International Agency for Research on Cancer

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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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INTRODUCTION

The number of staff at the Agency has had to remain substantially the same over the past few years, but this has not prevented an expansion of its activities and of its contribution to the implementation of cancer prevention and control at the international level. Although the statutes of the Agency do not specifically limit its spectrum of activities, it became clear during the early phase of its development, and was later reaffirmed by the Agency's Governing Council, that its activities should be concentrated predominantly, although not exclusively, on investigations of cancer etiology and on the dissemination of information useful for the prevention of cancer. It was also agreed that these two activities should be paralleled by laboratory activities, which would provide support to field studies, generate hypotheses to be verified by epidemiological surveys, and ensure maintenance of the essential and enriching links with progress made in basic research. It was also emphasized that the Agency must maintain its character of a research institution.

The Agency is an almost unique body in the world in that there has been, since its inception, a real coexistence between epidemiologists and experimentalists. Multidisciplinarity is therefore a daily occurrence at the Agency and is not limited to occasional encounters. The experience of the Agency is, in fact, that true multidisciplinarity can be attained only by mechanisms that provide and maintain continuous links between different disciplines; there is little doubt that working under the same roof contributes considerably to this goal. In order to obtain a desirable integration of different experiences and competences, however, there must also be a willingness to accept a regime of continuous education. The Agency can be proud of having at least started in the right direction and of having produced already some evidence of the success of its approach to cancer prevention and control.

In keeping with its international role, the Agency aims at generating information that can be used all over the world—in industrialized countries, as well as in countries in various stages of development. As is illustrated in detail in this report, emphasis has been placed on providing information that can be used to implement primary prevention; however, much attention is also given to those initiatives that permit early detection of some of the most common cancers, and the containment of mortality, and to intervention studies which may serve as models for large-scale initiatives.

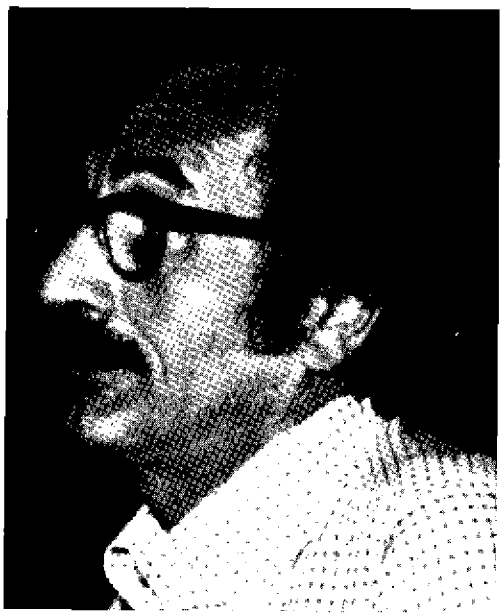
Descriptive Epidemiology

The publication *Cancer Incidence in Five Continents* has become an almost obligatory point of reference for anybody conducting a study on the geographical distribution of tumours, or on time trends, and an invaluable source of information for public health officials and cancer researchers in

Fig. 1. New members of the Scientific Council 1984–1987

Professor D. Henschler

Professor J. Pontén



Dr B. Terracini

general. The fifth volume in this series, which will cover the period 1978–1982, is already in preparation, with input from about 30 more registries, in addition to the 82 that contributed to the fourth volume. The Agency's Unit of Descriptive Epidemiology has expanded its collaboration with and its support to numerous centres in Africa, Asia, Oceania and South America, in order to collect and standardize data from areas in which there are no population-based registries. The first outcome of this collaborative effort will be a monograph on the relative frequency of cancers in this large part of the world. The data in the monograph, together with those in *Cancer Incidence in Five Continents,* will permit a more accurate estimate of the global cancer burden, and an analysis of trends over time and will provide guidelines for setting priorities for intervention.

The collaboration established with cancer registries all over the world in the preparation of *Cancer Incidence in Five Continents* has also made possible the planning and conduct of several ad-hoc studies, one of which relates to the calculation of precise incidence rates for the years 1970–1979 for childhood cancers in several parts of the world, including an accurate characterization of the histological types of the tumour.

Another of the many activities of the Unit of Descriptive Epidemiology is to establish, with the help of experts, an internationally accepted code of registry practice in relation to confidentiality. It is vital to several epidemiological surveys that information from certain countries in which it is not made available become accessible, by adopting measures that will guarantee that confidentiality is preserved. A particularly pertinent example is that this would allow the completion of a cancer mortality atlas, presently in preparation, covering the countries of the European Economic Community. Incidence atlases for several other individual countries are already in preparation.

The Clearing-House for On-Going Research in Cancer Epidemiology produces a Directory that, from its inception, has undergone progressive refinement with the inclusion of several useful cross indices. It has become an invaluable source of information for epidemiologists and for all cancer researchers.

Occupational Hazards

It is of considerable significance that the continuation of the international collaborative study on the possible long-term hazards of inhalable man-made mineral fibres has been approved by all parties concerned, i.e., national collaborators in the various countries in which the study was initiated, as well as the man-made mineral fibres industry through its Joint European Medical Research Board. The results of the further five-year follow-up will be available in 1985 and should be decisive for assessing the possible risks associated with exposure to these fibres and for verifying the significance of the slight increase in lung cancer risk observed in workers in some of the factories 30 years after first employment. This study on production workers is complemented by a study under way on a large cohort of man-made mineral fibre users, namely construction workers.

Another complementary study is an investigation of the possible role of naturally-occurring fibres in the causation of mesotheliomas in central Turkey where that tumour is particularly frequent. Erionite fibres, which have been shown experimentally to be even more active than blue asbestos in producing mesotheliomas, appear to be the most likely etiological agents.

International collaborative studies to determine if there is a relationship between silica dust and lung cancer, and to establish a register of persons exposed to phenoxy acid herbicides are entering the implementation phase. The case-control study on the long-term effects of pesticides on

human health in Colombia is now approaching its conclusion: statistical analysis of the data on malformations, together with an evaluation of the actual level of exposure to pesticides, will determine whether parental exposure to pesticides has a teratogenic effect.

SEARCH

The programme that maintains the original acronym SEARCH (Surveillance of Environmental Agents Related to Cancer in Humans) now includes a network of case-control studies, a series of studies in Singapore, an investigation on the usefulness of work histories to trace exposure to potential carcinogens, and a survey of existing collections of human biological materials.

By promoting the conduct of research projects in different and dispersed populations, the case-control studies network (CCSN) will allow important findings to be submitted to the test of reproducibility at an early stage of research. This important component of SEARCH will promote and stimulate international collaboration and will provide technical assistance and advice from both in-house and external experts. The three studies presently in various phases of implementation are on cancers of the pancreas, bile duct and gallbladder; on brain tumours in adults; and on brain tumours in children.

The studies in Singapore, a country in which the Agency has established fruitful collaboration over many years and in which there is an excellent cancer registry, appear promising. The diverse population and widespread medical care of high quality offer unusual opportunities for carrying out studies, in particular on diet and case-control studies on colon cancer.

Endogenous Formation of N-*Nitroso Compounds*

A number of studies have been initiated which take advantage of a method recently developed in the Agency's laboratory, by Drs Ohshima and Bartsch, for estimating quantitatively the in-vivo formation of *N*-nitroso compounds. These studies are good examples of the real integration of laboratory and epidemiology activities at the Agency: most of the studies, in particular those on human subjects with precancerous lesions of the oesophagus and stomach and those on subjects from high- and low-risk areas for cancers at those sites, have been planned and are carried out in close collaboration between experimentalists and epidemiologists. Of particular interest is a study aimed at assessing the possible role of the nitrosated betel-quid-specific alkaloids in the causation of oral cancer, which occurs frequently in betel quid chewers in India, and in other south-east Asian countries.

The growing interest in *N*-nitroso compounds and in their possible role in human cancer was confirmed by the success of the 8th International Meeting on *N*-Nitroso Compounds, which was organized jointly by Canadian and Agency scientists. This success was demonstrated both by the attendance of scientists from 19 countries and, more importantly, by the quality of the scientific contributions.

Environmental Hazards of Natural Origin

Another series of projects in which hypotheses developed by epidemiologists and/or experimentalists are investigated by a multidisciplinary approach includes a study to characterize opium pyrolysates and to ascertain their role in combination with certain dietary deficiencies, in the

causation of œsophageal cancer in northern Iran. Another study relevant to this project is one being undertaken in Singapore to follow up individuals who were registered as opium addicts in the 1950s.

