–592

Mays, C.W. (1982) Risk estimates for liver. In: *Critical Issues in Setting Radiation Dose Limits. Proceedings of the 17th Annual Meeting of the National Council on Radiation Protection and Measurements 8–9 April 1981*, Washington DC, National Council on Radiation Protection and Measurements, pp. 182–200

Mays, C.W. (1988) Alpha-particle-induced cancer in humans. *Health Phys*., **55**, 637–652

Mays, C.W. & Finkel, M.P. (1980) RBE of α-particles vs β-particles in bone sarcoma induction. In: *Proceedings of the 5th International Congress of IRPA*, Jerusalem, Israel Society for Radiation Protection, Vol. II, pp. 661–665

Mays, C.W. & Lloyd, R.D. (1966) ^{90}Sr and ^{89}Sr dose estimates for the fetus and infant. *Health Phys.*, **12**, 1225–1236

Mays, C.W., Lloyd, R.D., Taylor, G.N. & Wrenn, M.E. (1987) Cancer incidence and lifespan vs. α-particle dose in beagles. *Health Phys*., **52**, 617–624

Mayya, Y.S., Prasad, S.K., Nambiar, V.J., Kotrappa, P. & Somasundaram, S. (1986) Measurement of ^{220}Rn in exhaled breath of Th plant workers. *Health Phys*., **51**, 737–744

McClellan, R .O. & Bustad, L.K. (1964) Toxicity of significant radionuclides in large animals. *Ann. N.Y. Acad. Sci*., **111**, 793–811

McClellan, R.O., McKenney, J.R. & Bustad, L.K. (1962) Dosimetry of caesium-137 in sheep. *Nature*, **194**, 1145–1146

McClellan, R.O., Barnes, J.E., Boecker, B.B., Chiffelle, T.L., Hobbs, C.H., Jones, R.K., Mauderley, J.L., Pickrell, J.A. & Redman, H.C. (1970) Toxicity of beta-emitting radionuclides inhaled in fused clay particles — An experimental approach. In: Nettesheim, P., Hanna, M.J., Jr & Deatherage, J.W., eds, *Morphology of Experimental Respiratory Carcinogenesis* (AEC Symposium Series 21; CONF-700501), Oak Ridge, TN, Technical Information Services, pp. 395–415

McCunney, R.J., Masse, F. & Galanek, M. (1999) Occupational ingestion of P-32: The value of monitoring techniques to determine dose. *J. occup. environ. Med*., **41**, 878–883

McDevitt, M.R., Sgouros, G., Finn, R.D., Humm, J.L., Jurcic, J.G., Larson, S.M. & Scheinberg, D.A. (1998) Radioimmunotherapy with alpha-emitting nuclides. *Eur. J. nucl. Med.*, **25**, 1341–1351

McInroy, J.F., Kathren, R.L., Voelz, G.L. & Swint, M.J. (1991) US Transuranium Registry report on the ^{239}Pu distribution in a human body. *Health Phys.*, **60**, 307–333

McInroy, J.F., Gonzales, E.R. & Miglio, J.J. (1992) Measurements of thorium isotopes and ^{222}Ra in soft tissues and bones of a deceased Thorotrast patient. *Health Phys*., **63**, 54–71

McKay, H.A.C. (1971) *Principles of Radiochemistry*, London, Butterworths, pp. 118–120

Melo, D.R., Lipsztein, J.L., Oliveira, C.A., Lundgren, D.L., Muggenburg, B.A. & Guilmette, R.A. (1997) A biokinetic model for 137Cs. *Health Phys*., 73, 320–332

Métivier, H., Masse, R., Nolibé, D. & Lafuma, J. (1975) $^{239}PuO_2$ aerosol inhalation with emphasis on pulmonary connective tissue modifications. *Inhaled Part.*, **4**, 583–595

Métivier, H., Masse, R., Legendre, N. & Lafuma, J. (1978) Pulmonary connective tissue modifications induced by internal α irradiation. 1. Effect of time and dose on alterations following inhalation of plutonium-239 dioxide aerosol in rat. *Radiat. Res*., **75**, 385–396

Métivier, H., Wahrendorf, J. & Masse, R. (1984) Multiplicative effect of inhaled plutonium oxide and benzo(a)pyrene on lung carcinogenesis in rats. *Br. J. Cancer*, **50**, 215–221

Métivier, H., Bourges, J., Fritsch, P., Nolibe, D. & Masse, R. (1986) Gastrointestinal absorption of neptunium in primates: Effect of ingested mass, diet, and fasting. *Radiat. Res.*, **106**, 190–200

Metting, N.F., Palayoor, S.T., Macklis, R.M., Atcher, R.W., Liber, H.L. & Little, J.B. (1992) Induction of mutations by bismuth-212 α particles at two genetic loci in human B-lymphoblasts. *Radiat. Res*., **132**, 339–345

Méwissen, D.J., Rust, J.H., Haren, J. & Cluten, M.J. (1978) Assessment of dose–response relationship in carcinogenesis following low radiation dosage. In: *Late Biological Effects of Ionizing Radiation*, Vol. II (IAEA-SM-225/404), Vienna, International Atomic Energy Agency, pp. 291–313

Méwissen, D.J., Ugarte, A.S. & Rust, J.H. (1984) [Hereditary intestinal tumour observed after irradiation of multiple generations of a male germinal cell line of C57BL/6 mice.] *C.R. Soc. Biol*., **178**, 230–235 (in French)

Méwissen, D.J., Rust, J.H. & Rust, J. (1987) [Comparative incidence of reticulo-endothelial tumours in C57BL mice after exposure to tritiated water.] *C.R. Soc. Biol*., **181**, 439–444 (in French)

Meyer, G.-J., Waters, S.L., Coenen, H.H., Luxen, A., Maziere, B. & Langström, B. (1995) PET radiopharmaceuticals in Europe: Current use and data relevant for the formulation of summaries of product characteristics (SPCs). *Eur. J. nucl. Med.*, **22**, 1420–1432

Migunova, N.I., Moroz, G.S., Okladnikova, N.D., Tokarskaya, Z.B. & Khokhryakov, V.F. (1978) [Liver and spleen hemangiosarcomas in female workers of the plutonium plant.] *Bull. Radiat. Med.*, **4**, 67–72 (in Russian)

Mill, A.J., Wells, J., Hall, S.C. & Butler, A. (1996) Micronucleus induction in human lymphocytes: Comparative effects of X-rays, alpha particles, beta particles and neutrons and implications for biological dosimetry. *Radiat. Res*., **145**, 575–585

Miller, S.C., Bruenger, F.W., Kuswik-Rabiega, G. & Lloyd, R.D. (1992) Decorporation of plutonium by oral administration of a partially lipophilic polyaminocarboxylic acid. *Health Phys.*, **63**, 195–197

Miller, S.C., Bruenger, F.W., Kuswik-Rabiega, G., Liu, G. & Lloyd, R.D. (1993) Duration and dose-related effects of an orally administered, partially lipophilic polyaminocarboxylic acid on the decorporation of plutonium and americium. *J. Pharmacol. exp. Ther.*, **267**, 548–554

Miller, R.C., Randers-Pehrson, G., Geard, C.R., Hall, E.J. & Brenner, D.J. (1999) The oncogenic transforming potential of the passage of single α particles through mammalian cell nuclei. *Proc. natl Acad. Sci. USA*, **96**, 19–22

Mitchel, R.E.J., Jackson, J.S. & Heinmiller, B. (1999) Inhaled uranium ore dust and lung cancer risk in rats. *Health Phys.*, **76**, 145–155

M'Kacher, R., Schlumberger, M., Legal, J.D., Violot, D., Beron-Gaillard, N., Gaussen, A. & Parmentier, C. (1998) Biological dosimetry in thyroid cancer patients after repeated treatments with iodine-131. *J. nucl. Med.*, **39**, 825-829

Modan, B. & Lilienfeld, A.M. (1965) Polycythemia vera and leukemia. The role of radiation treatment. A study of 1222 patients. *Medicine*, **44**, 305–344

Modan, B., Padeh, B., Kallner, H., Akstein, E., Meytes, D., Czerniak, P., Ramot, B., Pinkhas, J. & Modan, M. (1970) Chromosomal aberrations in polycythemia vera. *Blood*, **35**, 28–38

Moe, A.J. (1995) Placental amino acid transport. *Am. J. Physiol.*, **268**, C1321–C1331

Moeller, D.W. (1996) Radiation sources: Consumer products. In: Hendec, W.R. & Edwards, F.M., eds, *Health Effects of Exposure to Low-level Ionizing Radiation*, Bristol, Institute of Physics, pp. 287–313

Mohelská, H., Parízek, O., Hyncica, V. & Hartlová. E. (1988) Early endosteal bone response to incorporated plutonium-238 in mice. *J. Hyg. Epidemiol. Microbiol. Immunol.*, **32**, 7–16

Mole, R.H. (1986) Leukaemia induction in man by radionuclides and some relevant experimental and human observations. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 1–13

Mole, R.H. (1990) Radon and leukaemia (Letter to the Editor). *Lancet*, **335**, 1336

Momeni, M.H., Williams, J.R., Jow, N. & Rosenblatt, L.S. (1976) Dose rates, dose and time effects of ^{90}Sr + ^{90}Y and ^{226}Ra on beagle skeleton. *Health Phys.*, **30**, 381–390

Moniz, E. (1932) [Anatomical, physiological and clinical aspects of cerebral arteriography — New Thorotrast technique.] *Rev. med. Suisse Romande*, **52**, 193–207 (in French)

Monteiro Gil, O., Oliveira, N.G., Rodrigues, A.S., Laires, R., Ferreira, T.C., Limbert, E., Léonard, A., Gerber, G. & Rueff, J. (2000) Cytogenetic alterations and oxidative stress in thyroid cancer patients after iodine-131 therapy. *Mutagenesis*, **15**, 69–75

Moolgavkar, S.H., Luebeck, E.G., Krewski, D. & Zielinski, J.M. (1993) Radon, cigarette smoke, and lung cancer: A re-analysis of the Colorado Plateau uranium miners' data. *Epidemiology*, **4**, 204–217

Morgan, J.P., Pool, R.R. & Kirsh, I.E. (1983) Comparison of radiological changes in humans and beagles with skeletal deposits of radium. *Health Phys.*, **44** (Suppl. 1), 353–363

Morgan, A., Holmes, A. & Pratley, F.W. (1990) Solubility in the rat lung of actinides associated with estuarine silt from West Cumbria. *J. Radiol. Prot.*, **10**, 135–142

Morgan, A., Haines, J.W. & Harrison, J.D. (1991) The incorporation of plutonium by the embryo and fetus of rats and guinea pigs. *Int. J. Radiat. Biol.*, **59**, 1395–1413

Morgan, W.F., Day, J.P., Kaplan, M.I., McGhee, E.M. & Limoli, C.L. (1996) Genomic instability induced by ionizing radiation. *Radiat. Res.*, **146**, 247–258

Morgenstern, H. (1995) Ecologic studies in epidemiology: Concepts, principles, and methods. *Annu. Rev. public Health*, **16**, 61–81

Mori, T., Kato, Y., Kumatori, T., Maruyama, T. & Hatakeyama, S. (1983) Epidemiological follow-up study of Japanese Thorotrast cases — 1980. *Health Phys*., **44** (Suppl. 1), 261–272

Mori, T., Kumatori, T., Hatakeyama, S., Irie, H., Mori, W., Fukutomi, K., Baba, K., Maruyama, T., Ueda, A., Iwata, S., Tamai, T. & Akita, Y. (1989) Current (1986) status of the Japanese follow-up study of the Thorotrast patients, and its relationships to the statistical analysis of the autopsy series. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology

Mori, T., Kato, Y., Matsudaira, H., Akita, Y., Fukutomi, K., Hatakeyama, S., Tanooka, H., Marayama, T. & Kumatori, T. (1995) Recent results in the first series of the Japanese follow-up study of Thorotrast patients and their relationships with statistical analyses of autopsy series. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 181–191

Mori, T., Fukutomi, K., Kato, Y., Hatakeyama, S., Machinami, R., Tanooka, H., Ishikawa, Y. & Kumatori, T. (1999a) 1998 results of the first series of follow-up studies on Japanese Thorotrast patients and their relationships to an autopsy series. *Radiat. Res*., **152**, S72–S80

Mori, T., Kido, C., Fukutomi, K., Kato, Y., Hatakeyama, S., Machinami, R. Ishikawa, Y., Kumatori, T., Sasaki, F., Hirota, Y., Kiyosawa, K., Hayashi, S., Tanooka, H. & Sobue, T. (1999b) Summary of entire Japanese Thorotrast follow-up study: Updated 1998. *Radiat. Res*., **152**, S84–S87

Moroz, G.S. (1976) [Lung cancer in occupationally exposed persons.] *Bull. Radiat. Med.*, **2**, 12–18 (in Russian)

Moroz, B.B. & Parfenov, Y.D. (1972) Metabolism and biological effects of polonium-210. In: *Atomic Energy Review*, Vienna, Internal Atomic Energy Agency, Vol. 10, pp. 175–232

Morrison, H.I., Semenciw, R.M., Mao, Y. & Wigle, D.T. (1988) Cancer mortality among a group of fluorspar miners exposed to radon progeny. *Am. J. Epidemiol*., **128**, 1266–1275

Morrison, H.I., Villeneuve, P.J., Lubin, J.H. & Schaubel, D.E. (1998) Radon-progeny exposure and lung cancer risk in a cohort of Newfoundland fluorspar miners. *Radiat. Res*., **150**, 58–65

Moskalev, J.I., Buldakov, L.A., Lyaginskaya, A.M., Ovcharenko, E.P. & Egorova, T.M. (1969) Experimental study of radionuclide transfer through the placenta and their biological action on the fetus. In: Sikov, M.R. & Mahlum, D.D., eds, *Radiation Biology of the Fetal and Juvenile Mammal* (CONF-690501), Springfield, VA, National Technical Information Service, pp. 153–160

Moskalev, Y.I., Lyaginskaya, A.M., Zalckin, G.A., Nisimov, P.G., Romanova, I.B. & Korneev, Y.Y. (1989) Carcinogenic effects in rat progeny exposed perinatally to radionuclides. In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publication No. 96), Lyon, IARC*Press*, pp. 403–419

Mountford, P.J. (1997) Risk assessment of the nuclear medicine patient. *Br. J. Radiol*., **70**, 671–684

Muggenburg, B.A., Felicetti, S.A. & Silbaugh, S.A. (1977) Removal of inhaled radioactive particles by lung lavage — A review. *Health Phys.*, **33**, 213–220

Muggenburg, B.A., Hahn, F.F., Griffith, W.C., Boecker, B.B. & Lloyd, R.D. (1995) The biological effects of ^{224}Ra injected into dogs. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium*, Singapore, World Scientific, pp. 299–305

Muggenburg, B.A., Hahn, F.F., Griffith, W.C., Lloyd, R.D. & Boecker, B.B. (1996a) The biological effects of ^{224}Ra injected into dogs. *Radiat. Res.*, **146**, 171–186

Muggenburg, B.A., Guilmette, R.A., Mewhinney, J.A., Gillett, N.A., Mauderly, J.L., Griffith, W.C., Diel, J.H., Scott, B.R., Hahn, F.F. & Boecker, B.B. (1996b) Toxicity of inhaled plutonium dioxide in beagle dogs. *Radiat. Res.*, **145**, 361–381

Muggenburg, B.A., Boecker, B.B., Hubbs, A.F., Hahn, F.F., Snipes, M.B., Diel, J.H., Newton, G.J. & Griffith, W.C. (1998) Toxicity of inhaled $^{91}YCl_3$ in dogs. *Radiat. Res.*, **150**, 212–226

Muirhead, C.R., Butland, B.K., Green, B.M.R. & Draper, G.J. (1991) Childhood leukaemia and natural radiation (Letter to the Editor). *Lancet*, **337**, 503–504

Müller, T. (1968) On the clearance of Thorotrast, a dextrin stabilized colloid. *Acta pharmacol. toxicol.*, **26**, 491–500

Müller, J. & Kusiak, R. (1989) Lung cancer risk in uranium miners. In: Harley, N.H., eds, *Radon, Proceedings of the Twenty-fourth Annual Meeting, 30–31 March, 1988*, Bethesda, MD, National Council on Radiation Protection and Measurements, pp. 12–29

Müller, W.A., Gössner, W., Hug, O. & Luz, A. (1978) Late effects after incorporation of the short-lived alpha-emitters ^{224}Ra and ^{227}Th in mice. *Health Phys.*, **35**, 33–55

Müller, W.A., Luz, A., Schäffer, E.H. & Gössner, W. (1983) The role of time-factor and RBE for the induction of osteosarcomas by incorporated short-lived bone-seekers. *Health Phys.*, **44** (Suppl. 1), 203–212

Müller, W.-U., Streffer, C., Molls, M. & Glück, L. (1987) Radiotoxicities of [^{3}H]thymidine and of [^{3}H]arginine compared in mouse embryos *in vitro*. *Radiat. Res.*, **110**, 192–198

Müller, W.A., Luz, A., Murray, A.B. & Linzner, U. (1990) Induction of lymphoma and osteosarcoma in mice by single and protracted low α doses. *Health Phys.*, **59**, 305–310

Murzina, L.D., Muksinova, K.N. & Sokhranich, A.L. (1988) [Disorders of hematopoiesis induced by plutonium-239 dioxide]. *Radiobiologiia*, **28**, 847–852 (in Russian)

Mussalo-Rauhamaa, H., Jaakkola, T., Miettinen, J.K. & Laiho, K. (1984) Plutonium in Finnish Lapps — An estimate of the gastrointestinal absorption of plutonium by man based on a comparison of the plutonium content of Lapps and southern Finns. *Health Phys.*, **46**, 549–559

Muth, H. (1989) History of the German Thorotrast studies. Motivation and development of the studies in relation to similar investigations in other countries. In: Taylor, D.M., Mays, C.M., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiation, pp. 93–97

Muth, M., Rajewsky, B., Hantke, H.-J. & Aurand, K. (1960) The normal radium content and the Ra-226/Ca ratio of various foods, drinking water and different organs and tissues of the human body. *Health Phys.*, **2**, 239–245

Nagasawa, H. & Little, J.B. (1992) Induction of sister chromatid exchanges by extremely low doses of α-particles. *Cancer Res.*, **52**, 6394–6396

Nagasawa, H. & Little, J.B. (1999) Unexpected sensitivity to the induction of mutations by very low doses of alpha-particle radiation: Evidence for a bystander effect. *Radiat. Res.*, **152**, 552–557

Naharin, A., Lubin, E. & Feige, Y. (1969) Transfer of ^{144}Ce to mouse embryos and offspring via placenta and lactation. *Health Phys.*, **17**, 717–722