No satisfactory etiological hypothesis has yet been advanced to explain the occurrence of the complex syndrome known as 'Balkan nephropathy' and of the consequent high incidence of urinary-tract tumours. In a joint effort with Bulgarian and British scientists, the possible role of ochratoxin A, a mycotoxin present in food consumed by populations at high risk for nephropathy, is presently under investigation.

The IARC Monographs *and* Manuals

The Agency's *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* have for several years been considered throughout the world as an authoritative source of information on the carcinogenicity of environmental chemicals. According to the results of a recent enquiry, they are used regularly by many scientists and by regulatory and governmental agencies. The validity of the information provided by the *Monographs* series is due to the scientific accuracy achieved by the painstaking work of Agency staff and the dedicated contribution of the many external experts who convene in Lyon from all over the world. One of the factors that has made possible the publication of scientifically unassailable information may be the Agency's policy of considering only data that are published or that have been accepted for publication in assessing carcinogenicity. The use only of published information not only permits any reader to verify the original source of information but also, more importantly, makes it possible to follow the reasoning of the experts in reaching their conclusions. The most recent *Monographs* are numbers 34 and 35, which are the last two in a series of four volumes devoted to polynuclear aromatic compounds, and number 36 which comprises 15 individual monographs on allyl compounds, aldehydes, epoxides and peroxides.

Following a procedure initiated several years ago, early in 1984 a group of experts was convened in Lyon to advise the Agency on selecting chemicals and exposures to complex mixtures to be considered for evaluation in the *Monographs* in the near future.

Another Agency series that has become known worldwide is that of the *Manuals of Selected Methods of Analysis of Environmental Carcinogens.* The volumes in this series provide essential information on the sampling and analysis of chemicals in the environment for which there is evidence of carcinogenicity or which are suspected of being carcinogenic. The most recent volume was devoted to *N*-nitroso compounds; volumes on certain elements, on halogenated alkanes and alkenes and on passive smoking are in advanced phases of preparation.

A project that had a relatively modest start, but that now reveals its importance, is focused on the review and critical analysis of methods for the destruction of carcinogenic wastes from laboratories. Five volumes have been published in this series, and two more are in preparation.

Liver Cancer

Several Agency projects are aimed at generating information that can be used for the prevention of liver cancer, which is particularly frequent in large areas of Africa and south-east Asia. In Swaziland, a complex study sponsored principally by UNEP had, as a primary objective, assessment of whether improvement of agricultural practices could result in a substantial reduction in the

aflatoxin contamination of food and, concurrently, determination of the prevalence of markers of hepatitis B virus infection in the population. Although the analysis of the data is not yet completed, it would appear that the programme was effective in reducing the level of aflatoxin in food, at least in some areas. In parallel, the increasing risk of liver cancer was confirmed for individuals who are chronic carriers of the hepatitis B virus.

A project carried out in the Philippines is aimed at detecting if, and to which extent, maternal transmission of infection with hepatitis B virus plays a role in increasing the risk of developing liver cancer later in life.

The Agency is also involved in two intervention studies on hepatitis B virus vaccines—one in Singapore, where the Agency is collaborating with the local university; and another planned in the Gambia, where the Agency collaborates with the Ministry of Health of the Gambia and the Medical Research Council Unit in the Gambia. The plan for the latter study was discussed in great depth and has now received full approval from all parties concerned.

Considerable progress has been made in several laboratories all over the world, including those at the Agency, toward developing methods for monitoring aflatoxins and their metabolites in body fluids. These methods will permit estimation of individual exposure levels to the toxin. The project for assuring quality control of analytical methods to detect aflatoxins in food commodities is continuing, with the participation of 260 laboratories in 65 countries.

Œsophageal and Oral Cancer

An intervention study in China, with the aim of preventing the occurrence of lesions in the œsophagus that appear to be precursors of œsophageal cancer, was initiated in 1983 and is now well advanced. Compliance with the treatment has been good, and the treatment has succeeded in elevating body levels of some micronutrients, in particular of riboflavin and retinol. Laboratory studies carried out in parallel indicate that individuals living in an area where there is a high risk of œsophageal cancer are exposed through their diet to *N*-nitroso compounds; these studies have also shown the presence of modified nucleosides, interpretable as premutagenic lesions, in DNA isolated from œsophageal tumours.

Following an initial screening programme for lesions of oral and œsophageal mucosa, such as leukoplakia and œsophagitis, in an area of Uzbekistan where oral cancer is particularly frequent, an intervention study has been initiated. The study is aimed at verifying if supplementing the diet with vitamin A, β-carotene and riboflavin will result in a reduction of the lesions. The role of specific cultural habits, such as the use of *nass*, cigarette smoking and alcohol consumption is taken into consideration.

A long-term test in rodents is also under way to verify the role of zinc deficiency in modulating the carcinogenicity of low doses of *N*-nitroso compounds.

Nutrition and Cancer

A proposal for a prospective study on diet and related factors in human cancer in Malmö, Sweden, was reviewed further and discussed by Swedish and Agency scientists; an agreement has been reached to initiate a methodological study to obtain accurate characterization of dietary habits, which will include an assessment of the validity of indices of nutrient intake. This meth-

odological preamble will also provide information necessary for the final design of a long-term prospective study, which will require for its implementation a considerable investment of manpower and funds.

The role of diet is also being investigated in a study of cancer of the gastrointestinal tract in Belgium, where different mortality rates for gastric and rectal cancers in the Flamand and Walloon parts of the country appear to be related to differences in food patterns. Similar studies are under way in the south of France and in Majorca. An interesting finding within the multi-facet project on alcohol and cancer is that any alcoholic beverage is cirrhogenic, whatever the concentration of alcohol, and that the decisive factor is the actual amount of ethanol ingested.

In an exemplary exploitation of a study already in progress, a project has been initiated in Iceland within a study of cardiovascular diseases to relate a number of factors, prominent among which are those related to nutritional status, to the risk of developing cancer of the breast and of other sites. Among other side results, preliminary data indicate that there is no association between serum levels of uric acid, which has been proposed as a protective agent, and cancer at any site.

In parallel to these epidemiological studies, the role of dietary components in the development of cancer is being investigated experimentally. On the basis of the epidemiological finding of a correlation between dietary lipids and cancers at several sites, including breast, colon and lung, groups of rats given a low level of *N*-nitrosodimethylamine are being fed with high- and low-fat, equicaloric diets. The subsequent incidence of tumours will be related to a series of biochemical parameters that are being monitored. The study has been conceived so as to allow also for measurements to be made at the individual level by noninvasive methods.

Another method being developed to quantify exposures to endogenous carcinogens and their precursors is the use of microencapsulated trapping agents.

Viruses and Human Cancer

As a follow-up to its long-term involvement in the study of Burkitt's lymphoma, the Agency organized a symposium late in 1983 to review recent progress made in the understanding of this disease and to define and stimulate future research. In a study on Burkitt's lymphoma in France, it was found that less than 20% of lymphomas are associated with Epstein-Barr virus and that some of the few cases that are associated with this virus developed following infectious mononucleosis. In contrast, the majority of Burkitt's lymphoma cases observed in Algeria, a country with an incidence of the disease comparable to that in Europe, are associated with Epstein-Barr virus. This phenomenon may be related to age at primary infection, which, in turn, may be related to socio-economic status.

Measurement of Individual Variations in Susceptibility

Several projects on this topic, involving experimental animals and human tissues, are under way or nearing completion. In particular, a complex study to detect changes in biochemical markers during and after administration of *N*-nitrosodiethylamine or *N*-ethyl-*N*'-nitrosourea, and investigation of whether early markers of genetic damage can be used to identify individual cancer risks, is being brought to completion, and the results are in the final stage of analysis. In another set of studies, monoclonal antibodies against different cytochrome P-450 isozymes are being used to

determine the role of these enzymes in the metabolism of carcinogens and, possibly, to determine individual variations in the risk of developing cancer. In a different approach, individuals are classified as slow or fast metabolizers of the anti-hypertensive drug debrisoquine, in an attempt to assess individual drug handling capacity.

Mechanisms of Carcinogenesis

Different capacities to repair DNA damage are related directly to different susceptibilities to tumour induction. This finding has been further confirmed by the identification of differences in repair capacity between parenchymal and nonparenchymal liver cells of rats exposed to *N*-nitrosodimethylamine. It has been found that the increased repair of O^6-methylguanine observed in rats exposed chronically to this nitrosamine occurs only in parenchymal cells. Non-parenchymal cells have a low repair capacity, which correlates well with the later occurrence of haemangiosarcomas.