Naharin, A., Feige, Y., Lubin, E. & Sadeh, T. (1974) Internal deposition of ingested cerium in suckling mice. *Health Phys.*, **27**, 207–211

Najean, Y., Deschamps, A., Dresch, C., Daniel, M.T., Rain, J.D. & Arrago, J.P. (1988) Acute leukemia and myelodysplasia in polycythemia vera. A clinical study with long-term follow-up. *Cancer*, **61**, 89–95

Narra, V.R., Howell, R.W., Thank, K.H. & Rao, D.V. (1991) Radiotoxicity of ^{125}I-iododeoxyuridine in pre-implantation mouse embryos. *Int. J. Radiat. Biol*., **60**, 525–532

Narra, V.R., Harapanhalli, R.S., Howell, R.W., Sastry, K.S.R. & Rao, D.V. (1994) Vitamins as radioprotectors *in vivo*. I. Protection by vitamin C against internal radionuclides in mouse testes: Implications to the mechanism of damage caused by the Auger effect. *Radiat. Res*., **137**, 394–399

National Academy of Sciences (1991) *Comparative Dosimetry of Radon in Mines and Homes*, Washington DC, National Academy Press

National Cancer Institute (1997) *Estimated Exposures and Thyroid Doses Received by the American People from Iodine-131 in Fallout Following Nevada Atmospheric Nuclear Bomb Tests* (NIH Publication No. 97-4264), Bethesda, MD, US Department of Health and Human Services, National Institutes of Health

National Council on Radiation Protection and Measurements (1977) *Protection of the Thyroid Gland in the Event of Releases of Radioiodine* (NCRP Report No. 55), Bethesda, MD

National Council on Radiation Protection and Measurements (1979) *Tritium and Other Radionuclide Labelled Organic Compounds Incorporated in Genetic Material* (NCRP Report 63), Bethesda, MD

National Council on Radiation Protection and Measurements (1985) *Induction of Thyroid Cancer by Ionizing Radiation. Recommendations of the National Council on Radiation Protection and Measurements* (NCRP Report No. 80), Bethesda, MD

National Council on Radiation Protection and Measurements (1987a) *Ionizing Radiation Exposure of the Population of the United States* (NCRP Report No. 93), Bethesda, MD

National Council on Radiation Protection and Measurements (1987b) *Genetic Effects from Internally Deposited Radionuclides* (NCRP Report 89), Bethesda, MD

National Council on Radiation Protection and Measurements (1991) *Some Aspects of Strontium Radiobiology* (NCRP Report No. 110), Bethesda, MD

National Council on Radiation Protection and Measurements (1998) *Radionuclide Exposure of the Embryo Fetus* (NCRP Report 128), Bethesda, MD

National Radiological Protection Board (2000) *Health Risks from Radon*, Oxford

National Research Council (1991) *Panel on Dosimetric Assumptions Affecting the Application of Radon Risk Estimates. Comparative Dosimetry of Radon in Mines and Homes*, Washington DC, National Academy Press

Negri, E., Ron, E., Franceschi, S., Dal Maso, L., Mark, S.D., Preston-Martin, S., McTiernan, A., Kolonel, L., Kleinerman, R., Land, C., Jin, F., Wingren, G., Galanti, M.R., Hallquist, A., Glattre, E., Lund, E., Levi, F., Linos, D., Braga, C. & La Vecchia, C. (1999) A pooled analysis of case–control studies of thyroid cancer. I. Methods. *Cancer Causes Control*, **10**, 131–142

Nekolla, E.A., Kellerer, A.M., Kuse-Isingschulte, M., Eder, E. & Spiess, H. (1999) Malignancies in patients treated with high doses of radium-224. *Radiat. Res*., **152**, S3–S7

Nekolla, E.A., Kreisheimer, M., Kellerer, A.M., Kuse-Isingschulte, M., Gössner, W. & Spiess, H. (2000) Induction of malignant bone tumors in radium-224 patients: Risk estimates based on the improved dosimetry. *Radiat. Res*., **153**, 93–103

Neton, J., Lo Sasso, T., Cohen, N. & Wrenn, M.E. (1979) *Cross-placental Transfer of $^{243/244}$Cm in the Baboon* (COO-3382-18), New York, New York University, Institute of Environmental Medicine, pp. V1–V6

Nikiforov, Y. & Gnepp, D.R. (1994) Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991–1992) from the Republic of Belarus. *Cancer*, **74**, 748–766

Nikipelov, B.V., Lizlov, A.F. & Koshurnikova, N.A. (1990) [The experience of the first nuclear enterprise (exposure levels and personnel health).] *Priroda*, **2**, 30–38 (in Russian)

Nikolaevskaya, N.G., Sokhranich, A.L., Uriadnitskaia, T.I. & Muksinova, K.N. (1988) [Structural chromosomal damages in myelokaryocytes exposed to plutonium-239 dioxide.] *Radiobiologiia*, **28**, 509–512 (in Russian)

Nikula, K.J., Muggenburg, B.A., Chang, I.-Y., Griffith, W.C., Hahn, F.F. & Boecker, B.B. (1995) Biological effects of ^{137}CsCl injected in beagle dogs. *Radiat. Res.*, **142**, 347–361

Nikula, K.J., Muggenburg, B.A., Griffith, W.C., Carlton, W.W., Fritz, T.E. & Boecker, B.B. (1996) Biological effects of ^{137}CsCl injected in beagle dogs of different ages. *Radiat. Res.*, **146**, 536–547

Nilsson, A. (1970) Pathologic effects of different doses of radiostrontium in mice. Dose effect relationship in ^{90}Sr-induced bone tumours. *Acta radiol. ther. phys. biol*., **9**, 155–176

Nilsson, A. (1971) Radiostrontium-induced carcinomas of the external ear. *Acta radiol. ther. phys. biol.*, **10**, 321–328

Nilsson, A. & Broomé-Karlsson, A. (1976) The pathology of americium-241. *Acta radiol. ther. phys. biol*., **15**, 49–70

Nilsson, A., Bierke, P., Walinder, G. & Broomé-Karlsson, A. (1980) Age and dose related carcinogenicity of ^{90}Sr. *Acta radiol. oncol*., **19**, 223–228

Nofal, M.M. & Beierwaltes, W.H. (1964) Persistent chromosomal aberrations following radioiodine therapy. *J. nucl. Med*., **5**, 840–850

Nolibe, D., Maase, R. & Lafuma, J. (1981) The effect of neonatal thymectomy on lung cancers induced by rats by plutonium dioxide. *Radiat. Res.*, **87**, 90–99

Nussbaum, E. & Hursh, J.B. (1957) Rn-222 solubility in rat tissues. *Science*, **125**, 552–553

Nusynowitz, M.L. (1999) Thyroid imaging. *Lippincotts prim. Care Pract.*, **3**, 546–555

Ober, S., Bannasch, P. & Spiethoff, A., (1994) Precancerous hepatic lesions induced by fractionated neutron radiation and Thorotrast. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides*, Singapore, World Scientific, pp. 365–368

OECD (Organization for Economic Cooperation and Development) (1996) *Fourth Annual Report: Occupational Exposures at Nuclear Power Plants: 1969–1994*, Paris, Nuclear Energy Agency

OECD (Organization for Economic Cooperation and Development) (1998) *Sixth Annual Report: Occupational Exposures at Nuclear Power Plants: 1986–1996*, Paris, Nuclear Energy Agency

Oghiso, Y. & Yamada, Y. (1999) Carcinogenesis in mice after injection of soluble plutonium citrate. *Radiat. Res*., **152**, S27–S30

Oghiso, Y., Yamada, Y., Ishigure, N., Fukuda, S., Iida, H., Yamada, Y., Sato, H., Koizumi, A. & Inaba, J. (1994a) High incidence of malignant lung carcinomas in rats after inhalation of $^{239}PuO_2$. *J. Radiat. Res*., **35**, 222–235

Oghiso, Y., Yamada, Y. & Iida, H. (1994b) Differential induction of bone and hematopoietic tumors in C3H mice after the injection of ^{239}Pu citrate. *J. Radiat. Res*., **35**, 236–247

Oghiso, Y., Yamada, Y. & Iida H. (1997) High frequency of leukemic lymphomas with osteosarcomas but no myeloid leukaemias in C3H mice after ^{239}Pu citrate injection. *J. Radiat. Res*., **38**, 77–86

Oghiso, Y., Yamada, Y., Iida, H. & Inaba, J. (1998) Differential dose responses of pulmonary tumour types in the rat after inhalation of plutonium dioxide aerosols. *J. Radiat. Res.*, **39**, 61–72

Oka, M. (1930) [Clinical use of roentgenologic imagery, a new method for representation of spleen and liver (‘splenography’).] *Fortschr. geb. Röntgenstrahl*., **41**, 892–898 (in German)

Omar, R.Z., Barber, J.A. & Smith, P.G. (1999) Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br. J. Cancer*, **79**, 1288–1301

O’Mara, R.E. (1976) Skeletal scanning in neoplastic disease. *Cancer*, **37**, 480–486

Osechinsky, I.V., Martirosov, A.R., Proshin, A.D., Michailov, G.N., Miliutina, G.I., Singerman, B.V., Abramova, M.M., Shorin, D.U., Kobeliatsky, V.F., Abdulkadyrov, K.M. & Samuskevitch, I.G. (1994) [Epidemiological register of leukaemia and other hemoblastoses in Bryansky district as an instrument of investigation of consequences of Chernobyl accident]. *Gematol. Tranfuziol.*, **3**, 32–36 (in Russian)

Osgood, E.E. (1964) Contrasting incidence of acute monocytic and granulocytic leukemias in ^{32}P treated patients with polycythemia vera and chronic lymphocytic leukemia. *J. Lab. clin. Med*., **64**, 560–573

Otake, M. & Schull, W.J. (1990) Radiation-related posterior lenticular opacities in Hiroshima and Nagasaki atomic bomb survivors based on the DS86 dosimetry system. *Radiat. Res.*, **121**, 3–13

Ovcharenko, E..P. & Fomina, T.P. (1982) [Effects of intravenous administration of ^{237}Np oxalate on gonads of rats and on their progeny.] *Radiobiologiia*, **22**, 374–378 (in Russian)

Ovcharenko, E.P. & Fomina, T.P. (1983) [Combined effect of external γ-irradiation and intratracheal administration of ^{239}Pu on the reproductive function of female rats and on their progeny.] *Radiobiologiia*, **23**, 110–113 (in Russian)

Pacchierotti, F., Andreozzi, U., Russo, A. & Metalli, P. (1983) Reciprocal translocations in ageing mice and in mice with long-term low-level ^{239}Pu contamination. *Int. J. Radiat. Biol*., **43**, 445–450

Pacini, F., Vorontsova, T., Demidchik, E.P., Molinaro, E., Agate, L., Romei, C., Shavrova, E., Cherstvoy, E.D., Ivashkevitch, Y., Kuchinskaya, E., Schlumberger, M., Ronga, G., Filesi, M. & Pinchera, A. (1997) Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: Comparison with naturally-occurring thyroid carcinoma in Italy and France. *J. clin. Endocrinol. Metab*., **82**, 3563–3569

Padovani, L., Caporossi, D., Tedeschi, B., Vernole, P., Nicoletti, B. & Mauro, F. (1993) Cytogenetic study in lymphocytes from children exposed to ionizing radiation after the Chernobyl accident. *Mutat. Res*., **319**, 55–60

Papke, K., Kellerer, A.M., Korber, D., Nekolla, E., Roedler-Vogelsang, T. & Spiess, H. (1995) Mammary carcinomas in patients treated with Rn-224. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 249–254

Paquet, F., Poncy, J.-L., Ham, G.J., Prosser, S.L. & Harrison, J.D. (1998) Transfer of polonium, neptunium, plutonium and americium to the primate fetus. *Radiat. Prot. Dosim*., **79**, 303–306

Parfenov, Y.D. & Poluboyarinova, Z.I. (1973) Polonium-210 metabolism in rabbits after a single intravenous and intratracheal injection. *Int. J. Radiat. Biol*., **23**, 487–493

Park, J.F., Lund, J.E., Ragan, H.A., Hackett, P.L. & Frazier, M.E. (1976) Bone tumours induced by inhalation of $^{238}PuO_2$ in dogs. *Recent Results Cancer Res*., **54**, 17–35

Park, J.F., Buschbom, R.L., Dagle, G.E., James, A.C., Watson, C.R. & Weller, R.E. (1997) Biological effects of inhaled $^{238}PuO_2$ in beagles. *Radiat. Res*., **148**, 365–381

Parr, R.M. (1968) The radioactivity of Thorotrast and its in vitro distribution between the various physical phases. In: *The Dosimetry and Toxicity of Thorotrast. IAEA Meeting Vienna, 4–7 October 1965* (IAEA Technical Report 106), Vienna, International Atomic Energy Agency, pp. 5–19

Parshkov, E.M., Chebotareva, I.V., Sokolov, V.A. & Dallas, C.E. (1997) Additional thyroid dose factor from transportation sources in Russia after the Chernobyl disaster. *Environ. Health Perspectives*, **105** (Suppl. 6), 1491–1496

Pauwels, E.K.J., Thomson, W.H., Blokland, J.A.K., Schmidt, M.E., Bourguignon, M., El-Maghraby, T.A.F., Broerse, J.J. & Harding, L.K. (1999) Aspects of fetal thyroid dose following iodine-131 administration during early stages of pregnancy in patients suffering from benign thyroid disorders. *Eur. J. nucl. Med.*, **26**, 1453–1457

Percy, C. & Sobin, L. (1983) Surveillance, epidemiology, and end results lung cancer data applied to the World Health Organization's classifications of lung tumors. *J. natl Cancer Inst.*, **70**, 663–666

Pershagen, G., Liang, Z.-H., Hrubec, Z., Svensson, C. & Boice, J.D., Jr (1992) Residential radon exposure and lung cancer in Swedish women. *Health Phys.*, **63**, 179–186

Pershagen, G., Åkerblom, G., Axelson, O., Clavensjö, B., Damber, L., Desai, G., Enflo, A., Lagarde, F., Mellander, H., Svartengren, M. & Swedjemark, G.A. (1994) Residential radon exposure and lung cancer in Sweden. *New Engl. J. Med.*, **330**, 159–164

Pesternikov, V.M., Nifatov, A.P. & Surov, A.I. (1972) [Time of possible occurrence of bone tumors in human exposed to plutonium-239 (preliminary communication).] *Bull. Radiat. Med*., **2**, 24–28 (in Russian)

Peterson, L.E., Zhumadilov, Z.S., Kripalani, S., Progulo, Y.V., Wheeler, T.M., Gusev, B.I., Arem, R., Yonov, S. & Weinberg, A.D. (1998) Diagnosis of benign and malignant thyroid disease in the East Kazakhstan region of the Republic of Kazakhstan: A case review of pathological findings for 2525 patients. *Cancer Res. Ther. Control*., **5**, 307–312

Peto, J. (1990) Radon and the risks of cancer. *Nature*, **345**, 389–390

Piantadosi, S. (1994) Invited commentary: Ecologic biases. *Am. J. Epidemiol*., **139**, 761-764

Pickrell, J.A., Diel, J.H., Slauson, D.O., Halliwell, W.H. & Mauderly, J.L. (1983) Radiation-induced pulmonary fibrosis resolves spontaneously if dense scars are not formed. *Exp. mol. Pathol*., **38**, 22–32

Pietrzak-Flis, Z., Radwan, I., Major, Z. & Kowalska, M. (1982) Tritium incorporation in rats chronically exposed to tritiated food or tritiated water for three successive generations. *J. Radiat. Res.*, **22**, 434–442

Pinel, J., Fearn, T., Darby, S.C. & Miles, J.C.H. (1995) Seasonal correction factors for indoor radon measurements in the United Kingdom. *Radiat. Protect. Dosim.*, **58**, 127–132

Plotnikova, L.A. (1965) [Biodistribution of ^{239}Pu.] *Bull. Radiat. Med.*, **1**, 9–16 (in Russian)

Pochin, E.E. (1983) *Sizewell B Inquiry. The Biological Bases of the Assumptions Made by NRPB in the Calculation of Health Effects. Proof of Evidence* (NRPB/P/2 (rev.) and NRPB/P/2 (rev.)/Add. 1), Chilton, National Radiological Protection Board

Polednak, A.P. (1980) Fertility of women after exposure to internal and external radiation. *J. environ. Pathol. Toxicol*., **4**, 457–470

Polednak, A.P. & Frome, E.L. (1981) Mortality among men employed between 1943 and 1947 at a uranium-processing plant. *J. occup. Med.*, **23**, 169–178

Polednak, A.P., Stehney, A.F. & Lucas H.F. (1983) Mortality among male workers at a thorium-processing plant. *Health Phys*., **44** (Suppl. 1), 239–251

Pomerantseva, M.D., Ramaiya, L.K., Vilkina, G.A., Shevchenko, V.A., Vasilenko, I.J., Lyaginskaya. A.M. & Istomina, A.G. (1983) Genetic effects of radiocarbon in reproductive cells of male mice. *Mutat. Res*., **122**, 341–346

Pomerantseva, M.D., Ramaiya, L.K., Shevchenko, V.A., Vilkina, G.A., Lyaginskaya, A.M. & Dementiev, S.I. (1987a) [Induction of genetic damage by ^{238}Pu incorporated by germ cells of male mice.] *Radiobiologiia*, **27**, 206–211 (in Russian)

Pomerantseva, M.D., Shevchenko, V.A., Ramaiya, L.K., Vilkina, G.A., Lyaginskaya, A.M. & Goloshchapov P.V. (1987b) [The cytogenetic effect of ^{238}Pu-α-radiation on germ cells of male mice.] *Radiobiologiia*, **27**, 344–348 (in Russian)

Pomerantseva, M.D., Ramaiya, L.K., Shevchenko, V.A., Vilkina, G.A. & Lyaginskaya, A.M. (1988) [Evaluation of genetic consequences of incorporation of ^{238}Pu into the mammalian organism.] *Genetika*, **29**, 671–681 (in Russian)

Pool, R.R., Morgan, J.P., Parks, N.J., Farnham, J.E. & Littman, M.S. (1983) Comparative pathogenesis of radium-induced intracortical bone lesions in humans and beagles. *Health Phys*., **44** (Suppl. 1), 155–177

Popp, W., Vahrenholz, C., Schuster, H., Wiesner, B., Bauer, P., Täuscher, F., Plogmann, H., Morgenroth, K., Konietzko, N. & Norpoth, K. (1999) *p53* mutations and codon 213 polymorphism of *p53* in lung cancers of former uranium miners. *J. Cancer Res. Clin. Oncol.*, **125**, 309–312

Popplewell, D.S., Harrison, J.D. & Ham, G.J. (1991) Gastrointestinal absorption of neptunium and curium in humans. *Health Phys*., **60**, 797–805