A study of species differences in DNA repair capacity indicates that monkeys, like humans, have a greater capacity to repair DNA than do rats. Monkeys, however, have a much lower capacity to metabolize *N*-nitrosodimethylamine; this finding could explain the absence of a carcinogenic effect of this nitrosamine in monkeys. A qualitatively similar capacity to repair another main miscoding DNA adduct, O^4-methylthymidine, was found in rat, monkey and human liver samples.

Further studies are concerned with the identification of the relevant miscoding adducts that occur consequent to exposure to the human carcinogen, vinyl chloride.

Several experimental projects are centred on the study of mechanisms of tumour promotion. One of the main hypotheses is that the primary action of promoters, at least of the phorbol esters, is on the cellular membrane, and that the specific binding sites for promoters on the membrane are identical with protein kinase C. It has been found that tumour-promoting phorbol esters inhibit gap-junctional intercellular communication, and the resulting blocked communication may play an important role in carcinogenesis. Intercellular communication capacity is measured by a dye-transfer method developed in the Agency's laboratories based on the microinjection of fluorescent Lucifer Yellow EH into selected cells.

Tumour promotion, considered to be the second principal stage of carcinogenesis, can be subdivided into at least two further stages, and an attempt is being made to distinguish between the effects related to these two stages. Long-term in-vivo studies are aimed at determining if initiation can occur prenatally, if it involves organs other than the skin and on the quantitative effect of tumour inducers and promotors.

Cytogenetic Studies

The establishment of permanent cell lines derived from Burkitt's lymphoma cases at the Agency's laboratory and their distribution to many laboratories all over the world has permitted the use of human cells for important basic studies on the mechanisms of malignant transformation. Although an association with infection with Epstein-Barr virus has been confirmed in most cases of Burkitt's lymphoma, it is now clear that this virus cannot be the sole cause of the disease. Particular interest has therefore been generated by the finding of characteristic chromosomal anomalies not only in cultured cells but also in tumour samples, which may be at the origin of the

final transformation. Such anomalies may involve the translocation of a segment of chromosome 8 (8; q; 24) to an active region of a chromosome that carries genes for immunoglobulin heavy chains, such as chromosome 14. The molecular significance of these chromosomal rearrangements is being studied extensively in many laboratories all over the world.

The possible role of genetic transposition in the occurrence of tumours other than those of the haematopoetic system is also being studied in cases of Ewing's sarcoma.

In a different approach, detailed data on chromosomal aberrations have been collected by Dr Mitelman in Lund, Sweden, for over 5000 cancer cases; this probably represents the largest collection of its kind in the world. Information on occupational and environmental exposures as well as on hereditary disorders can be retrieved to investigate possible relationships between karyotypic pattern of cancer cells and etiological factors.

Development of Statistical Methodology

Following the considerable success encountered by the monograph *Analysis of Case-control Studies*, a second volume in this series, *Analysis of Cohort Studies*, by the same authors, is in an advanced phase of preparation.

The Unit of Biostatistics and Field Studies has devoted a large part of its activity to identifying possible sources of error and to defining new approaches to the quantification of risks. One of the most important components of such evaluation is correct estimation of exposure levels. A review of available epidemiological data on human carcinogens has confirmed that even when they provide convincing qualitative evidence of a carcinogenic effect they are, in most cases, insufficient to make a quantitative assessment; exceptions to this rule are tobacco, alcohol, radiation, asbestos and, possibly, a few medical drugs.

Particular emphasis is also placed on the analysis of experimental data from both long-term and short-term tests, since such data may contribute substantially to quantitative risk estimation.

An analysis of risks associated with therapeutic agents used in treating cancer will permit improvements in therapeutic procedures; long-term sequelae can thus be avoided in surviving cancer patients, the number of which is bound to increase further with the relative success that radiation and chemotherapy are obtaining today. Two studies are under way: one related to risks deriving from exposure to low and moderate doses of ionizing radiation for the therapy of cervical cancer, and the other to risks of second malignancies following chemotherapy for cancer.

Evaluation of Programmes for the Early Detection of Cancer

An important finding from a large collaborative study on the effectiveness of screening for cancer of the cervix is that the considerable variations reported from the many centres involved may be due less to the natural history of the disease than to the varying quality of screening. This finding emphasizes once more the importance of providing precise, simple guidelines for screening programmes, which can be adopted, with the necessary modifications related to local conditions, almost universally. There is not the slightest doubt that screening programmes for cervical cancer can virtually eliminate mortality from this disease.

There is now convincing evidence that mortality from breast cancer can also be reduced substantially by implementing a correct screening programme. Highly encouraging results have

been obtained recently in two breast cancer projects in the Netherlands, and the screening programme in Iceland has fully confirmed its effectiveness.

Collection and Use of Human Biological Material

An inventory of collections, or 'banks', of human biological specimens has permitted the Agency to identify 312 such banks. The material stored most commonly is serum, but many centres have also over the last few years initiated collection of other materials. Since the principal purpose of these collections is to provide support to epidemiological surveys, the second step, following identification of the banks, was to identify populations that might be suitable for studies of the relation between measurable preclinical status and subsequent disease.

Few scientists appear to be aware that collections of biological samples offer a great potential for analytical studies, especially if the collections meet a few basic requirements, such as possibility of identifying donors, of long-term preservation of samples and of retrieval and aliquoting.

Following a meeting in Lyon with representatives of those banks that have substantial possibilities for carrying out follow-ups, an agreement was reached on two initial projects: one on the levels of dehydroepiandrosterone sulfate in premenopausal breast cancer cases, and one on the occurrence of hepatitis B surface antigen in Caucasians who developed primary liver carcinoma.

A separate, ad-hoc initiative involves the collection of lymphoblastoid cell lines from families in which there are multiple cases of cancer and from 'normal' families, to evaluate whether genetic conditions predisposing to cancer can be identified.

Education and Training

The Agency was able to grant 12 research training fellowships in 1984, three of which are to be spent in Lyon. The distribution of disciplines in which the fellowships are granted indicates that it is still difficult to find candidates suitable for training in epidemiology.

Three courses in epidemiology were held in the last year in Yaoundé, in Lima and in Rome. These courses were, as in the past, very well attended.

The expansion of the Agency's publications programme is probably one of the best measures of the growing contribution of the Agency's activities to the understanding of the cause and the prevention of human cancer. The *Scientific Publications* series now counts 56 published volumes, with seven in press; and 33 volumes have been published in the *Monographs* series, with three in press.

Funding

The regular budget for 1984 was US$ 9,169,000.

Personnel

At 30 June 1984 the Agency's staff of 151 consisted of 42 scientists, 44 technicians and 65 administrative and secretarial staff.

L. TOMATIS
Director, IARC

I. STUDIES ON ETIOLOGY AND PREVENTION

1. STUDIES ON GEOGRAPHICAL DISTRIBUTION AND TIME TRENDS

(*a*) *Cancer Incidence in Five Continents, Vol. V* (Dr C. S. Muir, Miss S. Whelan and Mr M. Smans; in collaboration with Dr J. A. H. Waterhouse and Miss J. Powell, Birmingham and West Midlands Regional Cancer Registry, UK; and Dr T. M. Mack, Los Angeles County Cancer Surveillance Program, USA)

Volume IV of *Cancer Incidence in Five Continents* covered, in the main, the years 1973–1977. The fifth volume in the series would thus normally relate to 1978 - 1982. However, the 9th Revision of the *International Classification of Diseases* (ICD-9) came into operation in many, but not all, countries in 1979. The 82 registries that contributed data to the fourth volume of *Cancer Incidence in Five Continents,* and a further 37 potential new contributors, have thus been surveyed to assess the degree of difficulty that would be involved in providing data for 1978 coded to the 9th Revision of the ICD. Most contributors will be able to convert ICD-8 data for this year, and at an Editorial Board meeting held in Birmingham, UK in February 1984 it was decided to publish data for the five-year period 1978–1982.

Given the steady increase in the geographical coverage achieved by this series of monographs, and the consequent increase in its size, it has been decided not to include any special studies, e.g., histology, in Volume V, but to concentrate on presenting the basic data in as much detail as possible. For the first time, contributing registries will be given the possibility of sending data on magnetic tape on a case-by-case basis instead of being restricted to the site, sex and five-year age-group format. Urban and rural data will be requested from those registries able to provide such a breakdown, and will be included with the main tables rather than in a separate chapter. The major change proposed in the tables is the addition of two columns to those presenting the age-specific rates, giving the relative frequency of the numbers and of the incidence-standardized rates. Each data set will be accompanied by a 'pie' diagram showing the relative frequency of the five leading sites for each sex.