Popplewell, D.S., Ham, G.J., McCarthy, W. & Lands, C. (1994) Transfer of plutonium across the human gut and its urinary excretion. *Radiat. Prot. Dosim*., **53**, 241–244

Prabhavathi, P.A., Fatima, S.K., Padmavathi, P., Kumari, C.K. & Reddy, P.P. (1995) Sister-chromatid exchanges in nuclear fuel workers. *Mutat. Res*., **347**, 31–35

Prabhavathi, P.A., Fatima, S.K., Rao, M.S. & Reddy, P.P. (2000) Analysis of chromosomal aberration frequencies in the peripheral blood lymphocytes of smokers exposed to uranyl compounds. *Mutat. Res.*, **466**, 37–41

Preston, D.L., Kusumi, S., Tomonaga, M., Izumi, S., Ron, E., Kuramoto, A., Kamada, N., Dohy, H., Matsuo, T., Nonaka, H., Thompson, D.E., Soda, M. & Mabuchi, K. (1994) Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma, and multiple myeloma 1950–1987. *Radiat. Res.*, **137**, S68–S97

Priest, N.D. (1990) The distribution and behaviour of heavy metals in the skeleton and body: Studies with bone-seeking radionuclides. In: Priest, N.D. & Van de Vyver, F.L., eds, *Trace Metals and Fluoride in Bones and Teeth*, Boca Raton, FL, CRC Press, pp. 83–139

Priest, N.D., Newton, D., Day, J.P., Talbot, R.J. & Warner, A.J. (1995a) Human metabolism of aluminium-26 and gallium-67 injected as citrates. *Hum. exp. Toxicol.*, **14**, 287–293

Priest, N.D., Freemont, A., Humphreys, J.A.H. & Kathren, R.L. (1995b) Histopathology and ^{241}Am microdistribution in skeletal USTUR Case 246. *Health Phys.*, **69**, 330–337

Prise, K.M., Davies, S. & Michael, B.D. (1987) The relationship between radiation-induced DNA double-strand breaks and cell kill in hamster V79 fibroblasts irradiated with 250 kVp X-rays, 2.3 MeV neutrons or ^{238}Pu alpha-particles. *Int. J. Radiat. Biol.*, **52**, 893–902

Prise, K.M., Folkard, M., Davies, S. & Michael, B.D. (1989) Measurement of DNA damage and cell killing in Chinese hamster V79 cells irradiated with aluminum characteristic ultrasoft X-rays. *Radiat. Res.*, **117**, 489–499

Prisyazhniuk, A., Pjatak, O.A., Buzanov, V.A., Reeves, G.K. & Beral, V. (1991) Cancer in the Ukraine, post-Chernobyl (Letter to the Editor). *Lancet*, **338**, 1334–1335

Prisyazhniuk, A., Gristchenko, V., Zakordonets, V., Fouzik, N., Slipeniuk, Y. & Ryzhak, I. (1995) The time trends of cancer incidence in the most contaminated regions of the Ukraine before and after the Chernobyl accident. *Radiat. environ. Biophys.*, **34**, 3–6

Prisyazhniuk, A., Fedorenko, Z., Okeanov, A., Ivanov, V., Starinsky, V., Gristchenko, V. & Remennik, L. (1996) Epidemiology of cancer in population living in contaminated territories of Ukraine, Belarus, Russia after the Chernobyl accident. In: Karaoglou, A., Desmet, G., Kelly, G.N. & Menzel, H.G., eds, *The Radiological Consequences of the Chernobyl Accident. Proceedings of the First International Conference, Minsk, Belarus, 18 to 22 March 1996* (EUR 16544 EN), Luxembourg, Office for Official Publications of the European Communities, pp. 909–921

Prosser, J.S., Izard, B.E., Brown, J.K., Hetherington, E.L., Lambrecht, R.M., Cato, L., Wallace, M., Whitwell, J., Wiseman, J. & Hoschl, R. (1993) Induction of micronuclei in peripheral blood lymphocytes of patients treated for rheumatoid or osteo-arthritis of the knee with dysprosium-165 hydroxide macroaggregates or yttrium-90 silicate. *Cytobios*, **73**, 7–15

Prosser, S.L., McCarthy, W.M. & Lands, C. (1994) The plutonium content of human fetal tissue and implications for fetal dose. *Radiat. Prot. Dosim.*, **55**, 49–55

Przygodzki, R.M., Finkelstein, S.D., Keohavong, P., Zhu, D., Bakker, A., Swalsky, P.A., Soini, Y., Ishak, K.G. & Bennett, W.P. (1997) Sporadic and thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations in K-*ras*-2. *Lab. Invest.*, **76**, 153–159

Purrott, R.J., Edwards, A.A., Lloyd, D.C. & Stather, J.W. (1980) The induction of chromosome aberrations in human lymphocytes by *in vitro* irradiation with α-particles from plutonium-239. *Int. J. Radiat. Biol.*, **38**, 277–284

Qiao, Y.-L., Taylor, P.R., Yao, S.-X., Schatzkin, A., Mao, B.-L., Lubin, J., Rao, J.-Y., McAdams, M., Xuan, X.-Z. & Li, J.-Y. (1989) Relation of radon exposure and tobacco use to lung cancer among tin miners in Yunnan province, China. *Am. J. ind. Med.*, **16**, 511–521

Raabe, O.G., Parks, N.J. & Book, S.A. (1981) Dose–response relationships for bone tumours in beagles exposed to ^{226}Ra and ^{90}Sr. *Health Phys*., **40**, 863–880

Raabe, O.G., Book, S.A. & Parks, N.J. (1983) Lifetime bone cancer dose–response relationships in beagles and people from skeletal burdens of ^{226}Ra and ^{90}Sr. *Health Phys*., **44** (Suppl. 1), 33–48

Radford, E.P., Jr & Hunt, V.R. (1964) Polonium-210: A volatile radioelement in cigarettes. *Science*, **143**, 247–249

Radford, E.P. & St Clair Renard, K.G. (1984) Lung cancer in Swedish iron miners exposed to low doses of radon daughters. *New Engl. J. Med*., **310**, 1485–1494

Radt, P. (1930) [A new method for roentgenologic imagery of liver and spleen by injection of a contrast medium (hepato-splenography).] *Med. Klin.*, **51**, 1888–1891 (in German)

Rajewsky, B., Belloch-Zimmermann, V., Löhr, E. & Stahlhofen, W. (1965) ^{226}Ra in human embryonic tissue, relationship of activity to the stage of pregnancy, measurement of natural ^{226}Ra occurrence in the human placenta. *Health Phys*., **11**, 161–169

Raju, M.R., Carpenter, S.G., Chmielewski, J.J., Schillaci, M.E., Wilder, M.E., Freyer, J.P., Johnson, N.F., Schor, P.L. & Sebring, R.J. (1987) Radiobiology of ultrasoft X rays. *Radiat. Res*., **110**, 396–412

Rallison, M.L., Dobyns, B.M., Keating, F.R., Rall, J.E. & Tyler, F.H. (1974) Thyroid disease in children. A survey of subjects potentially exposed to fallout radiation. *Am. J. Med.*, **56**, 457–463

Rallison, M.L., Lotz, T.M., Bishop, M., Divine, W., Haywood, K., Lyon, J.L. & Stevens, W. (1990) Cohort study of thyroid disease near the Nevada Test Site: A preliminary report. *Health Phys*., **59**, 739–746

Rathke, F.W. (1954) [Early and late damage after treatment with Peteosthor]. *Münch. med. Wschr*., **96**, 884–886 (in German)

Reincke, U., Burlington, H., Cronkite, E.P., Hillman, M & Laissue, J. (1975) Selective damage to erythroblasts by ^{55}Fe. *Blood*, **45**, 801–810

Reist, C.J., Foulon, C.F., Alston, K., Bigner, D.D. & Zalutsky, M.R. (1999) Astatine-211 labeling of internalizing anti-EGFRvIII monoclonal antibody using N-succinimidyl-5-[211At]astato-3-pyridinecarboxylate. *Nucl. Med. Biol*., **26**, 405–411

Rencova, J., Volf, V., Jones, M.M. & Singh, P.K. (1993) Relative effectiveness of dithiol and dithiocarbamate chelating agents in reducing retention of polonium-210 in rats. *Int. J. Radiat. Biol.*, **63**, 223–232

Rencova, J., Volf, V., Jones, M.M., Singh, P.K. & Filgas, R. (1995) Bis-dithiocarbamates: Effective chelating agents for mobilization of polonium-210 from rat. *Int. J. Radiat. Biol.*, **67**, 229–234

Reyes, M., Wilkinson, G.S., Tietjen, G., Voelz, G.L., Acquavella, M.S. & Bistline, R. (1984) Brain tumors at a nuclear facility. *J. occup. Med.*, **26**, 721–724

Riches, A.C., Herceg, Z., Bryant, P.E., Stevens, D.L. & Goodhead, D.T. (1997) Radiation-induced transformation of SV40-immortalized human thyroid epithelial cells by single exposure to plutonium α-particles *in vitro*. *Int. J. Radiat. Biol*., **72**, 515–521

Richter, H.E., Lohrer, H.D., Hieber, L., Kellerer, A.M., Lengfelder, E. & Bauchinger, M. (1999) Microsatellite instability and loss of heterozygosity in radiation-associated thyroid carcinomas of Belarussian children and adults. *Carcinogenesis*, **20**, 2247–2251

Riddell, A.E., Battersby, W.P., Peace, M.S. & Strong, R. (2000) The assessment of organ doses from plutonium for an epidemiological study of the Sellafield workforce. *J. Radiol. Protect.*, **20**, 275–286

Rigo, P., Paulus, P., Kaschten, B.J., Hustinx, R., Bury, T., Jerusalem, G., Benoit, T. & Foidart-Willems, J. (1996) Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur. J. nucl. Med.*, **23**, 1641–1674

Ritz, B. (1999) Radiation exposure and cancer mortality in uranium processing workers. *Epidemiology*, **10**, 531–538

Rivera, J. (1963) Strontium–calcium discrimination by the human placenta. *Nature*, **200**, 269–270

Robbins, J. & Adams, W.H. (1989) Radiation effects in the Marshall Islands. In: Nagataki, S., ed., *Radiation and the Thyroid, Proceedings of The 27th Annual Meeting of the Japanese Nuclear Medicine Society, Nagasaki, October 1–3, 1987*, Amsterdam, Excerpta Medica, pp. 11–24

Robertson, J.B., Koehler, A., George, J. & Little, J.B. (1983) Oncogenic transformation of mouse BALB/3T3 cells by plutonium-238 alpha particles. *Radiat. Res.*, **96**, 261–274

Robins, M.W. (1990) ^{224}Ra-induced osteopenia in male CBA mice. *Calcif. Tiss. int.*, **46**, 94–100

Rochalska, M. & Szot, Z. (1977) The incorporation of organically-bound tritium of food into some organs of the rat. *Int. J. Radiat. Biol.*, **31**, 391–395

Roedler, H.D. (1987) Assessment of fetal activity concentration and fetal dose for selected radionuclides based on animal and human data. In*:* Gerber, G.B., Métivier, H. & Smith, H., eds, *Age-related Factors in Radionuclide Metabolism and Dosimetry*, Dordrecht, Martinus Nijhoff, pp. 327–337

Ron, E., Lubin, J.H., Shore, R.E., Mabuchi, K., Modan, B., Pottern, L.M., Schneider, A.B., Tucker, M.A. & Boice, J.D., Jr (1995) Thyroid cancer after exposure to external radiation: A pooled analysis of seven studies. *Radiat. Res.*, **141**, 259–277

Ron, E., Doody, M.M., Becker, D.V., Brill, A.B., Curtis, R.E., Goldman, M.B., Harris, B.S.H., III, Hoffman, D.A., McConahey, W.M., Maxon, H.R., Preston-Martin, S., Warshauer, M.E., Wong, L., Boice, J.D., Jr for the Cooperative Thyrotoxicosis Therapy Follow-up Study Group (1998) Cancer mortality following treatment for adult hyperthyroidism. *J. Am. med. Assoc.*, **280**, 347–355

Rönnbäck, C. (1979) Effect of ^{90}Sr on ovaries of foetal mice depending on time for administration during pregnancy. *Acta radiol. oncol.*, **18**, 225–234

Rönnbäck, C. (1981a) Influence of ^{90}Sr-contaminated milk on the ovaries of foetal and young mice. *Acta radiol. oncol.*, **20**, 131–135

Rönnbäck, C. (1981b) Disturbances of fertility in female mice ^{90}Sr-contaminated as foetuses. *Acta radiol. oncol.*, **20**, 337–343

Rönnbäck, C. & Nilsson, A. (1982) Neoplasms in ovaries of CBA mice ^{90}Sr-treated as foetuses *Acta radiol. oncol.*, **21**, 121–128

Rönnbäck, C., Henricson, B. & Nilsson (1971) Effect of different doses of ^{90}Sr on ovaries of the foetal mouse. *Acta radiol.*, **Suppl. 310**, 200–209

Rooney, C., Beral, V., Maconochie, N., Fraser, P. & Davies, G. (1993) Case–control study of prostatic cancer in employees of the United Kingdom Atomic Energy Authority. *Br. med. J.*, **307**, 1391–1397

Roscoe, R.J. (1997) An update of mortality from all causes among white uranium miners from the Colorado Plateau study group. *Am. J. ind. Med.*, **31**, 211–222

Roscoe, R.J., Steenland, K., Halperin, W.E., Beaumont, J.J. & Waxweiler, R.J. (1989) Lung cancer mortality among nonsmoking uranium miners exposed to radon daughters. *J. Am. med. Assoc.*, **262**, 629–633

Roscoe, R.J., Deddens, J.A., Salvan, A. & Schnorr, T.M. (1995) Mortality among Navajo uranium miners. *Am. J. public Health*, **85**, 535–540

Rosemann, M., Milner, A. & Lambert, B.E. (1999) Chromosomal instability in haemopoietic cells of the foetus, mother and offspring after *in utero* irradiation of the CBA/Ca mouse. *Int. J. Radiat. Biol.*, **75**, 601–607

Rowland, R.E. (1994) *Radium in Humans: A Review of US Studies* (Report ANL/ER-3), Argonne, IL, Argonne National Laboratory.

Rowland, R.E. (1997) Bone sarcoma in humans induced by radium: A threshold response? *Radioprotection*, **32**, C1-331–C1-338

Rowland, R.E. & Marshall, J.H. (1959) Radium in human bone: The dose in microscopic volumes of bone. *Radiat. Res.*, **11**, 299–313

Rowland, R.E., Stehney, A.F., Brues, A.M., Littman, M.S., Keane, A.T., Patten, B.C. & Shanahan, M.M. (1978a) Current status of the study of ^{226}Ra and ^{228}Ra in humans at the Center for Human Radiobiology. *Health Phys.*, **35**, 159–166

Rowland, R.E., Stehney, A.F. & Lucas, H.F., Jr (1978b) Dose–response relationships for female radium dial workers. *Radiat. Res.*, **76**, 368–383

Rowland, R.E., Stehney, A.F. & Lucas, H.F. (1983) Dose–response relationships for radium-induced bone sarcomas. *Health Phys.*, **44** (Suppl. 1), 15–31

Rowland, R.E., Lucas, H.F. & Schlenker, R.A. (1989) External radiation doses received by female radium dial painters. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiation, pp. 67–72

Royal, H.D. (1999) Relative biological effectiveness of external radiation vs. I-131: Review of animal data. In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer*, Singapore, World Scientific, pp. 201–207

Rubin, P. & Casarett, G.W. (1972) A direction for clinical radiation pathology, the tolerance dose. In: Vaeth, J.M., ed., *Frontiers of Radiation Therapy and Oncology*, Vol. 6, Basel/Baltimore, Karger/University Park Press, pp. 1–16

Rundo, J. (1956) The radioactivity of Thorotrast. *Phys. Med. Biol.*, **1**, 138

Rundo, J. (1958) *Measurements and Dosimetry of Radioactive Isotopes Deposited within the Human Body with Special Reference to Colloidal Thorium Dioxide Following Intravenous Injection*, Thesis, University of London

Rundo, J. (1964) A survey of the metabolism of caesium in man. *Br. J. Radiol.*, **37**, 108–114

Rundo, J. & Turner, F.M. (1992) On the biological half-life of caesium in pregnant women and in infants. *Radiat. Prot. Dosim.*, **41**, 211–216

Ruosteenoja, E. (1991) *Indoor Radon and Risk of Lung Cancer: An Epidemiologic Study in Finland*, Doctoral Dissertation, Helsinki, Department of Public Health, University of Tampere, Helsinki, Finnish Government Printing Centre

Ruosteenoja, E., Mäkeläinen, I., Rytömaa, T., Hakulinen, T. & Hakama, M. (1996) Radon and lung cancer in Finland. *Health Phys.*, **71**, 185–189

Rutherford, E. & Soddy, F. (1902) The cause and nature of radioactivity. *Philos. Mag.*, **4**, 370–396

Sabin, F.R., Doan, C.A. & Forkner, C.E. (1932) The production of osteogenic sarcomata and the effects on lymph nodes and bone marrow of intravenous injections of radium chloride and mesothorium in rabbits. *J. exp. Med.*, **56**, 267–292

Saccomanno, G., Auerbach, O., Kuschner, M., Harley, N.H., Michels, R.Y., Anderson, M.W. & Bechtel, J.J. (1996) A comparison between the localization of lung tumors in uranium miners and in nonminers from 1947 to 1991. *Cancer*, **77**, 1278–83

Saha, G.B., Go, R.T. & MacIntyre, W.J. (1992) Radiopharmaceuticals for cardiovascular imaging. *Nucl. Med. Biol.*, **19**, 1–20

Saito, M. & Ishida, M.R. (1985) Estimation of absorbed dose in cell nuclei due to DNA-bound ^{3}H. *Health Phys.*, **48**, 465–473

Salassidis, K., Braselmann, H., Okladnikova, N.D., Pressl, S., Stephan, G., Snigiryova, G. & Bauchinger, M. (1998) Analysis of symmetrical translocations for retrospective biodosimetry in radiation workers of the Mayak nuclear-industiral complex (southern Urals) using FISH-chromosome painting. *Int. J. Radiat. Biol*., **74**, 431–439

Samet, J.M., Pathak, D.R., Morgan, M.V., Marbury, M.C., Key, C.R. & Valdivia, A.A. (1989) Radon progeny exposure and lung cancer risk in New Mexico U miners: A case–control study. *Health Phys. Soc.*, **56**, 415–421

Samet, J.M., Pathak, D.R., Morgan, M.V., Key, C.R., Valdivia, A.A. & Lubin, J.H. (1991) Lung cancer mortality and exposure to radon progeny in a cohort of New Mexico underground uranium miners. *Health Phys.*, **61**, 745–752