Contributors have been asked to send population-at-risk data and descriptive information on their registry to Lyon by October 1984, and to send their data by the beginning of March 1985, with a publication date of August 1986 in view.

At a further planning meeting held in Lyon on 19 April 1984, Dr T. Mack was welcomed to the Editorial Board as the representative of the International Association of Cancer Registries (see p. 105).

(*b*) *Global burden of cancer* (Dr D. M. Parkin and Dr C. S. Muir)

Estimates have been prepared of the annual number of new cancer cases that occurred around 1975, using data published in *Cancer Incidence in Five Continents* and material collected for the monograph *Cancer Occurrence in Developing Countries* (see p. 22), as well as other published

mortality and morbidity statistics. These estimates have now been published[1], and show that, within the total estimated annual number of new cancer cases of 5.9 million, the commonest five cancers are stomach (682 400 per year), lung (591 000 per year), breast (541 200 per year), colon/rectum (506 900 per year) and cervix uteri (459 400 per year).

It is proposed to examine recent changes in morbidity and mortality from these common tumours, using published data and material available at the Agency, to predict the likely changes in occurrence up to the year 2000.

(c) *Cancer in developing countries*

(i) *International collaborative study on relative frequency of cancer* (Dr D. M. Parkin, Miss S. Whelan and Mrs A. Arslan)

This project began in 1982 to bring together data on cancer occurrence from as many as possible of those centres in Africa, Asia, Oceania and South America which do not have population-based registries that provide data for *Cancer Incidence in Five Continents*. Such information is needed to increase the precision of estimates of the global cancer burden (see above) and trends over time. Collaborating centres thus include newly created registries and those without information on the denominator populations from which their registered cases come. Numerous hospitals, cancer centres and pathology laboratories have also provided case series (see Fig. 2).

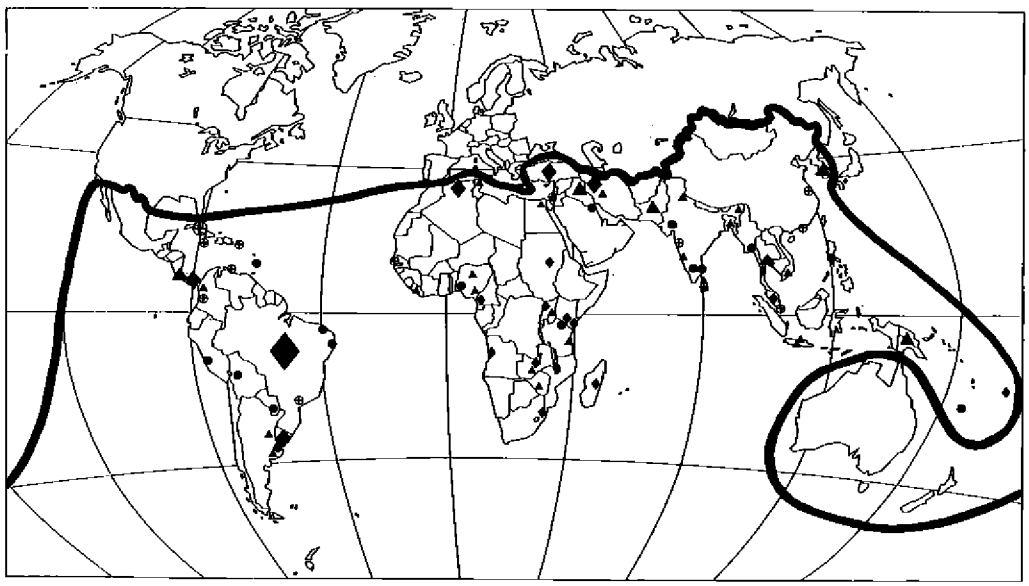


Fig. 2. Participants in an international study of relative frequency of cancer. ⊕, population-based registry represented in *Cancer Incidence in Five Continents Vol. IV*; ●, population-based registry not represented in that publication; ▲, hospital registry; ▲, multi-centre hospital-based study; ♦, pathology data from a single laboratory or registry; ◆, pathology data from multi-centre or national study

[1] Parkin, D. M., Stjernward, J. & Muir, C. S. (1984) *Bull. World Health Organ.*, **62**, 163–182

Data from 76 centres have been entered into the computer and prepared in a standard format. A standard reference population for developing countries has been devised on the basis of contributions from such countries in *Cancer Incidence in Five Continents*, and an age-standardized cancer ratio has been calculated from the data to permit comparison between the different centres. Whenever possible, a minimum incidence rate will be given. Information about the nature of each centre and the source of cases, collected by questionnaire, will be presented as a commentary to assist in the interpretation of the data in the tables.

Analysis is nearly complete, and it is anticipated that the monograph will be published in early 1985.

(ii) *Support to cancer registries* (Dr D. M. Parkin and Dr C. S. Muir)

The Unit of Descriptive Epidemiology continues to support and encourage cancer registration activities, especially in centres in Africa, Asia, Oceania and Central America.

Fiji: The collaborative research agreement with the Ministry of Health (DEB/81/023; principal investigator, Dr K. Singh, Pathology Department, CWM Hospital, Suva) has been renewed, and a visit was made to advise on updating and coordination of registration activities. Training for registry personnel has been arranged at the Singapore Cancer Registry.

India: The Agency, in association with the South East Asian Regional Office of WHO (Dr H. Zaman), has acted as consultant to the cancer registries supported by the Indian Council for Medical Research (Dr U. K. Luthra, New Delhi) for the past two years. Progress was reviewed at a meeting held at the Kidwai Memorial Institute of Oncology, Bangalore (Dr Krishna Bhargava) on 5–7 December 1983. The results obtained from the population-based registries at Bangalore, Bombay (Dr D. Jussawalla) and Madras (Dr V. Shanta) and from the hospital-based registries at Chandigarh, Punjab (Dr B. D. Gupta), Dibrugarh, Assam (Dr N. Zaman) and Trivandrum, Kerala (Dr M. Krishnan Nair) were presented in summary by Dr L. D. Sanghvi, Project Officer, National Cancer Registry of the Indian Council for Medical Research, Tata Memorial Hospital, Bombay.

In males, despite the wide variation in frequency of cancer of the upper alimentary tract and respiratory system, there was little difference between religious groups (Christian, Hindu, Muslim) in each centre, suggesting that the communities which reside in a given region have a degree of similarity of tobacco habits. No case of penile cancer was seen in a Muslim male in any registry, whereas frequencies of 3% to 4% were recorded in Hindus in Bangalore and Madras and in Sikhs. In these three populations, cervical cancer was also very frequent. The relative frequency of cancer of the cervix was considerably higher in Hindus than in Muslims and Christians. In Chandigarh, the frequency in Hindus (46%) and Sikhs (41%) was over twice that in Muslims (19%). Considerable variation was seen between centres in the distribution of oral cavity and pharyngeal cancers. In women, the predominant locations were buccal mucosa and anterior two-thirds of tongue, except in Dibrugarh, where the base of the tongue was the most commonly affected site. Gastric cancer appears to be more frequent in Bangalore and Madras (around 13% in males) than elsewhere (around 5%).

While the data presented were preliminary, it was felt nevertheless that the patterns were likely to be substantially correct and merited further investigation. In the coming year it was decided to design case-control studies as follows.

(1) *Dibrugarh*: pharyngeal cancer, with a view to examining the carcinogenicity of the various forms of areca nut (areca catechu) and tobacco used in this area.

(2) *Madras and Kerala*: stomach cancer, to attempt to learn more about the reasons for the unexpectedly high frequency of this site in southern India.

(3) *Bombay and Chandigarh*: oesophageal cancer, in view of the finding of high frequencies in Sikh women in the Punjab and the known high levels of this cancer in Bombay; and stomach cancer.

(4) *Bangalore*: oesophageal cancer.

It is most encouraging to note that the Indian Cancer Registries are developing as centres for etiological study, in addition to gathering data on incidence and frequency.

Morocco: A visit was made to Morocco to advise on the feasibility and requirements for the establishment of a cancer registry, in connection with the opening of the newly built National Cancer Institute (Director, Dr A. El-Hafed). External funding for this project is currently being sought.

Papua-New Guinea: A visit was made to assess the feasibility of re-activating the cancer registry, and, if possible, extending its coverage. There were several administrative problems to be overcome, and a detailed consultant report was recommended; in the meantime arrangements were made with the Department of Community Medicine, University of Papua-New Guinea (Dr K. Jamrozik) to extract the data recorded by the pathology registry for recent years (locum S. M. O., Dr R. Ashby). This will be entered onto computer readable medium so that analysis and comparison with data from earlier years can be carried out.

Swaziland: Financial support has been arranged to permit the continuation of cancer registration in Swaziland (DEB/83/07; Dr C. K. Mutoka, Central Public Health Laboratory, Manzini, Swaziland). Registration in this country is of particular interest in order to permit long-term monitoring of trends in occurrence of liver cancer (see p. 48).

Iraq: A training fellowship was arranged for Dr A. Al-Fouadi, Baghdad Cancer Registry, to permit detailed analysis of data collected by that registry over the seven-year period 1976–1982. The results of the study have been published[2].

The most frequent tumours in males were of the bladder (13.1%), lung (11.8%) and larynx (8.0%); and, in females, of the breast (19.4%) and bladder (6.2%) and non-Hodgkin's lymphoma (5.2%). Over half of the bladder cancer cases were squamous-cell in type, and there was a strong association between histological type and evidence of schistosomiasis.

(*d*) *Time trends* (Mr M. Smans; in collaboration with Dr J. A. H. Waterhouse, Birmingham and West Midlands Regional Cancer Registry, UK; and Dr E. Schifflers, University of Namur, Belgium)

Work continues on examination and interpretation of time trends in cancer incidence and mortality, with emphasis on examination of birth cohort effects. Despite assertions to the contrary, lung cancer excepted, there is little evidence of an increase in cancer in the UK or in the USA[3].

(*e*) *Social indicators of cancer in the European Economic Community* (Mr M. Smans)

Following provision of a series of colour diagrams and histograms depicting the age-standardized and cumulative rates for 1970–1974 for lung and other cancers for countries of the European Economic Community (EEC)[4], arrangements have been made to provide similar data for 1975–1979 to the statistical division of the EEC. This material, with supporting comments, will be included in the EUROSTAT publication series.

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[2] Al-Fouadi, A. & Parkin, D. M. (1984) *Int. J. Cancer*, **34** (in press)
[3] Devesa, S. S., Pollack, E. S. & Young, J. L. (1984) *Am. J. Epidemiol.*, **119**, 274–291
[4] IARC (1983) *Annual Report 1983*, Lyon, p. 33

2. DETERMINATION OF ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

(*a*) *Carcinogenic risk of inhalable particles* (Dr R. Saracci and Dr L. Simonato)

(i) *Man-made mineral fibre production* (Dr R. Saracci, Dr L. Simonato, Dr J. Estève and Miss B. Charnay; in collaboration with Dr M. Gardner, MRC Environmental Epidemiology Unit, School of Medicine, Southampton, UK; Dr O. Møller Jensen and Dr J. Olsen, Danish Cancer Registry, Copenhagen; Dr P. Westerholm, Swedish National Board of Occupational Safety and Health, Stockholm; Mr R. Maasing, Kabi AB Drug Co-operation, Stockholm; Dr A. Andersen, Norwegian Cancer Registry, Oslo; Dr P. A. Bertazzi and Dr C. Zocchetti, Clinic of Occupational Health Luigi Devoto, Milan, Italy; Dr R. R. Frentzel-Beyme and Dr J. Claude, German Cancer Research Centre, Heidelberg, FRG; and Dr L. Teppo, Finnish Cancer Registry, Helsinki; financed under contract with the Joint European Medical Research Board)

A protocol for extension of the follow-up of this study has been prepared by the Agency and approved by the national collaborators. All individuals still alive on 31 December 1977 will be followed up through 31 December 1982 for mortality in all countries and for cancer incidence in four countries. Workers first hired after 31 December 1977 will not be included in the follow-up at this stage of the study. Computerized files covering individuals eligible for follow-up have been prepared at the Agency and sent to the national collaborators for appropriate linkage.

The man-made mineral fibre industry, through the Joint European Medical Research Board, agreed to this opportunity to extend the study and to support it. A historical environmental investigation, coordinated by the Institute of Occupational Medicine in Edinburgh, will be carried out in the factories included in the study, in which information on past working conditions will be collected, with particular attention to past exposure levels to man-made mineral fibres and other contaminants. Eight of the thirteen factories had been visited by June 1984. The results of the epidemiological study will be available by June 1985.

(ii) *Man-made mineral fibre users* (Dr G. Engholm, Dr R. Saracci, Dr N. E. Day and Miss M. Blettner; in collaboration with Dr G. von Schmalensee and Dr A. Englund, Bygghälsan, The Swedish Foundation for Occupational Safety and Health in the Construction Industry, Stockholm)

This study is based on a follow-up of a cohort some 135 000 construction workers first enrolled when showing up for regular health check-ups. Follow-up is carried out primarily by computer record linkage to the national registries on deaths and cancers. It is a case-control study in which the cases are subjects who have developed respiratory cancers. Controls, selected from the same cohort, are subjects who have not developed respiratory cancers. Five controls are selected per case, with matching for year of birth and year of enrolment.

A first report on the study was presented at a WHO/EURO conference in Copenhagen in April 1982. The follow-up has since been extended, and the number of cases has increased to about 450. Analysis of the data will be completed in 1984.

(iii) *Mesothelioma in central Turkey* (Dr R. Saracci and Dr L. Simonato; in collaboration with Dr Y. I. Baris and Dr M. Artvinli, Department of Chest Diseases, Hacettepe University, Ankara, DEB/82/014; and Dr F. Pooley, Department of Mineral Sciences, University of Cardiff, UK)

As a further step in the characterization of the environment of villages in Central Turkey where clusters of mesothelioma cases have been recorded (Karain, Sarahidiv, Tüzkoy), lung specimens from sheep living in the villages have been examined and compared with specimens from sheep in villages with no excess of pleural or pulmonary malignant neoplasms. The results of the mineralogical examinations, currently in progress, point to a higher concentration of erionite fibres in lung specimens from villages affected by mesothelioma, thus confirming previous measurements of airborne fibres.

(iv) *Mesothelioma in Cyprus* (Dr L. Simonato; in collaboration with Dr C. Wagner and Dr K. McConnochie, Medical Research Council Pneumoconiosis Unit, Llandough Hospital, Penarth, Wales, UK; Dr F. Pooley, Department of Mineral Sciences, University of Cardiff, UK; and Dr Mavrides and Dr Cristofides, Thoracic Department of General Hospital, Cyprus)

One of the most ancient chrysotile mines in the world has been operating in Cyprus for several centuries. A report of cases of malignant mesothelioma by local doctors drew attention to the possible relationship between these findings and exposure to chrysotile or to chrysotile contaminated by tremolite. A team composed of local, MRC Pneumoconiosis Unit, and Agency scientists has been investigating the available evidence and new information on mesothelioma cases, on exposures in the occupational and general environment, and on lung specimens from sheep living in the Amiandos area where the mine is located.

(v) *Silicosis and lung cancer* (Dr L. Simonato and Dr R. Saracci)

Following discussions in June 1983[5], the Agency has decided to support a number of epidemiological investigations, different in design, but converging on the common aim of exploring the relationship between exposure to silica dust and the occurrence of lung cancer. These investigations include: a cohort study of pottery workers in the UK; a cohort study of anthracite miners in the north-west of Italy; a cross linkage between mortality and cancer incidence files and job titles involving exposure to silica dust to be performed in Scandinavian countries; and a cohort study of silicotics diagnosed during the period 1959–1963 in the Veneto region, north-east Italy. Nominal identification of the subjects to be included in these studies and follow-up operations are both in progress; results should be available during the first half of 1985 and will be discussed at an ad-hoc meeting.

(vi) *Evolution of lung cancer risk after cessation of asbestos exposure* (Dr A. Walker)

Review[6] of all published data from cohort studies with very long-term follow-up after first exposure to asbestos or with follow-up after definite cessation of asbestos exposure indicates that the relative risk of lung cancers begins eventually to decline in previously asbestos-exposed persons. The observed effects are not readily explained by misclassification of cause of death, nor by concurrent changes in intensity of asbestos exposure or in tobacco consumption. The effect may be due to extraordinarily high mortality in subgroups of the exposed population, or to the biological expression of a late-stage carcinogenic process involving asbestos. In either case, late declines in relative risks should be taken into account in any detailed assessment of the burden of lung cancer resulting from asbestos exposure.