Samet, J.M., Pathak, D.R., Morgan, M.V., Coultas, D.B., James, D.S. & Hunt, W.C. (1994) Silicosis and lung cancer risk in underground uranium miners. *Health Phys.*, **66**, 450–453

Sanders, C.L. (1972) Deposition patterns and the toxicity of transuranium elements in the lung. *Health Phys*., **22**, 607–615

Sanders, C L. (1992a) Life-span studies in rats exposed to $^{239}PuO_2$ aerosol. II. Nonpulmonary tumor formation in control and exposed groups. *J. environ. Pathol. Toxicol. Oncol.*, **11**, 265–277

Sanders, C.S. (1992b) Pleural mesothelioma in the rat following exposure to $^{239}PuO_2$. *Health Phys.*, **63**, 695–697

Sanders, C.L. & Lundgren, D.L. (1995) Pulmonary carcinogensis in the F344 and Wistar rat after inhalation of plutonium dioxide. *Radiat. Res*., **144**, 206–214

Sanders, C.L. & Mahaffey, J.A. (1978) Inhalation carcinogenesis of high-fired $^{244}CmO_2$ in rats. *Radiat. Res.*, **76**, 384–401

Sanders, C.L. & Mahaffey, J.A. (1981) Inhalation carcinogenesis of repeated exposures to high-fired $^{239}PuO_2$ in rats. *Health Phys.*, **41**, 629–644

Sanders, C.L. & Mahaffey, J.A. (1990) Inhalation carcinogenesis of repeated exposures to high-fired $^{244}CmO_2$ in rats. *Health Phys.*, **58**, 631–638

Sanders, C.L. & McDonald, K.E. (1992) Malignancy of proliferative pulmonary lesions in the Syrian hamster following inhalation of $^{239}PuO_2$. *J. environ. Pathol. Toxicol. Oncol.*, **11**, 151–156

Sanders, C.L., Dagle, G.E., Cannon, W.C., Craig, D.K., Powers, G.J. & Meier, D.M. (1976) Inhalation carcinogenesis of high-fired $^{239}PuO_2$ in rats. *Radiat. Res.*, **68**, 349–360

Sanders, C.L., Dagle, G.E., Cannon, W.C., Powers, G.J. & Meier, D.M. (1977) Inhalation carcinogenesis of high-fired $^{238}PuO_2$ in rats. *Radiat. Res.*, **71**, 528–546

Sanders, C.L., Dagle, G.E. & Mahaffey, J.A. (1992) Incidence of brain tumours in rats exposed to an aerosol of $^{239}PuO_2$. *Int. J. Radiat. Biol.*, **62**, 97–102

Sanders, C.L., Lauhala, K.E., McDonald, K.E. & Sanders, G.A. (1993a) Lifespan studies in rats exposed to $^{239}PuO_2$ aerosol. *Health Phys.*, **64**, 509–521

Sanders, C.L., Lauhala, K.E. & McDonald, K.E. (1993b) Lifespan studies in rats exposed to $^{239}PuO_2$ aerosol. III. Survival and lung tumours. *Int. J. Radiat. Biol.*, **64**, 417–430

Sankaranarayanan, K., Van Duyn, A., Loos, M.J. & Natarajan, A.T. (1989) Adaptive response of human lymphocytes to low-level radiation from radioisotopes or X-rays. *Mutat. Res.*, **211**, 7–12

dos Santos Silva, I., Jones, M., Malveiro, F. & Swerdlow, A. (1999) Mortality in the Portugese Thorotrast Study. *Radiat. Res.*, **152**, S88–S92

Sasaki, M.S., Takatsuji, T., Ejima, Y., Kodama, S. & Kido, C. (1987) Chromosome aberration frequency and radiation dose to lymphocytes by alpha-particles from internal deposit of Thorotrast. *Radiat. Environ. Biophys.*, **26**, 227–238

Satow, Y., Hori, H. & Lee, J.Y. (1989) Teratogenic effect of fission neutron and tritium water on rat embryo. *Sangyo Ika Daigaku Zasshi*, **11**, 416-431

Saunders, M.G., Taylor, D.M. & Trott, N.G. (1973) The dosimetry of ^{67}Ga citrate in man. *Br. J. Radiol.*, **46**, 456–463

Schajowicz, F. (1993) *Histological Typing of Bone Tumours*, 2nd Ed., *WHO International Classification of Tumours*, Berlin, Springer-Verlag

Schales, F. (1978) Brief history of ^{224}Ra usage in radiotherapy and radiobiology. *Health Phys.*, **35**, 25–32

Schiepers, C. & Hoh, C.K. (1998) Positron emission tomography as a diagnostic tool in oncology. *Eur. Radiol.*, **8**, 1481–1494

Schieve, L.A., Davis, F., Roeske, J., Handler, A., Freels, S., Stinchcomb, T. & Keane, A. (1997) Evaluation of internal alpha-particle radiation exposure and subsequent fertility among a cohort of women formerly employed in the radium dial industry. *Radiat. Res.*, **147**, 236–244

Schlenker, R.A. & Keane, A.T. (1987) Radium uptake in utero. In*:* Gerber, G.B., Métivier, H. & Smith, H., eds, *Age-related Factors in Radionuclide Metabolism and Dosimetry*, Dordrecht, Martinus Nijhoff, pp. 339–346

Schlenker, R.A., Keane, A.T. & Unni, K.K. (1989) Radium 226 and 228 in humans. Comparison of radium-induced and natural bone sarcomas by histological type, subject age and site of occurrence. In: Taylor, D.M., Mays, C.W., Gerber, G.B. & Thomas, R.G., eds, *Risks from Radium and Thorotrast* (BIR Report 21), London, British Institute of Radiology

Schmahl, W. & Kollmer, W.E. (1981) Radiation induced meningeal and pituitary tumours in the rat after prenatal application of strontium-90. *J. Cancer Res. clin. Oncol.*, **100**, 13–18

Schmahl, W., Kollmer, W.E., Berg, D. & Kriegel, H. (1979) Postnatal effects on Wistar rat pituitary morphology and function after application of strontium-90 on day 18 of pregnancy. In: *Biological Implications of Radionuclides Released from Nuclear Industries*, Vol. 1 (IAEA-SM-237/20), Vienna, International Atomic Energy Agency, pp. 329–337

Schmidt, P. & Kiefer, J. (1998) Deletion-pattern analysis of α-particle and X-ray induced mutations at the HPRT locus of V79 Chinese hamster cells. *Mutat. Res.*, **421**, 149–161

Schmitt-Hannig, A., Drenkard, S. & Wheatley, J. (1995) *Study on Consumer Products Containing Radioactive Substances in the EU Member States*, Luxembourg, Office for Official Publications of the European Communities

Schneider, A.B., Ron, E., Lubin, J., Stovall, M. & Gierlowski, T.C. (1993) Dose–response relationships for radiation-induced thyroid cancer and thyroid nodules: Evidence for the prolonged effects of radiation on the thyroid. *J. clin. Endocrinol. Metab.*, **77**, 362–369

Schoenberg, J.B., Klotz, J.B., Wilcox, H.B., Nicholls, G.P., Gil-del-Real, M.T., Stemhagen, A. & Mason, T.J. (1990) Case–control study of residential radon and lung cancer among New Jersey women. *Cancer Res.*, **50**, 6520–6524

Schoeters, G.E.R., Luz, A. & Vanderborght, O.L.J. (1983) 226Ra induced bone-cancers: The effects of a delayed Na-alginate treatment. *Int. J. Radiat. Biol.*, **43**, 231–247

Schoeters, G.E.R., Maisin, J.R. & Vanderborght, O.L.J. (1991) Toxicity of ^{241}Am in male C57BL mice: Relative risk versus ^{226}Ra. *Radiat. Res.*, **126**, 198–205

Schreml, W. & Fliedner, T.M. (1977) Distribution of tritiated compounds (tritiated thymidine and tritiated water) in the mother–fetus system and its consequences for the radiotoxic effect of tritium. *Curr. Topics Radiat. Res. Q.*, **12**, 255–277

Schwartz, G. & Dunning, D.E. (1982) Imprecision in estimates of dose from ingested 137-Cs due to variability in human biological characteristics. *Health Phys.*, **43**, 631–645

Searle, A.G., Beechey, C.V., Green, D. & Humphreys, E.R. (1976) Cytogenetic effects of protracted exposures to alpha-particles from plutonium-239 and to gamma-rays from colbalt-60 compared in male mice. *Mutat. Res.*, **41**, 297–310

Seidel, A. & Volf, V. (1972) Removal of internally deposited transuranium elements by Zn-DTPA. *Health Phys.*, **22**, 779–783

Seltzer, R.A., Kereiakes, J.G. & Saenger, E.L. (1964) Radiation exposure from radioisotopes on paediatries. *New Engl. J. Med.*, **271**, 84–90

Sevan'kaev, A.V., Lloyd, H. & Braselmann, H. (1995) A survey of chromosomal aberrations in lymphocytes of Chernobyl liquidators. *Radiat. Prot. Dosim.*, **58**, 85–91

Ševc, J., Kunz, E., Tomášek, L., Placek, V. & Horácek, J. (1988) Cancer in man after exposure to Rn daughters. *Health Phys.*, **54**, 27–46

Ševc, J., Tomášek, L., Kunz, E., Placek, V., Chmelevsky, D., Barclay, D. & Kellerer, A.M. (1993) A survey of the Czechoslovak follow-up of lung cancer mortality in uranium miners. *Health Phys.*, **64**, 355–369

Shanahan, E.M., Peterson, D., Roxby, D., Quintana, J., Morley, A.A. & Woodward, A. (1996) Mutation rates at the glycophorin A and HPRT loci in uranium miners exposed to radon progeny. *Occup. environ. Med.*, **53**, 439–444

Sharma, K. & Saini, M.R. (1993) Embryonic/fetal mortality after exposure to tritiated water in pregnant Swiss albino mice during different gestation periods. *Indian J. exp. Biol.*, **31**, 98–100

Sharpe, W.D. (1983) Chronic radium intoxication: Radium osteonecrosis and cancer in relation to ^{226}Ra burdens. *Health Phys*., **44** (Suppl. 1), 149–154

Sheu, J.-C., Sung, J.-L., Chen, D.-S., Yang, P.-M., Lai, M.-Y., Lee, C.-S., Hsu, H.-C., Chuang, C.-N., Yang, P.-C., Wang, P.-C., Lin, Y.-T. & Lee, C.-Z. (1985) Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterology*, **89**, 259–266

Shilnikova, N.S., Koshurnikova, N.A., Bolotnikova, M.G., Nifatov, A.P., Okatenko, P.V., Khokhryakov, V.F. & Romanov S.A. (1995) [Mortality from malignant liver neoplasms among personnel of 'Mayak' complex.] *Radiat. Risk*, **5**, 151–155 (in Russian)

Sikov, M.R. (1969) Effect of age on the iodine-131 metabolism and the radiation sensitivity of the rat thyroid. *Radiat. Res*., **38**, 449–459

Sikov, M.R. (1972) Effect of age on the morphologic response of the rat thyroid to irradiation by iodine-131. *Radiat. Res*., **49**, 233–244

Sikov, M.R. (1982) Fetal and juvenile radiotoxicity. In: *Pacific Northwest Laboratory Annual Report for 1981* (PNL-4100 PTI), Springfield, VA, National Technical Information Service, pp. 113–117

Sikov, M.R. (1983) Fetal and juvenile radiotoxicity. In: *Pacific Northwest Laboratory Annual Report for 1982* (PNL-4699 PT1), Springfield, VA, National Technical Information Service, pp. 89–93

Sikov, M.R. (1985) Fetal and juvenile radiotoxicity. In: *Pacific Northwest Laboratory Annual Report for 1984* (PNL-5500 PT1), Springfield, VA, National Technical Information Service, pp. 43–47

Sikov, M.R. (1987a) Fetal and juvenile radiotoxicity. In: *Pacific Northwest Laboratory Annual Report for 1986* (BNWL-6100 PT1), Springfield, VA, National Technical Information Service, pp. 47–50

Sikov, M.R. (1987b) Placental transfer of the actinides and related heavy elements. In: Gerber, G.B., Métivier, H. & Smith, H., eds, *Age-related Factors in Radionuclide Metabolism and Dosimetry*, Dordrecht, Martinus Nijhoff, pp. 303–314

Sikov, M.R. (1989) Tumour development following internal exposures to radionuclides during the perinatal period following prenatal exposure to radiation. In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publication No. 96), Lyon, IARC*Press*, pp. 403–419

Sikov, M.R. & Hui, T.E. (1996) *Contribution of Maternal Radionuclide Burden to Prenatal Radiation Doses* (NUREG/CR-5631, PNL-7445 Rev. 2), Washington DC, US Nuclear Regulatory Commission

Sikov, M.R. & Kelman, B.J. (1989) Factors affecting the placental transfer of actinides. *Health Phys.*, **57**, 109–114

Sikov, M.R. & Lofstrom, J.E. (1957) The dosimetry and lethal effects of maternally administered phosphorus-32 after 14 and 17 days of gestation in the rat. *Phys. Med. Biol*., **2**, 157–168

Sikov, M.R. & Mahlum, D.D. (1968) Cross-placental transfer of selected actinides in the rat. *Health Phys*., **14**, 205–208

Sikov, M.R. & Mahlum, D.D. **(**1972**)** Age-dependence of ^{239}plutonium metabolism and effect in the rat. In: Stover, B.J. & Jee, W.S.S., eds, *Radiobiology of Plutonium*, Salt Lake City, J.W. Press, pp. 261–272

Sikov, M.R. & Mahlum, D.D. (1975) Toxicity of ^{241}Am and ^{244}Cm after administration at nine days of gestation in the rat (Abstract). *Radiat. Res.*, **62**, 565

Sikov, M.R. & Noonan, T.R. (1957) The effects of irradiation with phosphorus-32 on the viability and growth of rat embryos. *Radiat. Res*., **7**, 541–550

Sikov, M.R. & Noonan, T.R. (1958) Anomalous development induced in the embryonic rat by the maternal administration of radiophosphorus. *Am. J. Anat*., **103**, 137–162

Sikov, M.R., Lofstrom, J.E. & Noonan, T.R. (1958) Effects of maternally administered P^{32} on fetal development. In: *Proceedings of the Second International Conference on Peaceful Uses of Atomic Energy*, London, Pergamon Press, pp. 71–75

Sikov, M.R., Mahlum, D.D. & Howard, E.B. (1972) Effect of age on the morphologic response of the rat thyroid to irradiation by iodine-131. *Radiat. Res*., **49**, 233–244

Sikov, M.R., Zwicker, G.M., Hess, J.O. & Mahlum, D.D. (1978) Late effects of perinatally administered plutonium. In: Mahlum, D.D, Sikov, M.R., Hackett, P.L. & Andrew, X., eds, *Developmental Toxicology of Energy-related Pollutants* (CONF-771017), Springfield, VA, National Technical Information Service, pp. 361–374

Sikov, M.R., Buschbom, R.L., Carr, D.B., Dagle, G.E., Hackett, P.L., Kelman, B.J., Mahlum, D.D., McClanahan, B.J., Rommereim, D.N. & Sasser, L.B. (1986) *Fetal and Juvenile Radiotoxicity, Pacific Northwest Laboratory Annual Report for 1985*, Richland, Pacific Northwest Laboratory, pp. 45–49

Sikov, M.R., Mahlum, D.D., Dagle, G.E., Daniel, J.L. & Goldman, M. (1989) Mechanistic explanations for the elevated susceptibility of the perinatal thyroid gland to radiogenic cancer. In: Park, J.F. & Pelroy, R.A., eds, *Multilevel Health Effects Research: From Molecules to Man*, Columbus, OH, Battelle Press, pp. 283–293

Sikov, M.R., Cross, F.T., Mast, T.J., Palmer, H.E., James, A.C., & Thrall, K.D. (1992) Developmental toxicology of radon exposures. In: Cross, F.T., ed., *Indoor Radon and Lung Cancer: Reality or Myth? Twenty-ninth Hanford Symposium on Health and the Environment*, Columbus, OH, Battelle Press, pp. 677–691

Silberstein, E.B. (1993) The treatment of painful osseous metastases with phosphorus-32 labeled phosphates. *Semin. Oncol.*, **20** (Suppl. 2), 10–21

da Silva Horta, J., da Silva Horta, M.E., Cayolla da-Motta, L. & Tavares, M.H. (1978) Malignancies in Portuguese Thorotrast patients. *Health Phys*., **35**, 137–151

Simmons, D.J. & Holtzman, R.B. (1983) Plugged Haversian canals and local dose in radium cases. *Health Phys*., **44** (Suppl. 1), 179–186

Simmons, J.A., Cohn, P. & Min, T. (1996) Survival and yields of chromosome aberrations in hamster and human lung cells irradiated by alpha particles. *Radiat. Res*., **145**, 174–180

Simon, S.L., Till, J.E., Lloyd, R.D., Kerber, R.L., Thomas, D.C., Preston-Martin, S., Lyon, J.L. & Stevens, W. (1995) The Utah Leukemia Case–Control Study: Dosimetry methodology and results. *Health Phys.*, **68**, 460–471

Slauson, D.O., Hahn, F.F., Benjamin, S.A., Chiffelle, T.L. & Jones, R.K. (1976) Inflammatory sequences in acute pulmonary radiation injury. *Am. J. Pathol*., **82**, 549–572

Slauson, D.O., Hahn, F.F. & Chiffelle, T.L. (1977) The pulmonary vascular pathology of experimental radiation pneumonitis. *Am. J. Pathol*., **88**, 635–654

Smida, J., Zitzelsberger, H., Kellerer, A.M., Lehmann, L., Minkus, G., Negele, T., Spelsberg, F., Hieber, L., Demidchik, E.P., Lengfelder, E. & Bauchinger, M. (1997) *p53* Mutations in childhood thyroid tumours from Belarus and in thyroid tumours without radiation history. *Int. J. Cancer*, **73**, 802–807

Smith, T. & Edmonds, C.J. (1984) Radiation dosimetry in the treatment of thyroid carcinoma by ^{131}I. *Rad. Prot. Dosim.*, **5**, 141–149

Smith, H. & Stather, J.W. (1976) *Human Exposure to Radiation Following the Release of Radioactivity from a Reactor Accident: A Quantitative Assessment of the Biological Consequences* (NRPB Report 52), Harwell, National Radiological Protection Board

Smith, D.I., Lord, D.J. & Tait, S.D.R. (1991) Ionising radiation exposure to the Dounreay workforce during 1987 and 1988. *Radiat. Protect. Dosim.*, **36**, 177–181

Smith, B.J., Field, R.W. & Lynch, C.F. (1998) Residential ^{222}Rn exposure and lung cancer: Testing the linear no-threshold theory with ecologic data. *Health Phys.*, **75**, 11–17