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[5] IARC (1983) *Annual Report 1983*, Lyon, p. 36
[6] Walker, A. M. (1984) *J. occup. Med.*, **26**, 422–426

(*b*) *International study of people exposed to dioxin-contaminated substances* (Dr R. Saracci, Dr J. Wahrendorf and Mr J. Wilbourn; financed by the National Institute of Environmental Health Sciences of the USA, through Contract No. NO1-ES-1-5009)

A meeting of potential collaborators in the Agency project on the establishment and maintenance of an international register of persons exposed to phenoxy acid herbicides and contaminants was held in Lyon on 13 and 14 October 1983, convened as the last step in the feasibility assessment of the registry carried out by the Agency[7]. Dr Patricia Honchar was appointed as an adviser for the preparation of the meeting. It was attended by an IARC-NIEHS Advisory Panel, formed of Professor O. Axelson, Dr M. Fingerhut, Dr R. Neal and Dr R. R. Suskind, to provide advice and recommendations to the NIEHS on the development of the project on the basis of the documents presented and discussions held at the meeting.

Following a brief description of the background of the project, of the feasibility assessment conducted in 1983, and of the dioxin registry already implemented within the USA, potential cohorts for the registry were described by meeting participants. In most cases, these presentations described the progress of on-going investigations of exposed cohorts and noted additional potential groups for the registry beyond those discovered during the feasibility assessment.

General issues with regard to the registry, including definition, purpose and criteria, were also discussed. The meeting complemented the positive results of the feasibility assessment, which indicate that scientific interest in the project is present among potential collaborators, and that cohorts for study through the registry are available. As a result, the Advisory Panel formulated a number of recommendations for the actual establishment of the registry project, covering: the design of a protocol, including minimum data requirements and scope for each type of information to be collected for the registry; major but not exclusive emphasis on cancer; the ways in which data from the different centres can be efficiently pooled. The Agency is currently proceeding with implementation of these recommendations at the technical level; it is envisaged that the project, as reviewed at the meeting, will be completed within a two-year period.

(*c*) *Case-control study of long-term effects of pesticides on human health in Colombia* (Dr N. Muñoz and Dr N. Day; in collaboration with Dr M. Restrepo, Dr C. Hernandez, Dr J. E. Parra and Dr A. Giraldo, National Institute of Health, Bogota; Dr J. Davies and Dr C. Pfaffenberger, Department of Epidemiology and Public Health, University of Miami, FL, USA; and Dr J. Litvak, WHO Regional Office for the Americas, Washington DC; financed by the US Environmental Protection Agency through the WHO Regional Office in Washington DC)

The initial number of children reported by their parents as being malformed was 561, but three were found to be duplicates (reported by both parents), leaving the total number of cases at 558. Two controls matched by the age of the mother at pregnancy and birth order were selected. A questionnaire seeking demographic data, reproductive history, exposure to known or suspected teratogens, and occupational history with detailed information on type of job in floriculture, was completed for parents of cases and controls. The diagnosis of malformation for the cases or normality for the controls was validated by a physical examination of the children performed by a paediatrician and a geneticist. The clinical records of all cases and selected controls, including

[7] IARC (1983) *Annual Report 1983*, Lyon, p. 36

photographs, were reviewed by Dr L. Holmes, teratologist from the Massachusetts General Hospital, in July 1983 and February 1984. Selected children were also re-examined by Dr Holmes. Table 1 shows the coverage of the interviews with parents and the physical examinations of their children.

Table 1. Coverage of interviews with parents and physical examinations of their children

	Initial number of children	Parents interviewed					Children examined	
		Mother	Father	Both	Total no.	%	No.	%
Cases	558	302	19	172	493	88.4	493	88.4
Controls	1116	499	44	320	863	77.3	817	73.2

After the physical examination, cases were defined as those children with major congenital malformations (Groups A, B, and C) or with mental retardation (group F) and controls as normal children or those with minor malformations (groups H and I) (Table 2).

Table 2. Final diagnosis of cases and control children

Group		Cases	Controls	Total
A.	Hereditary malformations			
	A-1 Chromosomal anomalies	1	0	1
	A-2 Monogenic conditions	10	5	15
	A-3 Multifactorial heredity	49	6	55
B.	Malformations that could be attributed to factors with recognized or suspected teratogenic effects[a]	0	0	0
C.	Malformations of unknown origin	65	23	88
D.	Anthropometric abnormalities	5	12	17
E.	Birth marks	9	21	30
F.	Mental retardation	15	1	16
G.	Others (convulsive and other syndromes)	33	14	47
H.	Minor malformations	185	558	743
I.	Normal	31	177	208
J.	Others (non-examined, validated with review of clinical records)	16	0	16
	TOTALS	419[b]	817	1236

[a] Teratogenic viruses, certain drugs, mercury, alcohol, but not pesticides

[b] To this total should be added 74 children who died from different causes, making a total of 493 case children.

Statistical analysis of the data will begin in June 1984. Exposure to known and suspected teratogens and to pesticides will be compared between cases and controls. The development of an index of pesticide exposure will be attempted using the detailed information on job history in

floriculture obtained by interview, the data on pesticide use obtained by review of the floriculture company records, and the results of measurement of selected pesticides or metabolites in blood, urine and air samples.

Between August 1982 and December 1983, a survey on pesticide use for the years 1981 and 1982 was completed for 55 of the 58 floriculture companies that participated in the prevalence survey. The following information was obtained for each company: number of workers in each job category, type and extension of flower culture, and names and amount of pesticides used.

The results of the pilot study carried out by the University of Miami and described in the IARC *Annual Report* of 1982[8] can be summarized as follows: The serum of virtually all workers contained *p, p'*-DDT, *p, p'*-DDE and dieldrin residues at respective ranges of <2.0–51.4, 6.2–191.3 and <1.0–2.95 μg/l. When the workplace air of two companies was analysed for 31 common pesticide residues, only endosulfan I and II were detected at quantifiable levels, at maximum amounts of 1.55 and 0.61 ng/m³. Tetrahydrophthalimide was detected in urine samples of only three participants—one in the cutting and pruning area and two in the sorting area of Flor de America. Their total exposures to captan and maximum urinary levels were 135 μg/m³ and 34 pg/μl, 525 μg/m³ and 52 pg/μl, and 1201 μg/m³ and 37 pg/μl, respectively. Generally, office workers ranked lowest on the exposure scale, sorters ranked highest, and cultivators and pruners fell in between.

(*d*) *Passive smoking and respiratory cancers* (Dr R. Saracci and Dr S. Preston-Martin)

As a first step in this new programme, a working group on approaches to the investigation of cancer risk from passive smoking was held in Lyon on 12 and 13 April 1984. The group, after reviewing on-going work in the area of passive smoking and cancer, formulated two broad categories of suggestions for research, particularly at the international level:

(1) methodological investigations both to clarify the interpretation of existing results and to ensure that on-going studies provide answers as unequivocal as possible; and

(2) multicentric epidemiological studies to investigate the relation between passive smoking and respiratory cancers.

Work has started on the first lines: in particular, a comparison is under way of questionnaires used in studies already performed in different countries, and an investigation is in process of responses to questionnaires *versus* levels of urinary cotinine (as an indication of smoke absorbed) in population samples. The feasibility of multicentric studies, which represent the second line of research suggested by the Working Group, is being explored.

(*e*) *The SEARCH programme* (Dr A. Walker, Dr R. Saracci, Dr N. Day and Dr J. Velema)

The Agency's programme of *S*urveillance of *E*nvironmental *A*spects *R*elated to *C*ancer in *H*umans includes a variety of projects, described each under its own heading elsewhere in this Report: the case-control studies network (see below); studies in Singapore (p. 32); banks of biological materials (p. 130); and use of job histories in case-control studies (p. 47).

[8] IARC (1983) *Annual Report 1982*, Lyon, p. 26

(*f*) *Case-control studies network (the SEARCH programme)* (Dr A. Walker, Dr R. Saracci and Dr J. Velema)

Through the SEARCH case-control studies network (CCSN), the Agency promotes the conduct of coordinated multi-centre case-control studies of cancers of current interest to the Agency and its collaborators. The most important goal of the CCSN is to permit the replication of research protocols in dispersed and dissimilar populations, so that important findings are subjected to the test of reproducibility at an early stage in research. The programme offers collaborators the opportunity to obtain peer advice at all phases of study design, implementation and analysis, and makes available both in-house and external technical experts to assist collaborators in carrying through their studies.