Sobolev, B., Likhtarev, I., Kairo, I., Tronko, N., Oleynik, V. & Bogdanova, T. (1996) Radiation risk assessment of the thyroid cancer in Ukrainian children exposed due to Chernobyl. In: Karaoglou, A., Desmet, G., Kelly, G.N. & Menzel, H.G., eds, *The Radiological Consequences of the Chernobyl Accident* (EUR 16544 EN), Luxembourg, Office for Official Publications of the European Communities, pp. 741–748

Soini, Y., Welsh, J.A., Ishak, K.G. & Bennett, W.P. (1995) *p53* Mutations in primary hepatic angiosarcomas not associated with vinyl chloride exposure. *Carcinogenesis*, **16**, 2879–2881

Sonnabend, E., Spiess, H. & Mays, C.W. (1986) Tooth breakage in patients injected with ^{224}Ra. *Strahlentherapie*, **80** (Suppl.), 60–64

Sontag, W., Wirth, R., Luz, A., Schäffer, E. & Volf, V. (1997) Dosimetry and pathology of ^{237}Np in female rats. *Hum. exp. Toxicol.*, **16**, 89–100

Speert, H., Quimby, E.H. & Werner, S.C. (1951) Radioiodine uptake by the fetal mouse thyroid and resultant effects in later life. *Surg. Gynecol. Obst.*, **93**, 230–242

Speizer, F.E. & Frank, N.R. (1966) The uptake and release of SO_2 by the human nose. *Arch. environ. Health*, **12**, 725–728

Spiers, F.W. & Beddoe, A.H. (1983) Sites of incidence of osteosarcoma in the long bones of man and the beagle. *Health Phys.*, **44** (Suppl. 1), 49–64

Spiers, F.W., Beddoe, A.H., King, S.D., Hayter, C.J., Smith, A.H., Burkinshaw, L. & Roberts, B.E. (1976) The absorbed dose to bone marrow in the treatment of polycythemia by ^{32}P. *Br. J. Radiol.*, **49**, 133–140

Spiers, F.W., King, S.D. & Beddoe, A.H. (1977) Measurements of endosteal surface areas in human long bones: Relationship to sites of occurrence of osteosarcoma. *Br. J. Radiol.*, **50**, 769–776

Spiers, F.W., Lucas, H.F., Rundo, J. & Anast, G.A. (1983) Leukaemia incidence in the US dial workers. *Health Phys.*, **44** (Suppl. 1), 65–72

Spiess, H. (1956) [Acute radiation-induced damages after treatment with Peteosthor in children]. *Dtsch. med. Wschr.*, **81**, 1053–1054 (in German)

Spiess, H. (1995) The RA-224 study: Past, presence and future. In: van Kaick, G., Karaoglou, A. & Kellerer, A.M., eds, *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (EUR 15877 EN), Singapore, World Scientific, pp. 157–163

Spiess, H. & Mays, C.W. (1970, 1971) Bone cancers induced by ^{224}Ra (ThX) in children and adults. *Health Phys.*, **19**, 713–729 and Corrigendum. *Health Phys.*, **20**, 543–545 (1971)

Spiess, H. & Mays, C.W. (1979a) Exostoses induced by ^{224}Ra (ThX) in children. *Eur. J. Pediatr.*, **132**, 271–276

Spiess, H. & Mays, C.W. (1979b) Liver diseases in patients injected with ^{224}Ra. *Environ. Res.*, **18**, 55–60

Spiess, H., Mays, C.W. & Spiess-Paulus, E. (1986) Growth retardation in children injected with 224-Ra. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 45–50

Spiethoff, A., Wesch, H., Höver, K.-H. & Wegener, K. (1992) Contributed paper. The combined and separate action of neutron radiation and zirconium dioxide on the liver of rats. *Health Phys.*, **63**, 111–118

Stabin, M.G., Tagesson, M., Thomas, S.R., Ljungberg, M. & Strand, S.E. (1999) Radiation dosimetry in nuclear medicine. *Appl. Radiat. Isot.*, **50**, 73–87

Stather, J.W. & Greenhalgh, J.R. (1983) *The Metabolism of Iodine in Children and Adults* (NRPB Report 140), Chilton, National Radiological Protection Board Report

Stather, J.W. & Phipps, A.W. (1998) The work of Committee 2 of ICRP in developing dose coefficients for the embryo and fetus. *Radiat. Prot. Dosim.*, **79**, 299–302

Stather, J.W., Adams, N., Gray, S.A. & Rees, M. (1987) Comparative studies on the transfer of radionuclides to the fetus in the rat — Implications for human dosimetry. In: Gerber, G.B., Métivier, H. & Smith, H., eds, *Age-related Factors in Radionuclide Metabolism and Dosimetry*, Dordrecht, Martinus Nijhoff, pp. 371–380

Stather, J.W., Muirhead, C.R., Edwards, A.A., Harrison, J.D., Lloyd, D.C. & Wood, N.R. (1988) *Health Effects Models Developed from the 1988 UNSCEAR Report* (NRPB Report 226), Chilton, National Radiological Protection Board, pp. 6–7

Stebbings, J.H. (1998) Radium and leukemia: Is current dogma valid? *Health Phys.*, **74**, 486–488

Stebbings, J.H. (1999) A case study of selected medical findings among plutonium injectees. *Health Phys*., **76**, 477–488

Stebbings, J.H., Lucas, H.F. & Stehney, A.F. (1984) Mortality from cancers of major sites in female radium dial workers. *Am. J. ind. Med*., **5**, 435–459

Stefani, F.H., Spiess, H. & Mays, C.W. (1986) Cataracts in patients injected with ^{224}Ra. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 51–59

Stegelmeier, B.L., Gillett, N.A., Rebar, A.H. & Kelly, G. (1991) The molecular progression of plutonium-239-induced rat lung carcinogenesis: Ki-*ras* expression and activation. *Mol. Carcinog*., **4**, 43–51

Stehney, A.F. (1999) Organ distribution of thorium in thorium workers: Good agreement with new models of the International Commission on Radiological Protection. *Radiat. Res*., **152**, S110–S114

Stehney, A.F., Polednak, A.P., Rundo, J., Brues, A.M., Lucas, H.F., Jr., Patten, B.C. & Rowland, R.E. (1980) *Health Status and Body Radioactivity of Former Thorium Workers, Interim Report* (NUREG/CR-1420; ANL-80-37), Washington DC, US Nuclear Regulatory Commission

Steinbuch, M., Weinberg, C.R., Buckley, J.D., Robison, L.L. & Sandler, D.P. (1999) Indoor residential radon exposure and risk of childhood acute myeloid leukaemia. *Br. J. Cancer*, **81**, 900–906

Stenhouse, M.J. & Baxter, M.S. (1977a) Bomb 14C and human radiation burden. *Nature*, **267**, 825–827

Stenhouse, M.J. & Baxter, M.S. (1977b) Bomb 14C as a biological tracer. *Nature*, **267**, 828–832

Stenström, K., Leide-Svegborn, S., Erlandsson, B., Hellborg, R., Mattsson, S., Nilsson, L.E., Nosslin, B., Skog, G. & Wiebert, A. (1996) Application of accelerator mass spectrometry (AMS) for high-sensitivity measurements of $^{14}CO_2$ in long-term studies of fat metabolism. *Appl. Radiat. Isot.*, **47**, 417–422

Stevens, W., Atherton, D.R., Bates, D., Lloyd, R.D., Buster, D.S. & Bruenger, F.W. (1977) Retention and distribution of ^{241}AmIII in neonatal beagles. *Health Phys.*, **33**, 553–559

Stevens, W., Thomas, D.C., Lyon, J.L., Till, J.E., Kerber, R.A., Simon, S.L., Lloyd, R.D., Elghany, N.A. & Preston-Martin, S. (1990) Leukemia in Utah and radioactive fallout from the Nevada test site. A case–control study. *J. Am. med. Assoc.*, **264**, 585–591 [Published erratum appears in *J. Am. med. Assoc.* (1991), **265**, 461]

Stevenson, A.C., Bedford, J., Dolphin, G.W., Purrott, R.J., Lloyd, D.C., Hill, A.G.S., Hill, H.F.H., Gumpel, J.M., Williams, D., Scott, J.T., Ramsey, N.W., Bruckner, F.E. & Fearn, C.B.D'A. (1973) Cytogenetic and scanning study of patients receiving intra-articular injections of gold-198 and yttrium-90. *Ann. rheum. Dis.*, **32**, 112–123

Stewart, N.G. & Crooks, R.N. (1958) Long-range travel of the radioactive cloud from the accident at Windscale. *Nature*, **182**, 627–628

Stidley, C.A. & Samet, J.M. (1993) A review of ecologic studies of lung cancer and indoor radon. *Health Phys.*, **65**, 234–251

Stidley, C.A. & Samet, J.M. (1994) Assessment of ecologic regression in the study of lung cancer and indoor radon. *Am. J. Epidemiol.*, **139**, 312–322

Stover, B.J. & Jee, W.S.S. (1963) Some effects of long-term alpha irradiation on the composition and structure of bone. *Health Phys.*, **9**, 267–275

Stover, B.J., Bruenger, F.W. & Stevens, W. (1970) Association of americium with ferritin in the canine liver. *Radiat. Res.*, **43**, 173–186

Stradling, G.N., Gray, S.A., Moody, J.C., Hodgson, A., Raymond, K.N., Durbin, P.W., Rodgers, S.J., White, D.L. & Turowski, P.N. (1991) The efficacy of DFO-HOPO, DTPA-DX and DTPA for enhancing the excretion of plutonium and americium from the rat. *Int. J. Radiat. Biol.*, **59**, 1269–1277

Stradling, G.N., Gray, S.A., Ellender, M., Moody, J.C., Hodgson, A., Pearce, M., Wilson, I., Burgada, R., Bailly, T., Leroux, Y.G.P., El Manouni, D., Raymond, K.N. & Durbin, P.W. (1992) The efficacies of 3,4,3-LIHOPO and DTPA for enhancing the excretion of plutonium and americium from the rat: Comparison with other siderophore analogues. *Int. J. Radiat. Biol.*, **62**, 487–497

Stram, D.O., Langholz, B., Huberman, M. & Thomas, D.C. (1999a) Correcting for exposure measurement error in a reanalysis of lung cancer mortality for the Colorado Plateau uranium miners cohort. *Health Phys.*, **77**, 265–275

Stram, D.O., Langholz, B., Huberman, M. & Thomas, D. (1999b) Measurement error corrections for the analysis of lung cancer mortality in the Colorado Plateau uranium miners cohort. In: Ron, E. & Hoffman, F.O., eds, *Uncertainties in Radiation Dosimetry and their Impact on Dose–Response Analyses* (NIH Publication No. 99-4541), Bethesda, MD, National Cancer Institute, pp. 192–199

Straume, T. & Carsten, A.L. (1993) Tritium radiobiology and relative biological effectiveness. *Health Phys.*, **65**, 657–672

Streffer, C., van Beuningen, D. & Elias, S. (1977) Comparative effects of tritiated water and thymidine on the preimplanted mouse embryo *in vitro*. *Curr. Topics Radiat. Res. Q.*, **12**, 182–193

Stroud, A.N. (1977) Chromosome aberrations induced in Syrian hamster lung cells by inhaled $^{238}PuO_2.ZrO_2$ particles. *Radiat. Res.*, **69**, 583–590

Stsjazhko, V.A., Tsyb, A.F., Tronko, N.D., Souchkevitch, G. & Baverstock, K.F. (1995) Childhood thyroid cancer since accident at Chernobyl (Letter to the Editor). *Br. med. J.*, **310**, 801

Sullivan, M.F. (1980) Absorption of actinide elements from the gastrointestinal tract of rats, guinea pigs and dogs. *Health Phys.*, **38**, 159–171

Sullivan, M.F. & Gorham, L.S. (1982) Further studies on the absorption of actinide elements from the gastrointestinal tract of neonatal animals. *Health Phys.*, **43**, 509–519

Sullivan, M.F. & Ruemmler, P.S. (1986) Effectiveness of DTPA therapy when administered intragastrically or intraperitoneally to remove Pu from adult or neonatal rats. *Health Phys.*, **51**, 641–646

Sullivan, D.J., McDonald, T.P. & Bell, M.C. (1969) Acute radiotoxicity of ^{144}Ce–^{144}Pr after intravenous administration to sheep. *Cornell Vet.*, **59**, 236–249

Sullivan, M.F., Ruemmler, P.S., Beamer, J.L., Mahony, T.D. & Cross, F.T. (1978) Acute toxicity of beta-emitting radionuclides that may be released in a reactor accident and ingested. *Radiat. Res.*, **73**, 21–36

Sullivan, M.F., Miller, B.M. & Ryan, J.L. (1983) Absorption of thorium and protactinium from the gastrointestinal tract in adult mice and rats and neonatal rats. *Health Phys.*, **44**, 425–428

Sullivan, M.F., Cross, F.T. & Dagle, G.E. (1987) Dosimetry of the gastrointestinal tract. In: Gerber, G.B., Métivier, H. & Smith, H., eds, *Age-related Factors in Radionuclide Metabolism*, Dordrecht, Martinus Nijhoff, pp. 49–66

Sundell-Bergman, S. & Johanson, K.J. (1980) Repairable and unrepairable DNA strand breaks induced by decay of ^{3}H and ^{125}I incorporated into DNA of mammalian cells. *Radiat. environ. Biophys.*, **18**, 239–248

Sundell-Bergman, S., Bergman, R. & Johanson, K.J. (1985) Chromosome damage induced by decay of ^{3}H and ^{125}I incorporated into DNA of Chinese hamster cells. *Mutat. Res.*, **149**, 257–263

Sutow, W.W., Conard, R.A. & Griffith, K.M. (1965) Growth status of children exposed to fallout radiation on the Marshall Islands. *Pediatrics*, **36**, 721–731

Svensson, C., Pershagen, G. & Hrubec, Z. (1988) A comparative study on different methods of measuring Rn concentrations in homes. *Health Phys.*, **55**, 895–902

Svensson, C., Pershagen, G. & Klominek, J. (1989) Lung cancer in women and type of dwelling in relation to radon exposure. *Cancer Res.*, **49**, 1861–1865

Svoboda V. & Bubeníková, D. (1990) Hemoblastoses in mice contaminated with low activities of ^{239}Pu. *Neoplasma*, **37**, 639–646

Svoboda, V., Kofránek, V., Kotašková, Z., Bubeníková, D. & Dvorák, V. (1977) Planimetric evaluation and comparison of roentgenograms of osteogenic sarcomas induced by ^{226}Ra and ^{224}Ra in mice. *Neoplasma*, **24**, 311–318

Svoboda, V., Bubeníková, D. & Kotasková, Z. (1981) Myeloid leukaemia in ^{239}Pu-treated mice. *J. Cancer Res. clin. Oncol.*, **100**, 255–262

Svoboda, V., Bubeníková, D. & Kotasková, Z. (1982) Some quantitative micromorphological characteristics of granulocytic leukaemia in ^{239}Pu-injected mice and untreated controls. *Neoplasma*, **29**, 175–182

Svoboda, V., Sedlák, A., Kypenová, H. & Bubeníková, D. (1987) Long-term effects of low-level ^{239}Pu contamination on murine bone-marrow stem cells and their progeny. *Int. J. Radiat. Biol*., **52**, 517–526

Szot, Z., Rochalska, M., Wojewodzka, M., Chimiak, A. & Przychodzen, W. (1986) Removal of ^{239}Pu from mice with 3,4,3 LICAM(C) or N,N′N″,N‴-tetra(2,3-dihydroxybenzoyl)-spermine. *Radiat. environ. Biophys.*, **25**, 31–35

Szur, L. & Lewis, S.M. (1966) The haematological complications of polycythaemia vera and treatment with radioactive phosphorus. *Br. J. Radiol*., **39**, 122–130

Takeda, H. (1991) Incorporation and distribution of tritium in rats after chronic exposure to various tritiated compounds. *Int. J. Radiat. Biol.*, **59**, 843–853

Takeda, H., Nishimura, Y. & Inaba, J. (1994) Transfer of tritium to prenatal and neonatal rats from their mothers exposed to tritiated compounds. *Radiat. Prot. Dosim*., **53**, 281–284

Talbot, R.J. & Moores, S.R. (1985) The development and interlobar distribution of plutonium-induced pulmonary fibrosis in mice. *Radiat. Res*., **103**, 135–148

Talbot, R.J., Newton, D., Warner, A.J., Walters, B. & Sherlock, J.C. (1993) Human uptake of ^{137}Cs in mutton. *Health Phys*., **64**, 600–604

Talbott, E.O., Youk, A.O., McHugh, K.P., Shire, J.D., Zhang, A., Murphy, B.P. & Engberg, R.A. (2000) Mortality among the residents of the Three Mile Island accident area: 1979–1992. *Environ. Health Perspectives*, **108**, 545–552

Tanosaki, S., Minamihisamatsu, M., Ishihara, T., Hachiya, M., Kumatori, T. & Akashi, M. (1999) Chromosome aberrations in bone marrow cells from Japanese patients with thorotrastosis. *Radiat. Res.*, **152** (Suppl.), S128–S132

Taplin (1979) The history of lung imaging with radionuclides. *Semin. nucl. Med.*, **9**, 178–185

Tawn, E.J., Hall, J.W. & Schofield, G.B. (1985) Chromosome studies in plutonium workers. *Int. J. Radiat. Biol*., **47**, 599–610

Taylor, D.M. (1986) The comparative carcinogenicity of ^{239}Pu, ^{241}Am and ^{244}Cm in the rat. In: Thompson, R.C. & Mahaffey, J.A., eds, *Life-span Radiation Effects Studies in Animals: What Can They Tell Us? Proceedings of the Twenty-second Hanford Life Sciences Symposium, Richmond, 27–29 September 1983*, Washington DC, US Department of Energy, pp. 404–412

Taylor, D.M. & Bligh, P.H. (1992) The transfer of ^{45}Ca, ^{85}Sr and ^{140}Ba from mother to newborn in rats. *Radiat. Prot. Dosim.*, **41**, 143–145

Taylor, G.N., Jee, W.S.S., Christensen, W.R., Rehfeld, C.E. & Nebeker, N. (1965) Thorium-228 induced fractures in beagles. In: Jee, W.S.S., ed., *Research in Radiobiology* (COO-119-232), Salt Lake City, University of Utah Press, pp. 74–87

Taylor, G.N., Dougherty, T.F., Mays, C.W., Lloyd, R.D., Atherton, D.R. & Jee, W.S.S. (1972a) Radium-induced eye melanomas in dogs. *Radiat. Res*., **51**, 361–373

Taylor, G.N., Jee, W.S.S., Williams, J.L. & Shabestari, L. (1972b) Hepatic changes induced by ^{239}Pu. In: Stover, B.J. & Jee, W.S.S., eds, *Radiobiology of Plutonium*, Salt Lake City, UT, J.W. Press, pp. 105–127

Taylor, G.N., Gardner, P. Mays, C.W., Wrenn, M.C. & Charrier, K. (1981) Incidence of plutonium-induced bone cancer in neutered mice. *Cancer Res*., **41**, 971–973

Taylor, G.N., Mays, C.W., Lloyd, R.D., Gardner, P.A., Talbot, L.R., McFarland, S.S., Pollard, T.A., Atherton, D.R., VanMoorhem, D., Brammer, D., Brammer, T.W., Ayoroa, G. & Taysum, D.H. (1983) Comparative toxicity of ^{226}Ra, ^{239}Pu, ^{241}Am, ^{249}Cf, and ^{252}Cf in C57BL/Do black and albino mice. *Radiat. Res.*, **95**, 584–601

Taylor, G.N., Mays, C.W., Lloyd, R.D., Jones, C.W., Rojas, J., Wrenn, M.E., Ayoroa, G., Kaul, A. & Riedel, W. (1986) Liver cancer induction by ^{241}Am and Thorotrast in deer mice and grasshopper mice. In: Gössner, W., Berber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 172–177

Taylor, G.N., Lloyd, R.D., Mays, C.W., Angus, W., Miller, S.C., Shabestari, L. & Hahn, F.F. (1991) Plutonium or americium-induced liver tumors in beagles. *Health Phys.*, **61**, 337–347

Taylor, G.N., Lloyd, R.D. & Mays, C.S. (1993) Liver cancer induction by ^{239}Pu, ^{241}Am and thorotrast in the grasshopper mouse, *Onychomys leukogaster*. *Health Phys.*, **64**, 141–146

Taylor, G.N., Lloyd, R.D., Mays, C.W., Miller, S.C., Jee, W.S.S., Mori, S., Shabestari, L. & Li, X. J. (1997) Relationship of natural incidence and radiosensitivity for bone cancer in dogs. *Health Phys.*, **73**, 679–683

Taylor, G.N., Lloyd, R.D. & Miller, S.C. (2000) Radium-induced eye melanomas in dogs. *Health Phys.*, **79**, 196–198

Terzaghi-Howe, M., Ford, J.R. & Turner, J.E. (1996) Influence of cell position relative to planar alpha-particle sources on survival and preneoplastic transformation of primary rat tracheal epithelial cells. *Radiat. Res.*, **145**, 432–441

Teta, M.J. & Ott, M.G. (1988) A mortality study of a research, engineering, and metal fabrication facility in western New York state. *Am. J. Epidemiol.*, **127**, 540–551

Thacker, J. (1986) The nature of mutants induced by ionising radiation in cultured hamster cells. *Mutat. Res.*, **160**, 267–275

Thacker, J., Stretch, A. & Goodhead, D.T. (1982) The mutagenicity of α-particles from plutonium-238. *Radiat. Res.*, **92**, 343–352

Thomas, R.G. (1999) Is radium the only radionuclide that displays a practical threshold dose? (Abstract) *Radiat. Res.*, **152**, S159

Thomas, R.G. & Smith, D.M. (1979) Lung tumours from PuO_2–ZrO_3 aerosol particles in Syrian hamsters. *Int. J. Cancer*, **24**, 594–599

Thomas, R.G., McClellan, R.O., Thomas, R.L., Chiffelle, T.L., Hobbs, C.H., Jones, R.K., Mauderly, J.L. & Pickrell, J.A. (1972) Metabolism, dosimetry and biological effects of inhaled ^{241}Am in beagle dogs. *Health Phys.*, **22**, 863–871

Thomas, R.G., Durbin, P.W., McInroy, J.F. & Healy, J.W. (1989) Estimation of human gonadal Pu and Ce concentrations from animal data. *Health Phys.*, **57**, 97–107

Thomas, D., Pogoda, J., Langholz, B. & Mack, W. (1994) Temporal modifiers of the radon–smoking interaction. *Health Phys.*, **66**, 257–262

Thompson, R.C. (1982) Neptunium — The neglected actinide: A review of the biological and environmental literature. *Radiat. Res.*, **90**, 1–32

Thompson, D.E., Mabuchi, K., Ron, E., Soda, M., Tokunaga, M., Ochikubo, S., Sugimoto, S., Ikeda, T., Terasaki, M., Izumi, S. & Preston, D.L. (1994) Cancer incidence in atomic bomb survivors. Part II. Solid tumors, 1958–1987. *Radiat. Res.*, **137**, S17–S67

Thornberg, C. & Mattsson, S. (2000) Increased ^{137}Cs metabolism during pregnancy. *Health Phys.*, **78**, 502–506

Tierney, L.A., Hahn, F.F. & Lechner, J.F. (1996) *p53*, *erb*B-2 and K-*ras* gene alterations are rare in spontaneous and plutonium-239-induced canine lung neoplasia. *Radiat. Res.*, **145**, 181–187

Till, J.E., Simon, S.L., Kerber, R., Lloyd, R.D., Stevens, W., Thomas, D.C., Lyon, J.L. & Preston-Martin, S. (1995) The Utah Thyroid Cohort Study: Analysis of the dosimetry results. *Health Phys.*, **68**, 472–483

Tirmarche, M., Raphalen, A., Allin, F., Chameaud, J. & Bredon, P. (1993) Mortality of a cohort of French uranium miners exposed to relatively low radon concentrations. *Br. J. Cancer*, **67**, 1090–1097

Tokarskaya, Z.B., Okladnikova, N.D. & Aristov, V.P. (1993) [Location of lung cancer in persons who worked with plutonium-239.] *Med. Tr. Prom. Ekol.*, **5-6**, 23–25 (in Russian)

Tokarskaya, Z.B., Okladnikova, N.D. & Belyaeva, Z.D. (1994) [Evaluation of radiation and non-radiation factors in the development of lung cancer in radiochemical plant employees.] *Vop. Onkol.*, **40**, 165–170 (in Russian)

Tokarskaya, Z.B., Okladnikova, N.D., Belyaeva, Z.D. & Drozhko, E.G. (1995) The influence of radiation and nonradiation factors on the lung cancer incidence among the workers of the nuclear enterprise Mayak. *Health Phys.*, **69**, 356–366

Tokarskaya, Z.B., Okladnikova, N.D. & Belyaeva, Z.D. (1996a) [The 'dose–response' mechanism of tumorigenesis in plutonium workers.] *Vop. Onkol.*, **42**, 48–52 (in Russian)

Tokarskaya, Z.B., Okladnikova, N.D., Belyaeva, Z.D. & Aristov, V.P. (1996b) [The influence of radiation and other factors on the genesis of different histological patterns of lung cancer in plutonium workers.] *Vop. Onkol.*, **42**, 43–47 (in Russian)

Tokarskaya, Z.B., Okladnikova, N.D., Belyaeva, Z.D. & Drozhko, E.G. (1997a) Multifactorial analysis of lung cancer dose–response relationships for workers at the Mayak nuclear enterprise. *Health Phys.*, **73**, 899–905

Tokarskaya, Z.B., Khokhryakov, V.F., Okladnikova, N.D., Belyaeva, Z.D. & Zhuntova, G.V. (1997b) [Radiation factors and smoking interaction at lung cancer incidence for workers at a nuclear enterprise.] *Radiat. Biol. Radioekol.*, **37**, 918–925 (in Russian)

Tolstykh, E.I., Degteva, M.O., Kozheurov, V.P. & Burmistrov, D.S. (1998) Strontium transfer from maternal skeleton to the fetus estimated on the basis of the Techa River data. *Radiat. Prot. Dosim.*, **79**, 307–310

Tomášek, L. & Darby, S.C. (1995) Recent results from the study of West Bohemian uranium miners exposed to radon and its progeny. *Environ. Health Perspectives*, **103**, 55–57

Tomášek, L. & Placek, V. (1999) Radon exposure and lung cancer risk: Czech cohort study. *Radiat. Res.*, **152**, S59–S63

Tomášek, L., Darby, S.C., Swerdlow, A.J., Placek, V. & Kunz, E. (1993) Radon exposure and cancers other than lung cancer among uranium miners in West Bohemia. *Lancet*, **341**, 919–923

Tomášek, L, Darby, S.C., Fearn, T., Swerdlow, A.J., Placek, V. & Kunz, E. (1994a) Patterns of lung cancer mortality among uranium miners in West Bohemia with varying rates of exposure to radon and its progeny. *Radiat. Res.*, **137**, 251–261

Tomášek, L., Swerdlow, A.J., Darby, S.C., Placek, V. & Kunz, E. (1994b) Mortality in uranium miners in West Bohemia: A long term cohort study. *Occup. environ. Med.*, **51**, 308–315

Toohey, R.E. & Kathren, R.L. (1995) Overview and dosimetry of the Hanford americium accident case. *Health Phys.*, **69**, 310–317

Török, P., Schmahl, W., Meyer, I. & Kistner, G. (1979) Effects of a single injection of tritiated water during organogeny on the prenatal and postnatal development of mice. In: *Biological Implications of Radionuclides Released from Nuclear Industries*, Vol. 1 (IAEA-SM-237/24), Vienna, International Atomic Energy Agency, pp. 241–253

Troch, P. (1949) *Peteosthor. Neue Wege des Heilens* [Peteosthor. New therapies], Braunschweig, Vieweg & Sohn (in German)

Tronko, M.D., Bogdanova, T.I., Komissarenko, I.V., Epstein, O.V., Oliynyk, V., Kovalenko, A., Likhtarev, I.A., Kairo, I., Peters, S.B. & LiVolsi, V.A (1999) Thyroid carcinoma in children and adolescents in Ukraine after the Chernobyl nuclear accident: Statistical data and clinicomorphologic characteristics. *Cancer*, **86**, 149–156

Tso, T.C., Harley, N. & Alexander, L.T. (1966) Sources of lead-210 and polonium-210 in tobacco. *Science*, **153**, 880–882

Tsyb, A.F., Ivanov, V.K., Airapetov, S.A., Gapin, E.A., Maksiutov, M.A., Rozhkov, O.V., Stadnik, O.E., Chekin, S.I. & Saakian, A.K. (1992) Epidemiological analysis of data on liquidators of the Chernobyl accident living in Russia. *Med. Radiol.*, **9/10**, 44–47

Tsyb, A.F., Shakhtarin, V.V., Lushnikov, E.F., Stepanenko, V.F., Snykov, V.P., Parshkov, E.M. & Trofimova, S.F. (1999) Development of cancer and non-cancer thyroid diseases in children and adolescents after the Chernobyl accident. In: Thomas, G., Karaoglou, A. & Williams, E.D., eds, *Radiation and Thyroid Cancer*, Singapore, World Scientific, pp. 79–87

Tubiana, M., Attie, E. & Parmentier, C. (1975) [Outcome of polycythaemia vera treated with radioactive phosphorus. A series of 303 patients followed for 12 to 24 years.] *Nouv. Presse méd.*, **4**, 1781–1786 (in French)

Twardock, A.R. (1967) Placental transfer of calcium and strontium in the guinea pig. *Am. J. Physiol.*, **213**, 837–842

Umeki, S., Kyoizumi, S., Kusunoki, Y., Nakamura, N., Saski, M., Mori, T., Ishikawa, Y., Cologne, J.B. & Akiyama, M. (1991) Flow cytometric measurements of somatic cell mutations in Thorotrast patients. *Jpn. J. Cancer Res.*, **82**, 1349–1353

Unni, K.K. (1996) *Dahlin's Bone Tumors, General Aspects and Data on 11,087 Cases*, 5th Ed., Philadelphia, Lippincott-Raven

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1977) *Sources and Effects of Ionizing Radiation* (United Nations Sales Publication E.77.IX.1), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1982) *Ionizing Radiation: Sources and Biological Effects* (United Nations Sales Publication E.82.IX.8), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1986) *Genetic and Somatic Effects of Ionizing Radiation* (United Nations Sales Publication E.86.IX.9), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1988) *Sources, Effects and Risks of Ionizing Radiation. 1988 Report to the General Assembly* (United Nations Sales Publication E.88.IX.7), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1993) *Sources and Biological Effects of Ionizing Radiation. 1993 Report to the General Assembly* (United Nations Sales Publication E.94.IX.2), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1994) *Sources and Effects of Ionizing Radiation, UNSCEAR 1994 Report to the General Assembly*, United Nations Sales Publication E.94.IX.11), New York, United Nations

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2000) *Sources and Effects of Ionizing Radiation*, Vols I and II (United Nations Sales Publications E.00.IX.3 and E.00.IX.4), New York, United Nations

Upton, A.C., Randolph, M.L. & Carklin, J.W. (1970) Late effects of fast neutrons and gamma-rays in mice as influenced by the dose-rate of irradiation: Induction of neoplasia. *Radiat. Res.*, **41**, 467–491

Usenko, V., Lepekhin, E., Lyzogubov, V., Kornilovska, I., Ushakova, G. & Witt, M. (1999) The influence of low doses ^{131}I-induced maternal hypothyroidism on the development of rat embryos. *Exp. Toxicol. Pathol.*, **51**, 223–227

Van Best, J.A. (1982) Comparison of thyroid function in mice after various injected activities of ^{123}I, ^{125}I and ^{131}I. *Int. J. Radiat. Biol.*, **42**, 545–557

Van Dam, F.J., Camps, J.A., Woldring, V.M., Natarajan, A.T., Van der Wall, E.E., Zwinderman, A.H., Lohman, P.H.M., Pauwels, E.K.J. & Tates, A.D. (1991) Radionuclide angiography with Tc-99m *in vivo* labeled erythrocytes does not lead to induction of mutations in the HPRT gene of human T-lymphocytes. *J. nucl. Med.*, **32**, 814–818

Van den Heuvel, R., Schoeters, G. & Vanderborght, O. (1987) Radiosensitivity to ^{241}Am of bone marrow stromal cells in offsprings of contaminated mice. In: Gerber, G.B., Métivier, H. & Smith, H., eds, *Age-related Factors in Radionuclide Metabolism and Dosimetry*, Dordrecht, Martinus Nijhoff, pp. 201–208

Van den Heuvel, R., Gerber, G.B., Leppens, H., Vander Plaetse, F. & Schoeters, G.E.R. (1995) Long-term effects on tumour incidence and survival from ^{241}Am exposure of the BALB/c mouse *in utero* and during adulthood. *Int. J. Radiat. Biol.*, **68**, 679–686

Van den Hooff, A. (1984) The part played by the stroma in carcinogenesis. *Perspectives Biol. Med.*, **27**, 498–509

de Vathaire, F., Schlumberger, M., Delisle, M.J., Francese, C., Challeton, C., de la Genardière, E., Meunier, F., Parmentier, C., Hill, C. & Sancho-Garnier, H. (1997) Leukaemias and cancers following iodine-131 administration for thyroid cancer. *Br. J. Cancer*, **75**, 734–739

Videbaek, A. (1950) Polycythemia vera. Course and prognosis. *Acta med. scand.*, **138**, 179–187

Virsik, R.P., Schäfer, C.H., Harder, D., Goodhead, D.T., Cox, R. & Thacker, J. (1980) Chromosome aberrations induced in human lymphocytes by ultrasoft Al_k and C_k X-rays. *Int. J. Radiat. Biol.*, **38**, 545–557

Viswanathan, K., Gierlowski, T.C. & Schneider, A.B. (1994) Childhood thyroid cancer. Characteristics and long-term outcome in children irradiated for benign conditions of the head and neck. *Arch. Pediatr. Adolesc. Med.*, **148**, 260–265

Voelz, G.L., & Lawrence, J.N.P. (1991) A 42-y medical follow-up of Manhattan Project plutonium workers. *Health Phys.*, **61**, 181–190

Voelz, G.L., Lawrence, J.N.P. & Johnson, E.R. (1997) Fifty years of plutonium exposure to the Manhattan Project plutonium worker: An update. *Health Phys.*, **73**, 611–619

Volf, V. (1986) Chelation therapy of incorporated plutonium-238 and americium-241: Comparison of LICAM(C), DTPA and DFOA in rats, hamsters and mice. *Int. J. Radiat. Biol.*, **49**, 449–462

Volkert, W.A., Goeckeler, W.F., Ehrhardt, G.J. & Ketring, A.R. (1991) Therapeutic radionuclides: Production and decay property considerations. *J. nucl. Med.*, **32**, 174–185

Vorobiova, M.I., Degteva, M.O., Burmistrov, D.S., Safronova, N.G., Kozheurov, V.P., Anspaugh, L.R. & Napier, B.A. (1999) Review of historical monitoring data on Techa River contamination. *Health Phys.*, **76**, 605–618

Vulpis, N. (1984) The induction of chromosome aberrations in human lymphocytes by *in vitro* irradiation with β particles from tritiated water. *Radiat. Res.*, **97**, 511–518

Wada, I., Horiuchi, H., Mori, M., Ishikawa, Y., Fukumoto, M., Mori, T., Kato, Y., Kitagawa, T. & Machinami, R. (1999) High rate of small *TP53* mutations and infrequent loss of heterozygosity in malignant liver tumors associated with Thorotrast: Implications for alpha-particle carcinogenesis. *Radiat. Res.*, **152**, S125–S127

Wagoner, J.K., Archer, V.E., Carroll, B.E., Holaday, D.A. & Lawrence, P.A. (1964) Cancer mortality patterns among US uranium miners and millers, 1950 through 1962. *J. natl Cancer Inst.*, **32**, 787–801

Wagoner, J.K., Arvher, V.E., Lundin, F.E., Jr, Holaday, D.A. & Lloyd, J.W. (1965) Radiation as the cause of lung cancer among uranium miners. *New Engl. J. Med.*, **273**, 181–188

Walinder, G. (1972) Late effects of irradiation on the thyroid gland in mice. I. Irradiation of adult mice. *Acta radiol. ther. phys. biol.*, **11**, 433–451

Walinder, G. & Rönnbäck, C. (1984) Neoplastic effects after prenatal irradiation. In: *Effects of Prenatal Irradiation with Special Emphasis on Late Effects* (EUR-8067), Luxembourg, Commission of the European Communities, pp. 101–115

Walinder, G. & Sjödén, A.-M. (1972) Late effects of irradiation on the thyroid gland in mice. II. Irradiation of mouse foetuses. *Acta radiol. ther. phys. biol.*, **11**, 577–589

Walinder, G. & Sjödén, A.-M. (1973) Late effects of irradiation on the thyroid gland in mice. III. Comparison between irradiation of foetuses and adults. *Acta radiol. ther. phys. biol.*, **12**, 201–208

Wang, B. & Zhou, X.-Y. (1995) Effects of prenatal exposure to low-dose β radiation from tritiated water on the neurobehavior of mice. *J. Radiat. Res.*, **36**, 103–111