Collaborating centres have access to incident cases of cancer from populations of at least one million persons; they furthermore have mechanisms available for the identification of random population controls, and for the interview of both cases and controls; they have data processing facilities and local operating funds. The Agency provides funds and facilities for regular conferences of collaborating investigators, central administrative and scientific coordination, common data processing, and ad-hoc technical expertise.

Cancers are determined to be of interest for study by current active collaborators and Agency staff in consultation with outside experts; these choices are further reviewed by the Scientific Council at its annual meetings. There are, at present, three CCSN studies in various phases of activity; on cancers of the pancreas, bile duct and gall bladder; on brain tumours in adults; and on brain tumours in children.

(i) *Cancers of the pancreas, bile duct and gall bladder* (Dr A. Walker, Dr R. Saracci and Dr J. Velema; in collaboration with Dr H. B. Bueno de Mesquita, National Institute for Public Health, Bilthoven, The Netherlands; Professor N. Choi, Manitoba Cancer Treatment and Research Foundation, Canada; Dr J. Pacheco de Souza, Public Health Department, São Paulo, Brazil; Dr A. McMichael, Commonwealth Scientific and Industrial Research Organization, Adelaide, Australia; Professor A. Miller, NCIC Epidemiology Unit, Toronto, Canada; Dr A. Simard, Montreal Cancer Institute, Canada; Dr W. Zatonski, Institute of Oncology, Warsaw)

Cancers of the pancreas, bile duct and gall bladder are the object of the first study conceived under the CCSN. The project was initiated in 1983, with pilot studies to ascertain the feasibility of obtaining data relating to lifestyle, particularly dietary and personal habits, and is now in the phase of active data collection phase, which will last until 1986.

The principal hypotheses under consideration are that:

(1) regular exposure to stimulators of cholecystokinin release predisposes to pancreatic cancer;

(2) fats from animal sources carry risks that are identifiably different from those associated with fats from vegetable sources;

(3) the timing and variability of food and alcohol consumption are risk factors for disease, over and above the simple effects of total quantity of exposure; and

(4) the diabetes associated with pancreatic cancer is associated with age at onset and insulin-dependence patterns that reflect chronic islet-cell toxicity.

In addition, data on a variety of known or candidate risk factors are being collected, both to control for confounding in the analysis and to evaluate older observations.

One of the most demanding aspects of this study is the dietary questionnaire. Centres that previously lacked specific expertise in obtaining retrospective diet histories have benefited from interchanges of personnel with experienced centres, allowing the construction of locally valid instruments following common principles of design. Technical personnel from collaborating centres have also visited the Agency in order to gain familiarity with analytic computer programmes.

In support of the collaborative case-control study, Agency staff have transformed the commonly agreed upon non-dietary questions into a detailed questionnaire, developed an interviewer's and coder's manual, and created an efficient data-base management package with accompanying codebook. Beyond this technical support, staff have requested and collated data from a number of previous studies in order to provide more detailed background information on diabetes and pancreatic cancer, and have reviewed current epidemiological literature for specific evidence that *N*-nitroso compounds (which are the most numerous substances that cause pancreatic cancer in laboratory animals) and alcohol are related to pancreatic cancer in humans.

(ii) *Brain tumours in adults* (Dr A. Walker, Dr J. Velema, Dr R. Saracci and Dr S. Preston-Martin; in collaboration with Dr A. Ahlbom, National Institute of Environmental Medicine, Stockholm; Dr J. Berkel, Netherlands Cancer Centre, Utrecht, The Netherlands; Dr N. Choi, Manitoba Cancer Treatment and Research Foundation, Canada; Dr G. Howe and Professor A. Miller, NCIC Epidemiology Unit, Toronto, Canada; Dr J. Potter, CSIRO, Adelaide, Australia; Dr A. Simard, Montreal Cancer Institute, Canada; Dr F. de Waard, National Institute for Public Health, Bilthoven, The Netherlands; Dr W. Zatonski, Institute of Oncology, Warsaw)

Following the decision to choose the brain as the second site to be studied in the CCSN, an expert group of current and potential collaborators met to review the current status of brain tumour epidemiology and to make specific recommendations for the design of a study. The group produced a background document[9] and proposed a population-based case-control study of primary neoplasms of the brain and cranial meninges (ICD-O codes 191, 192.0, 192.1, 'brain tumours'). Participating centres would have access to at least 150 newly diagnosed cases of brain tumours in adults 25–74 years of age over a three-year period beginning 1 January 1986. The purpose of the study would be to:

(1) Evaluate the role of *N*-nitroso compounds. Exposure to *N*-nitroso compounds, their precursors and modulators of their metabolism will be examined. Principal classes of exposure to be assessed will include diet, drinking-water, drugs, supplementary vitamins, cosmetics, tobacco, alcoholic beverages and occupation.
(2) Quantify the impact of certain well-known etiological factors: radiation and specific genetic syndromes
(3) Explore the relation between brain tumour incidence and a variety of other personal characteristics and exogenous exposures, such as: head trauma, birth order, menstrual and reproductive history, use of barbiturates, use of hair dyes, urban *versus* rural resi-

[9] Brain Tumour Study Group, IARC (1984) Some background data for the epidemiological study of brain tumours. Internal Working Document

dence, exposure to sick animals, toxoplasm antibody titres, blood type, ethnicity, exposures in certain industries and occupations (petrochemical, rubber, pharmaceutical, aircraft, paper products, construction industries; farmers, physicians, chemical engineers, welders, glassworkers; pesticides and vinyl chloride monomer), and certain specific diseases in subjects and their relatives (diabetes, epilepsy, neoplasms of the breast and of the central and peripheral nervous system).

Proceedings of the meeting, related documents and letters of intent from IARC have been distributed to potential collaborators, who are actively seeking local funding. The first meeting of funded collaborators will take place in the second half of 1985.

(iii) *Brain tumours in children* (Dr S. Preston-Martin, Dr A. Walker, Dr R. Saracci and Dr J. Velema; in collaboration with Dr J. Berkel, Cancer Centre, Utrecht, The Netherlands; Professor N. Choi, Manitoba Cancer Treatment and Research Foundation, Canada; Dr G. Howe, NCIC Epidemiology Unit, Toronto, Canada; Dr J. Potter, CSIRO, Adelaide, Australia; Dr F. de Waard, National Institute for Public Health, Bilthoven, The Netherlands; Dr W. Zatonski, Institute of Oncology, Warsaw)

Although etiological hypotheses about brain tumours in children are closely related to those in adults, essentially all aspects of study design, including case and control acquisition, questionnaire formulation and time periods of interest, are different for the paediatric tumours. Accordingly, the expert group described above recommended that a second protocol be formulated for brain tumours in children. Since a number of centres had already initiated local studies of childhood brain tumours, it was felt that the Agency could move most expeditiously by helping coordinate activities already under way in various parts of the world. Dr Susan Preston-Martin, the 1984 recipient of the Agency's Visiting Scientist Award, was asked to assume scientific responsibility for the coordinated effort.

(*g*) *Studies in Singapore* (Dr N. Day and Dr A. Walker)

Rapid economic development, an ethnically diverse population, widespread medical care of a high standard, and a well-established cancer registry make Singapore an area of unusual epidemiological potential. Agency programmes in Singapore have the combined aims of exploiting this opportunity in collaboration with Singaporean scientists, and of helping to establish in Singapore an independent capacity for epidemiological investigation.

(i) *Dietary studies* (Dr N. Day and Dr A. Walker; in collaboration with Dr H. P. Lee and Professor K. Shanmugaratnam, Singapore Cancer Registry; Dr B. Armstrong, University of Western Australia; and Dr K. Baghurst, CSIRO, Adelaide, Australia)

There is little current information about the Singapore diet. In order to set a reasonable basis for formulating specific dietary questions in future studies, it is first necessary to conduct a general survey of Singapore adults to uncover the range of variation in their current and past eating patterns. Construction of that survey instrument has been completed, and the survey is under way.

Some 200 families in which there are adults over the age of 40 have been selected at random on an income-stratified basis by the Government's Department of Statistics. Each family is visited by a dietary interviewer who arranges for the recording and weighing of all ingredients used to prepare the family's dishes during a two-day period. She interviews the family members over 40 years of age about their consumption of foods both in and out of the house for the same period, and she observes a family meal in order to calibrate the reported adult consumption against observed intake. For meals taken outside the home, the items eaten and the actual food stalls visited are noted down, and the food stalls are visited by a field worker who records items used in food preparation. In this way, for all adults in 200 random families, the ingredients of foods consumed on two successive days will be identified. Adults are further asked to characterize the changes in their personal consumption of various foods over the past two decades. These data will be compared with documented differences in the total food consumption (food disappearance) in Singapore over the same period, to determine:

(1) whether individuals tend to follow national patterns, changing proportionately, or whether particular population subgroups by themselves largely account for the national trends; and

(2) if the current inter-individual differences can also be taken as indicative of past differences.