Ward, J.F. (1994) The complexity of DNA damage: Relevance to biological consequences. *Int. J. Radiat. Biol.*, **66**, 427–432

Watanabe, N., Yokoyama, K., Kinuya, S., Shuke, N., Shimizu, M., Futatsuya, R., Michigishi, T., Tonami, N., Seto, H. & Goodwin, D.A. (1998) Radiotoxicity after iodine-131 therapy for thyroid cancer using the micronucleus assay. *J. nucl. Med.*, **39**, 436–440

Watson, G.E., Lorimore, S.A. & Wright, E.G. (1996) Long-term *in vivo* transmission of α-particle-induced chromosomal instability in murine haemopoietic cells. *Int. J. Radiat. Biol.*, **69**, 175–182

Waxweiler, R.J., Archer, V.E., Roscoe, R.J., Watanabe, A. & Thun, M.J. (1983) Mortality patterns among a retrospective cohort of uranium mill workers. In: *Epidemiology Applied to Health Physics, Proceedings of the 16th Mid-year Topical Meeting of the Health Physics Society, Albuquerque, NM, January 9–13*, McLean, VA, Health Physics Society, pp. 428–435

Wegener, K., Hasenohrl, K. & Wesch, H. (1983) Recent results of the German Thorotrast study — Pathoanatomical changes in animal experiments and comparison to human thorotrastosis. *Health Phys.*, **44** (Suppl. 1), 307–316

Weiner, R.E., McInroy, J.F. & Wegst, A.V. (1985) Determination of environmental levels of Pu, Am, U and Th in human fetal tissue (Abstract). *Health Phys.*, **49**, 141

Weiss, E.S., Olsen, R.E., Thompson, G.D.C. & Masi, A.T. (1967) Surgically treated thyroid disease among young people in Utah, 1948–1962, *Am. J. public Health*, **57**, 1807–1814

Weiss, E.S., Rallison, M.L., London, W.T. & Thompson, G.D.C. (1971) Thyroid nodularity in southwestern Utah school children exposed to fallout radiation. *Am. J. public Health*, **61**, 241–249

Weller, R.E., Buschbom, R.L., Park, J.F., Dagle, G.E. & Ragan, H.A. (1995a) Hematological effects of inhaled plutonium dioxide in beagles. *Radiat. Res*., **143**, 69–76

Weller, R.E., Dagle, G.E., Buschbom, R.L. & Park, J.F. (1995b) Examination of testicular tumours in the beagle dog exposed to inhaled plutonium. *Int. J. Radiat. Biol*., **68**, 63–70

Weller, R.E., Buschbom, R.L., Dagle, G.E., Ragan, H.A. & Park, J.F. (1995c) Hepatic effects of inhaled plutonium dioxide in beagles. *Radiat. Res*., **144**, 73–81

Welleweerd, J., Wilder, M.E., Carpenter, S.G. & Raju, M.R. (1984) Flow cytometric determination of radiation-induced chromosome damage and its correlation with cell survival. *Radiation Res.*, **99**, 44–51

Werner, S.C., Hamilton, H. & Nemeth, M.R. (1952) Therapeutic effects from repeated diagnostic doses of I^{131} in adult and juvenile hyperthyroidism. *J. clin. Endocrinol.*, **12**, 1349–1355

Wesch, H., van Kaick, G., Riedel, W., Kaul, A., Wegener, K., Hasenöhrl, K., Immich, H. & Muth, H. (1983) Recent results of the German Thorotrast study — Statistical evaluation of animal experiments with regard to the nonradiation effects in human thorotrastosis. *Health Phys*., **44** (Suppl. 1), 317–321

Wesch, H., Riedel, W., Hasenöhrl, K., Wegener, K., Kaul, A., Muth, H. & van Kaick, G. (1986) German Thorotrast study: Results of the long-term animal studies on the effect of incorporated radioactive and nonradioactive particles. In: Gössner, W., Gerber, G.B., Hagen & U., Luz, A., eds, *The Radiobiology of Radium and Thorotras*t, Munich, Urban & Schwarzenberg, pp. 186–188

Whaley, J.M. & Little, J.B. (1990) Efficient mutation induction by ^{125}I and ^{131}I decays in DNA of human cells. *Radiat. Res*., **123**, 68–74

Whaley, J.M., Kassis, A.I., Kinsey, B.M., Adelstein, S.J. & Little, J.B. (1990) Mutation induction by ^{125}iodoacetylproflavine, a DNA-intercalating agent, in human cells. *Int. J. Radiat. Biol*., **57**, 1087–1103

Whicker, F.W., Kirchner, T.B., Anspaugh, L.R. & Ng, Y.C. (1996) Ingestion of Nevada Test Site fallout: Internal dose estimates. *Health Phys.*, **71**, 477–486

White, R.G., Raabe, O.G., Culbertson, M.R., Parks, N.J., Samuels, S.J. & Rosenblatt, L.S. (1993) Bone sarcoma characteristics and distribution in beagles fed strontium-90. *Radiat. Res*., **136**, 178–189

White, R.G., Raabe, O.G., Culbertson, M.R., Parks, N.J., Samuels, S.J. & Rosenblatt, L.S. (1994) Bone sarcoma characteristics and distribution in beagles injected with radium-226. *Radiat. Res*., **137**, 361–370

Whitehouse, C.A., Tawn, E.J. & Riddell, A.E. (1998) Chromosome aberrations in radiation workers with internal deposits of plutonium. *Radiat. Res*., **150**, 459–468

WHO (1982) Histological typing of lung tumours. *Am. J. clin. Pathol*., **77**, 123–136

Wichmann, H.E., Kreienbrock, L., Kreuzer, M., Gerken, M., Dingerkus, G., Wellmann, J. & Keller, G. (1998a) *Lungenkrebsrisiko durch Radon in der Bundesrepublik Deutschland (West)* [*Risk for Lung Cancer from Radon in Western Germany*], Landsberg, Ecomed Verlagsgesellschaft

Wichmann, H.E., Kreienbrock, L., Kreuzer, M., Gerken, M., Dingerkus, G., Wellmann, J., Keller, G. & Kappel, R. (1998b) Results of the western German case–control study on indoor radon and lung cancer in the context of other epidemiological studies. In: *Radiation Protection 98, Scientific Seminar on Radiation Protection in Relation to Radon*, Luxembourg, Commission of the European Communities

Wichmann, H.E., Gerken, M., Wellmann, J., Kreuzer, M., Kreienbrock, L., Keller, G., Wölke, G. & Heinrich, J. (1999) *Lungenkrebsrisikso durch Radon in der Bundesrepublik Deutschland (Ost) — Thüringen und Sachsen [Risk for Lung Cancer from Radon in Eastern Germany — Thuringia and Saxony]*, Landsberg, Ecomed Verlagsgesellschaft

Wick, R.R. & Gössner, W. (1983) Follow-up study of late effects in ^{224}Ra treated ankylosing spondylitis patients. *Health Phys.*, **44**, 187–195

Wick, R.R. & Gössner, W. (1993) History and current uses of ^{224}Ra in ankylosing spondylitis and other diseases. *Environ. int.*, **19**, 467–473

Wick, R.R., Chmelevsky, D. & Gössner, W. (1986) ^{224}Ra: Risk to bone and haematopoietic tissue in ankylosing spondylitis patients. In: Gössner, W., Gerber, G.B., Hagen, U. & Luz, A., eds, *The Radiobiology of Radium and Thorotrast*, Munich, Urban & Schwarzenberg, pp. 38–44

Wick, R.R., Nekolla E.A., Gössner, W. & Kellerer, A.M. (1999) Late effects in ankylosing spondylitis patients treated with ^{224}Ra. *Radiat. Res.*, **152**, S8–S11

Wiethege, T., Wesch, H., Wegener, K., Müller, J.-M., Mehlhorn, J., Spiethoff, A., Schömig, D., Hollstein, M., Bartsch, H. & the German Uranium Miner Study, Research Group Pathology (1999) German uranium miner study — Pathological molecular genetic findings. *Radiat. Res.*, **152**, S52–S55

Wiggs, L.D., Cox-DeVore, C.A. & Voelz, G.L. (1991) Mortality among a cohort of workers monitored for ^{210}Po exposure: 1944–1972. *Health Phys.*, **61**, 71–76

Wiggs, L.D., Johnson, E.R., Cox-DeVore, C.A. & Voelz, G.L. (1994) Mortality through 1990 among white male workers at the Los Alamos National Laboratory: Considering exposures to plutonium and external ionizing radiation. *Health Phys.*, **67**, 577–588

Wiklund, K., Holm, L.-E. & Eklund, G. (1990) Cancer risks in Swedish Lapps who breed reindeer. *Am. J. Epidemiol.*, **132**, 1078–1082

Wiklund, K., Holm, L.-E. & Eklund, G. (1991) Mortality among Swedish reindeer breeding Lapps in 1961–85. *Arctic med. Res.*, **50**, 3–7

Wiley, L.M., Raabe, O.G., Khan, R. & Straume, T. (1994) Radiosensitive target in the early mouse embryo exposed to very low doses of ionizing radiation. *Mutat. Res.*, **309**, 83–92

Wilkinson, G.S., Tietjen, G.L., Wiggs, L.D., Galke, W.A., Acquavella, J.F., Reyes, M., Voelz, G.L. & Waxweiler, R.J. (1987) Mortality among plutonium and other radiation workers at a plutonium weapons facility. *Health Phys.*, **125**, 231–250

Williams, E.D. (1996) Editorial: Thyroid cancer and the Chernobyl accident. *J. clin. Endocrinol. Metab.*, **81**, 6–8

Williams, E.D., Cherstvoy, E., Egloff, B., Hofler, H., Vecchio, G., Bogdanova, T., Bragarnik, M. & Tronko, N.D. (1996) Interaction of pathology and molecular characterization of thyroid cancers. In: Karaoglou, A., Desmet, G., Kelly, G.N. & Menzel, H.G., eds, *The Radiological Consequences of the Chernobyl Accident. Proceedings of the First International Conference, Minsk, Belarus, 18 to 22 March 1996* (EUR 16544 EN), Luxembourg, Office for Official Publications of the European Commission, pp. 699–714

Wilson, A.R. & Spiers, F.W. (1967) Fallout caesium-137 and potassium in newborn infants. *Nature*, **215**, 470–474

Withers, H.R. (1986) Predicting late normal tissue responses. *Int. J. Radiat. Oncol. Biol. Phys.*, **12**, 693–698

Withers, H.R. (1989) Failla memorial lecture. Contrarian concepts in the progress of radiotherapy. *Radiat. Res.*, **119**, 395–412

Wolff, S.P. (1991) Leukaemia risks and radon (Letter to the Editor). *Nature*, **352**, 288

Wones, R., Radack, K., Martin, V., Mandell, K., Pinney, S. & Buncher, R. (1995) Do persons living near a uranium processing site have evidence of increased somatic cell gene mutations? A first study. *Mutat. Res.*, **335**, 171–184

Wood, J.W., Tamagaki, H., Neriishi, S., Sato, T., Sheldon, W.F., Archer, P.G., Hamilton, H.B. & Johnson, K.G. (1969) Thyroid carcinoma in atomic bomb survivors. Hiroshima and Nagasaki. *Am. J. Epidemiol.*, **89**, 4–14

Woodward, A., Roder, D., McMichael, A.J., Crouch, P. & Mylvaganam, A. (1991) Radon daughter exposures at the Radium Hill uranium mine and lung cancer rates among former workers, 1952–87. *Cancer Causes Control*, **2**, 213–220

Wrenn, M.E., Durbin, P.W., Howard, B., Lipsztein, J., Rundo, J., Still, E.T. & Willis, D.L. (1985) Metabolism of ingested U and Ra. *Health Phys.*, **48**, 601–633

Wrenn, M.E., Singh, N.P., Ruth, H., Rallison, M.L. & Burleigh, D.P. (1989) Gastrointestinal absorption of soluble uranium from drinking water by man. *Radiat. Prot. Dosim.*, **26**, 119–122

Wu, L.-J., Randers-Pehrson, G., Xu, A., Waldren, C.A., Geard, C.R., Yu, Z.-L. & Hei, T.K. (1999) Targeted cytoplasmic irradiation with alpha particles induces mutations in mammalian cells. *Proc. natl Acad. Sci USA*, **96**, 4959–4964

Xu, Z.-Y., Blot, W.J., Xiao, H.-P., Wu, A., Feng, Y.-P., Stone, B.J., Sun, J., Ershow, A.G., Henderson, B.E. & Fraumeni, J.F., Jr (1989) Smoking, air pollution and the high rates of lung cancer in Shenyang, China. *J. natl Cancer Inst.*, **81**, 1800–1806

Xuan, X.-Z,, Lubin, J.H., Li, J.-Y., Yang, L.-F., Sheng, L.Q., Lan, Y., Wang, J.-Z. & Blot, W.J. (1993) A cohort study in southern China of tin miners exposed to radon and radon decay products. *Health Phys.*, **64**, 120–131

Yachmenyov, V.A. & Isageva, L.W. (1996) Environmental monitoring in the vicinity of the Mayak atomic facility. *Health Phys.*, **71**, 61–70

Yakushina, V.I., Ivanov, A.E., Kirillov, S.A., Kurshakova, N.N., Mordasheva, V.V., Severin, S.F. & Drutman, R.D. (1972) [A case of lung cancer in a female worker of the plutonium plant.] *Bull. Radiat. Med.*, **2**, 29–40 (in Russian)

Yamada, T., Yukawa, O., Asami, K., & Nakazawa, T. (1982) Effect of chronic HTO β or ^{60}Co γ radiation on preimplantation mouse development *in vitro*. *Radiat. Res.*, **92**, 359–369

Yamaguchi, T., Yasukawa, M., Terasima, T. & Matsudaira, H. (1989) Induction of malignant transformation in mouse 10T1/2 cells by low-dose-rate exposure to tritiated water and gamma-rays at two different temperatures, 4 °C and 37 °C. *J. Radiat. Res.*, **30**, 112–121

Yamamoto, O., Yokoro, K., Seyama, T., Kinomura, A. & Nomura, T. (1990) HTO oral administration in mice. I: Threshold dose rate for haematopoietic death. *Int. J. Radiat. Biol.*, **57**, 543–549

Yamamoto, O., Seyama.T., Jo, T., Terato, H., Saito, T. & Kinomura, A. (1995) Oral administration of tritiated water (HTO) in mouse. II. Tumour development. *Int. J. Radiat. Biol.*, **68**, 47–54

Yamamoto, O., Seyama, T., Itoh, H. & Fujimoto, N. (1998) Oral administration of tritiated water (HTO) in mouse. III: Low dose-rate irradiaton and threshold dose-rate for radiation risk. *Int. J. Radiat. Biol.*, **73**, 535–541

Yao, S.-X., Lubin, J.H., Qiao, Y.L., Boice, J.D., Jr, Li, J.-Y., Cai, S.-K., Zhang, F.-M. & Blot, W.J. (1994) Exposure to radon progeny, tobacco use and lung cancer in a case–control study in southern China. *Radiat. Res.*, **138**, 326–336

Yngveson, A., Williams, C., Hjerpe, A., Lundeberg, J., Söderkvist, P. & Pershagen, G. (1999) *p53* mutations in lung cancer associated with residential radon exposure. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 433–438

Young, R.W. (1987) Acute radiation syndrome. In: Conklin, J.J. & Walker, R.I., eds, *Military Radiobiology*, New York, Academic Press, pp. 165–190

Zaire, R., Griffin, C.S., Simpson, P.J., Papworth, D.G., Savage, J.R.K., Armstrong, S. & Hulten, M.A. (1996) Analysis of lymphocytes from uranium mineworkers in Namibia for chromosomal damage using fluorescence in situ hybridization (FISH). *Mutat. Res.*, **371**, 109–113

Zaire, R., Notter, M., Riedel, W. & Thiel, E. (1997) Unexpected rates of chromosomal instabilities and alterations of hormone levels in Namibian uranium miners. *Radiat. Res.*, **147**, 579–584

Zakharova, M.L., Uriadnitskaia, T.I., Sokhranich, A.L., Revina, V.S. & Nifatov, A.P. (1988) [Frequency of structural chromosome aberrations in the hepatocytes of rats exposed to polymeric ^{239}Pu.] *Radiobiologiia*, **28**, 752–755 (in Russian)

von Zallinger, C. & Tempel, K. (1998) Transplacental transfer of radionuclides. A review. *J. vet. Med. A.*, **45**, 581–590

Zamenhof, S. & van Marthens, E. (1979) The effects of chronic ingestion of tritiated water on prenatal brain development. *Radiat. Res.*, **77**, 117–127

Zamenhof, S. & van Marthens, E. (1981) The effects of pre- and postnatal exposure to tritiated water for five generations on postnatal brain development. *Radiat. Res.*, **85**, 292–301

Zanzonico, P.B. & Becker, D.V. (1992) Radiation hazards in children born to mothers exposed to 131-iodine. In: Beckers, C. & Reinwein, D., eds, *The Thyroid and Pregnancy*, New York, John Wiley, pp. 189–202

Zivanovic, M.A., McCready, V.R. & Taylor, D.M. (1979) The urinary excretion of gallium-67 citrate in patients with neoplastic disease. *Eur. J. nucl. Med.*, **4**, 277–282

Zúñiga-González, S. (2000) [Thyroiditis following treatment with radioiodine (^{131}I). Case report and review of the literature.] *Gac. Méd. Méx.*, **136**, 65–69 (in Spanish)

GLOSSARY

Absorbed dose: mean energy imparted by *ionizing radiation* to an irradiated medium per unit mass, expressed in *grays* (Gy)

Absorbed fraction: the fraction of the photon energy (emitted within a specified volume of material) that is absorbed by the volume. The absorbed fraction depends on the source distribution, the photon energy, and the size, shape, and composition of the volume.

Absorption: the process by which radiation imparts some or all of its energy to any material through which it passes

Activity: the number of nuclear transformations occurring in a given quantity of material per unit time (see ***Curie***, ***Becquerel***)

Activity median aerodynamic diameter (AMAD): the diameter of a unit-density sphere with the same terminal settling velocity in air as that of the aerosol particle whose activity is the median for the entire aerosol

Acute radiation sickness: the complex symptoms and signs characterizing the condition resulting from excessive exposure of the whole body (or a large part of it) to ionizing radiation. Five Sv is fatal 50 percent of the time. The earliest of these symptoms are nausea, fatigue, vomiting, and diarrhea and these may be followed by loss of hair (epilation), hemorrhage, inflammation of the mouth and throat, and general loss of energy. In severe cases, where the radiation dose is relatively high, death may occur within two to four weeks. Those who survive six weeks after exposure of a single high dose of radiation may generally be expected to recover.

α-decay: *radioactive decay* in which an *α-particle* is emitted. This lowers the *atomic number* of the nucleus by two and its *mass number* by four.

α-particle: two neutrons and two protons bound as a single particle that is emitted from the nucleus of certain radioactive *isotopes* in the process of decay or *disintegration*; a positively charged particle indistinguishable from the nucleus of a helium atom

α-track: the track of ionized atoms left in any matter by an α-particle that has traveled through the matter

Annihilation radiation: the electromagnetic radiation emitted as a result of the combination and disappearance of an electron and a positron. Two γ-rays of 0.511 MeV energy are emitted in most cases.

Atom: the smallest particle of an element that cannot be divided or broken up by chemical means. It consists of a central core called the nucleus, which contains protons and neutrons and an outer shell of electrons.

Atomic mass (*u*): the mass of a neutral atom of a *nuclide*, usually expressed in terms of atomic mass units. The atomic mass unit is one-twelfth the mass of one neutral atom of carbon-12, equivalent to 1.66054×10^{-27} kg.

Atomic number (*Z*): the number of protons in the nucleus of a neutral atom of a nuclide

Atomic mass number (*A*): the number of *nucleons* (protons and neutrons) in the nucleus of an atom

Atomic weight: the weighted mean of the masses of the neutral atoms of an element expressed in atomic mass units

Auger electron: electron ejected from the surrounding shells due to the return to the ground state of an atom, ionized in an inner shell

Background radiation: the amount of radiation to which a population is exposed from natural sources, such as terrestrial radiation from naturally occurring *radionuclides* in the soil, cosmic radiation originating from outer space, and naturally occurring radionuclides deposited in the human body

Becquerel (Bq): SI unit of activity; equals that quantity of radioactive material in which one transformation (disintegration) occurs per second (1 Bq = 1 disintegration per second = 2.7×10^{-11} Ci).

β-decay: *radioactive decay* in which a β-particle is emitted or in which orbital *electron capture* occurs.

β-particle: charged particle emitted from the nucleus of an atom, with mass and charge equal to those of an electron

Biological half-time: The time required for a biological system, such as that of a human, to eliminate by natural processes half of the amount of a substance (such as a chemical substance or radioactive material) that has entered it

Body burden, radioactivity: the amount of radioactive material present in the total body

Boiling water reactor (BWR): a reactor in which water, used as both coolant and moderator, is allowed to boil in the core. The resulting steam can be used directly to drive a turbine and electrical generator, thereby producing electricity (see ***Light water reactor***).

Bone seeker: a radioisotope that tends to accumulate in the bones when it is introduced into the body. An example is strontium-90, which behaves chemically like calcium.

Bone surface: bone surface is the surface of bone as seen in a light microscope. It includes the endosteal and periosteal surfaces of *cortical bone*, the surfaces of *haversian canals*, the surfaces of resorption cavities, and the surfaces of trabeculae. It does not include the surfaces of lacunae or canaliculi. It should not be confused with the surfaces of the sub-microscopic bone crystals.

Burial: disappearance of pre-existing radioactive deposits from bone surfaces due to the continued deposition of new bone onto the contaminated surface

Bystander effect: the induction, by low levels of radiation, of genetic changes in cells that in themselves received no direct radiation exposure

Collective dose: the sum of the individual doses received in a given period of time by a specified population from exposure to a specified source of radiation

Collective dose commitment: infinite time integral of the product of the size of a specified population and the per caput ***dose rate*** to a given organ or tissue for that population

Collective effective dose equivalent: product of the number of exposed individuals and their average *effective dose* equivalent, expressed in person–sieverts

Committed dose equivalent: dose to some specific organ or tissue over 50 years after intake of radioactive material by an individual

Committed effective dose equivalent: *committed dose equivalent* for a given organ multiplied by a weighting factor (see ***Radiation weighting factor***, ***Tissue weighting factor***)

Compact bone: internal bone architecture consisting mainly of calcified tissue with small spaces (canals) occupied by blood vessels (see ***Trabecular bone***)

Cortical bone: bone tissue belonging to the cortex (the outer shell of a bone) and in which the arrangement of one canal with bone surrounding it is called a haversian system or osteon

Curie (Ci): the basic unit used to describe the intensity of radioactivity in a sample of material. The curie is equal to 3.7×10^{10} disintegrations per second, which is approximately the activity of 1 gram of radium. A curie is also a quantity of any radionuclide that decays at a rate of 3.7×10^{10} disintegrations per second. It is named for Marie and Pierre Curie, who discovered radium in 1898.

Decay chain or decay series: a sequence of radioactive decays (transformations) beginning with one nucleus. The initial nucleus, the parent, decays into a daughter nucleus that differs from the first by whatever particles were emitted during the decay. If further decays take place, the subsequent nuclei are also usually called daughters or progeny (see ***Decay product***)

Decay constant: see ***Disintegration constant***

Decay product: a new *isotope* formed as a result of radioactive decay. A nuclide resulting from the radioactive transformation of a *radionuclide*, formed either directly or as the result of successive *transformations* in a radioactive series. A decay product (daughter) may be either radioactive or stable.

Decay, radioactive: the decrease in the amount of any radioactive material with the passage of time due to the spontaneous emission from the atomic nuclei of either α- or β-particles, often accompanied by γ-radiation

Decorporation therapy (also: ***Chelation therapy***): procedure used to remove an internally deposited radionuclide from a person's body by administration of a metal-chelating agent to enhance excretion of the radionuclide. The chelating agent used most commonly today is a salt of diethylenetriaminepentaacetic acid, DTPA.

Depleted uranium: uranium having a percentage of ^{235}U smaller than the 0.7 percent found in natural uranium. It is obtained as a by-product from uranium isotope separation (see ***Enrichment***).

Deterministic effects (also: ***Non-stochastic effects***): the health effects, the severity of which varies with the dose and for which a threshold is believed to exist. Radiation-induced cataract formation is an example of a deterministic effect (see ***Stochastic effects***).

Disintegration constant (also: ***Decay constant***): the fraction of the number of atoms of a radioactive nuclide which decay in unit time; is the symbol for the decay constant in the equation $N = N_0e^{-t}$, where N_0 is the initial number of atoms present, and N is the number of atoms present after some time (t).

Disintegration, nuclear: a spontaneous nuclear *transformation* (radioactivity) characterized by the emission of energy and/or mass from the nucleus. When large numbers of nuclei are involved, the process is characterized by a definite half-life (see ***Transformation, nuclear***).

Dose rate: *absorbed dose* delivered per unit time

Effective dose: sum of *equivalent doses*, weighted by the appropriate *tissue weighting factors*, in all the tissues and organs of the body

Electron: subatomic charged particle. Negatively charged electrons are parts of stable atoms. Both negatively and positively charged electrons may be expelled from the radioactive atom when it disintegrates (see also **β-*particle***).

Electron capture: a mode of radioactive decay involving the capture of an orbital electron by its nucleus. Capture from a particular electron shell is designated as 'K-electron capture', 'L-electron capture', etc.

Electron volt (eV): unit of energy; 1 eV is equivalent to the energy gained by an electron in passing through a potential difference of 1 V.

Enriched material: (1) material in which the relative amount of one or more isotopes of a constituent has been increased; (2) uranium in which the abundance of the ^{235}U isotope is increased above normal

Enrichment, isotopic: An isotopic separation process by which the relative abundance of the *isotopes* of a given element is altered, thus producing a form of the element that has been enriched in one or more isotopes and depleted in others. In uranium enrichment, the percentage of uranium-235 in natural uranium is increased from 0.7 percent to > 90 percent in a gaseous diffusion process based on the different thermal velocities of the constituents of natural uranium (^{234}U, ^{235}U, ^{238}U).

Equilibrium, radioactive: In a radioactive series, the state that prevails when the ratios between the activities of two or more successive members of the series remains constant

Equivalent dose: obtained by weighting the *absorbed dose* in an organ or tissue by a *weighting factor* that reflects the biological effectiveness of the radiation that produces *ionization* within the tissue

γ-radiation: short-wavelength electromagnetic radiation of nuclear origin

Genomic instability (radiation-induced): a type of genome-wide instability in mammalian cells which is transmissible over many generations of cell replication and can lead to the enhancement of the mutation rate at multiple, unrelated loci

Gray (Gy): SI unit of absorbed dose, J/kg (1 Gy = 1 J/kg = 100 rad)

Half-life, radioactive: the time in which one half of the atoms of a particular radioactive substance disintegrates into another nuclear form. Measured half-lives vary from millionths of a second to billions of years. Also called physical or radiological half-life

Half-life, biological: the time required for the body to eliminate one half of the material taken in by natural biological means

Half-life, effective: the time required for a radionuclide contained in a biological system, such as a human or an animal, to reduce its activity by one-half as a combined result of radioactive decay and biological elimination

Haversian canals: cavities within mineralized bone in which run the blood vessels, lymph vessels and nerves. The canals are lined with connective tissue, the endosteum.

High-LET radiation (see also ***Linear energy transfer***): heavy, charged particles such as *protons* and *α-particles* that produce dense ionizing events close together on the scale of a cellular nucleus

Heavy water moderated reactor: a reactor that uses heavy water as its moderator. Heavy water is an excellent moderator and thus permits the use of unenriched uranium as a fuel.

Hot particle: a discrete radioactive fragment that is insoluble in water and is no larger than approximately 1 mm in any dimension

Hyperthyroidism (thyrotoxicosis): functional, metabolic state caused by excessive thyroid hormone

Hypothyroidism: functional, metabolic state caused by inadequate amounts of thyroid hormone

Ionization: the process by which a neutral atom or molecule acquires a positive or negative charge

Ionization path (track): the trail of ion pairs produced by ionizing radiation in its passage through matter

Ionizing radiation: radiation sufficiently energetic to dislodge electrons from an atom thereby causing an ion pair; includes *X-radiation* and *γ-radiation*, electrons (*β-particles*), *α-particles* (helium nuclei) and heavier charged atomic nuclei

Isobars: nuclides having the same *mass number* but different *atomic numbers*

Isotopes: atoms with the same number of protons, but different numbers of neutrons in their nuclei. Thus, carbon-12, carbon-13, and carbon-14 are isotopes of the element carbon, the numbers denoting the approximate atomic weights. Isotopes have very nearly the same chemical properties, but often different physical properties (for example, carbon-12 and -13 are stable, carbon-14 is radioactive).

Linear energy transfer (LET): average amount of energy lost per unit of particle track length. Low LET is characteristic of *electrons*, *X-rays* and *γ-rays*; high LET is characteristic of *protons* and *α-particles*.

Light water reactor: a term used to describe reactors using ordinary water as coolant, including boiling water reactors (BWRs) and pressurized water reactors (PWRs)

Low-LET radiation: light, charged particles such as *electrons* or *X-rays* and *γ-rays* that produce sparse ionizing events far apart on the scale of a cellular nucleus

Lung clearance class (days, D; weeks, W; years, Y): a classification scheme for inhaled material according to its rate of clearance from the pulmonary region of the lungs to the blood and the gastrointestinal tract. Also used are classes of F (fast), M (medium), and S (slow) clearance.

Mass Number (*A*): See ***Atomic mass number***

Mastoid process: conical prominence of the temporal bone of the human skull, situated behind the ear. It commonly becomes infected in cases of suppurative otitis media. The inner ear adjoins the hollow, spongy spaces within the mastoid process so that infection of the ear easily spreads to that area, causing pain and swelling. Surgical drainage of pus and injection of antibiotics usually eliminate mastoid infection and prevent its spread to nearby areas of the brain.

Neutron: elementary particle that is a constituent of all atomic nuclei except that of normal hydrogen; has no electric charge and a mass only very slightly greater than that of the *proton*.

Non-stochastic effects: see ***Deterministic effects***

Nucleon: common name for a constituent particle of the nucleus. Applied to a *proton* or *neutron*.

Nuclide: species of atom characterized by the constitution of its nucleus and hence by the number of *protons*, the number of *neutrons*, and the energy content

Parent: a *radionuclide* that, on *disintegration*, yields a specified nuclide either directly or as a later member of a radioactive series

Photon: quantum of *electromagnetic radiation* that has zero rest mass and energy equal to the product of the frequency of the radiation and Planck's constant; generated when a particle with an electric charge changes its momentum, in collisions between nuclei or *electrons* and in the *decay* of certain atomic nuclei and particles

Pressurized water reactor (PWR): a power reactor in which heat is transferred from the core to an exchanger by high-temperature water kept under high pressure in the primary system. Steam is generated in a secondary circuit. Many reactors producing electric power are pressurized water reactors (see ***Light water reactor***).

Progeny: the decay product or products resulting after a radioactive decay or a series of radioactive decays. The progeny can also be radioactive, and the chain continues until a stable nuclide is formed.

Proton: stable elementary particle with electric charge equal in magnitude to that of the *electron* but of opposite sign and with mass 1836.12 times greater than that of the electron. The proton is a hydrogen ion (i.e. a normal hydrogen atomic nucleus) and a constituent of all other atomic nuclei.

Rad (rad): the unit of absorbed dose equal to 0.01 Gy or J/kg in any medium (see ***Absorbed dose***)

Radiation, external: radiation from a source outside the body

Radiation, internal: radiation from a source within the body as a result of deposition of radionuclides in body tissues

Radiation track (see ***Ionization path***)

Radiation weighting factor (W_R): multiplier of the *absorbed dose* in an organ or tissue to account for the different biological effectiveness of the charged particles that produce the ionization within the tissue

Radioactivity: spontaneous nuclear transformations accomplished by emission of α- or β-particles from the nucleus (*radioactive decay*) or by the capture of an orbital electron. Each of these reactions may or may not be accompanied by emission of a photon.

Radioisotope: an unstable isotope of an element that decays or disintegrates spontaneously, emitting radiation. Approximately 5,000 natural and artificial radioisotopes have been identified.

Radionuclide: a radioisotope or radioactive nuclide characterized by the constitution of its nucleus

Reaction (nuclear): an induced nuclear disintegration (i.e., a process occurring when a nucleus interacts with a photon, an elementary particle, or another nucleus). In many cases the reaction can be represented by the symbolic equation: $X + a \rightarrow Y + b$ or, in abbreviated form, X(a,b)Y. X is the target nucleus, a is the incident particle or photon, b is an emitted particle or photon, and Y is the product nucleus.

Relative biological effectiveness (RBE): factor used to compare the biological effectiveness of *absorbed* radiation *doses* due to different types of radiation; more specifically, the experimentally determined ratio of an absorbed dose of a radiation in question to that of a reference radiation required to produce an identical biological effect in a particular experimental organism or tissue

SI units: the International System of Units as defined by the General Conference of Weights and Measures in 1960. These units are generally based on the meter/-kilogram/second units, with special quantities for radiation including the *becquerel*, *gray*, and *sievert*.

Sievert (Sv): the SI unit of any of the quantities expressed as equivalent or effective dose. The equivalent dose in sieverts is equal to the *absorbed dose*, in grays, multiplied by the *radiation-weighting factor*. The *effective dose* is the equivalent dose multiplied by the *tissue-weighting factor*.

Specific activity: radioactivity per unit mass of a radionuclide

Stochastic effects: effects that occur by chance, generally without a threshold level of dose, whose probability is proportional to the dose and whose severity is independent of the dose. In the context of radiation protection, the main stochastic effects are cancer and genetic effects (see ***Deterministic effects***).

Tissue weighting factor (W_T): multiplier of the *equivalent dose* to an organ or tissue used for radiation protection purposes to account for different sensitivities of different organs and tissues to the induction of stochastic effects of radiation

Trabecular bone: internal bone architecture consisting mainly of calcified trabeculae with relatively large spaces between, occupied by loose connective tissues and blood vessels (see ***Compact bone***)

Transformation, nuclear: the process by which a nuclide is transformed into a different nuclide by absorbing or emitting a particle.

X-radiation or X-rays: penetrating *electromagnetic radiation* whose wavelength is shorter than that of visible light; usually produced by bombarding a metallic target with fast *electrons* in a high vacuum; in nuclear reactions, it is customary to refer to *photons* originating in the nucleus as γ-radiation and those originating in the extranuclear part of the atom as *X-radiation*. Dose of X-rays is expressed in kVp, the maximum (p for peak) applied voltage (kV) that an X-ray machine can produce.

Working level (WL): any combination of short-lived radon daughters in one liter of air that will result in the emission of 1.3×10^5 MeV of potential α energy.

Working-level month (WLM): a unit of exposure to air concentrations of potential α energy released from radon daughters. One working-level month is defined as the exposure to an average of 1 WL for a working month of 170 hours or 3.5×10^{-3} Jh/m³.

SUPPLEMENTARY CORRIGENDA TO VOLUMES 1–77

Volume 63

Benzofuran monograph

p. 436:

2nd-3rd lines of last paragraph: *delete* and chromosomal aberrations.

p. 437:

Last line of table should read:

CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro*	–	–	280	US National Toxicology Program (1989)

p. 438

Last paragraph of section 5.4 Other relevant data should read:

Induction of gene mutation and sister chromatid exchange was seen in cultured rodent cells treated with benzofuran in single studies. Benzofuran was not mutagenic to bacteria.

Volume 69

p. 597:

Reference Rappe *et al.* (1978b) should read:

Rappe, C., Garå, A. & Buser, H.-R. (1978b) Identification of polychlorinated dibenzofurans (PCDFs) in commercial chlorophenol formulations. *Chemosphere*, **7**, 981–991

Reference Rappe *et al.* (1979b) should read:

Rappe, C., Buser, H.-R., Kuroki, H. & Masuda, Y. (1979b) Identification of polychlorinated dibenzofurans (PCDFs) retained in patients with Yusho. *Chemosphere*, **4**, 259–266

Volume 71, Part 1

p. 233, first line of 2nd paragraph of Section 2.2 Cohort studies, *replace* Shouqui *et al.* (1989) *by* Li *et al.* (1989).

p. 249:

Reference Shouqi *et al.* (1989) should read:

Li, S.Q., Dong, Q.N., Liu, Y.Q. & Liu, Y.G. (1989) Epidemiologic study of cancer mortality among chloroprene workers. *Biomed. Environ. Sci.*, **2**, 141–149

Volume 74

p. 111, line 7, sentence should read: ‘Thus, depleted uranium has a lower specific activity (12 200 Bq/g) than natural uranium (25 900 Bq/g), and its chemical toxicity predominates over the radiation effects when it is taken into the body in a soluble form (Agency for Toxic Substances and Disease Registry, 1998).’

CUMULATIVE CROSS INDEX TO *IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS*

The volume, page and year of publication are given. References to corrigenda are given in parentheses.

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Nitrofurantoin	*50*, 211 (1990)
Nitrofurazone (*see* Nitrofural)	
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N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	*1*, 181 (1972); *7*, 185 (1974); *Suppl. 7*, 67 (1987)
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2-Nitropropane	*29*, 331 (1982); *Suppl. 7*, 67 (1987); *71*, 1079 (1999)
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