There are no Singapore food tables *per se*; however, there do exist tables of nutrient composition of the ingredients of most foods eaten in Singapore, with the notable exception of fibre content, for which actual analyses must be made. These will be carried out in Singapore, using both specially prepared food items and items purchased at hawkers' stalls.

The dietary data will be analysed according to social class and ethnic group to derive bases for comparing cancer incidence rates in these categories. They would be examined further for principal components of dietary variation within Singapore, in order to construct a questionnaire for an interview which would be directed specifically at those aspects of diet that are most variable.

(ii) *Case-control study of colon cancer* (Dr N. Day and Dr A. Walker; in collaboration with Dr H. P. Lee, Singapore Cancer Registry; and Dr H. S. Goh, Singapore General Hospital)

This study is the planned sequel to the dietary survey described above. Given a dietary questionnaire that is suited to Singaporean eating habits, we will assess in a case-control study the findings of previous Agency studies showing a protective effect of fibre on the risk for colon cancer associated with high fat consumption.

(iii) *Follow-up of opium addicts* (Dr N. Day; in collaboration with Dr H. P. Lee and Professor K. Shanmugaratnam, Singapore Cancer Registry)

Earlier work in Iran suggested that ingestion of opium pyrolysates may increase risk for cancer of the oesophagus and, possibly, of the bladder. Further work in Singapore involves a follow-up of individuals registered as opium addicts in the 1950s, and additional analysis of material from the Singapore Cancer Registry. The former requires tracing of individuals on a list established some 25 years ago, and is planned to take place during the pause in the field work between the end of the population dietary studies and the start of the case-control studies, within the next 12 months. An analysis of the Singapore Cancer Registry material 1968–1982 is planned for the coming year.

(*h*) *Collaborative studies on in-vivo formation of* N-*nitroso compounds in human subjects* (Mr H. Ohshima, Dr N. Muñoz, Dr B. Pignatelli, Dr J. Nair, Mr C. Malaveille, Dr M. Friesen, Miss J. Michelon, Miss M. C. Bourgade, Miss M. Blettner, Dr J. Wahrendorf and Dr H. Bartsch; in collaboration with external institutions as listed below)

Endogenous formation of *N*-nitroso compounds has been suspected of being associated with an increased risk of cancer of the stomach, oesophagus and bladder, but convincing epidemiological evidence is lacking. The general objective of these pilot studies is to collect more data on endogenous nitrosation in human subjects with precancerous lesions of the oesophagus and stomach and in asymptomatic subjects from high- and low-risk areas for these cancers. In addition, data are collected from subjects exposed to different levels of precursors (amines, nitrosating agents) and nitrosation modifiers. Results obtained to date and on-going studies are summarized briefly in Table 3.

Table 3. Collaborative pilot studies on in-vivo formation of *N*-nitroso compounds in human subjects at increased risk for cancer of the stomach (studies 1–6, 9, 10), oesophagus (studies 7–10), oral cavity (study 11), bladder (study 12), liver (study 13) and breast (study 14) or exposed to different levels of precursor compounds and nitrosation modifiers (studies 15–23)

Study no.	Location (external investigator)	Year project started or ended	No. of subjects and sex	Description of study subjects[a]	Samples collected	Endpoints analysed[b]	Remarks (refs)
1	Rome (Crespi)	1981	50 M 50 M	CAG Healthy	Biopsies Gastric juice Urine	Gastroscopy, histology pH, bacterial count, total NOC NAA	In progress (1,2)
2		1984	10 M 10 M	CAG Healthy	Biopsies Gastric juice Urine	Histology pH, bacterial count, NAA NAA	In progress
3	Turku, Finland (Inberg, Aitio)	1981	20 M 20 M	Pernicious anaemia Duodenal ulcer	Biopsies Gastric juice Urine	Gastroscopy, histology NPRO	In progress
4	Akureyri, Iceland (Tulinius)	1984	20–30 M	Gastrectomy, CAG	Biopsies Gastric juice Urine	Gastroscopy, histology pH, total NOC NAA	In progress
5	Lyon, France (Lambert)	1982	20 M	Duodenal ulcer, before and after cimetidine treatment	Biopsies Gastric juice Urine	Gastroscopy, histology pH, total NOC NAA	In progress (2)

[a] CAG, chronic atrophic gastritis

[b] NOC, *N*-nitroso compounds; NAA, *N*-nitrosamino acids (*N*-nitrosoproline, *N*-nitrosothiazolidine 4-carboxylic acid, *N*-nitroso 2-methylthiazolidine 4-carboxylic acid); NPRO, *N*-nitrosoproline; SCN, thiocyanate; TSNA, tobacco-specific nitrosamines; BSNA, betel-nut-specific nitrosamines (*N*-nitrosoguvacoline, *N*-nitrosoguvacine)

Study no.	Location (external investigator)	Year project started or ended	No. of subjects and sex	Description of study subjects[a]	Samples collected	Endpoints analysed[b]	Remarks (refs)
6	Akita, Japan (Kamiyama)	1983	50 M F	Inhabitants from high- and low-risk areas for gastric cancer before and after vitamin C treatment	Blood Urine	Vitamins A, B_2, E, uric acid, Zn, Se NO_3, NAA Dietary questionnaires	Completed by end of 1984
7	Beijing (Lu)	1982	50 M F	Inhabitants from high- and low-risk areas for oesophageal cancer in northern China before and after vitamin C treatment	Urine	NO_3/NO_2, NAA	Completed (3,4,5)
8		1984	50 M F	Repeat of study no. 7 in different areas in northern China, before and after vitamin C treatment	Urine	NO_3/NO_2, NAA	Started spring 1984
9,10	Beijing (Chen) & Ithaca, USA (Campbell)	1984	15–25 M	Inhabitants (pooled samples) from 25–30 counties with different incidence rates for gastric & oesophageal cancer in China before & after vitamin C treatment	Urine	NO_3/NO_2, NAA, thioethers, mutagens (correlations with other nutritional & biochemical parameters)	Start in October 1984
11	Bombay, India (Bhide)	1984	50 M F	Chewers of betel quid (different compositions)	Saliva, blood Urine	NO_2, SCN, TSNA, NAA, BSNA TSNA, NAA, BSNA	In progress
12	Cairo (Ramses, El-Torkey)	1984	80 M	Subjects with and without *S. haematobium* infection and with or without bacteriuria	Urine	*S. haematobium* ova and bacterial count, NAA, NO_3/NO_2, mutagens	Feasibility under exploration
13	Paris (Habib)	1984	30 M F	Controls, hepatocellular carcinoma & liver cirrhosis patients with or without vitamin C treatment	Urine	NAA	Completed

Study no.	Location (external investigator)	Year project started or ended	No. of subjects and sex	Description of study subjects[a]	Samples collected	Endpoints analysed[b]	Remarks (refs)
14	Utrecht, The Netherlands (de Waard)	1984	20 F	High-risk breast cancer patients (DOM project)	Urine	NAA	Completed
15	IARC	1981	M	Volunteer ingesting different levels of nitrate & dietary nitrosation modifiers	Urine	NAA	Completed (6–12)
16	IARC	1983	20 M F	Volunteers, effect of phenolic compounds in beer	Urine	NAA	In progress
17	IARC	1984	15 M	Cigarette smokers & non-smokers	Urine	NAA	Completed (10)
18	Turin (Italy) (Vineis, Terracini)	1984	25–30 M	Non-smokers, smokers of blonde & black tobacco	Urine	TSNA, NAA, cotinine, mutagens	In progress
19	Oulu, Finland (Pelkonen)	1984	20 M F	Smokers & non-smokers	Blood, urine Urine	8 exposure indices to cigarette smoke NAA	Completed
20	Lille, France (Leclerc, Vincent)	1983	20–30 M F	Healthy volunteers on controlled high- and low-nitrate diets	Blood, saliva, urine Urine	NO_3/NO_2 levels NAA	Completed
21	Vancouver, Canada (Stich)	1983	30–40 M	Subjects on different diets: Eskimos (raw, boiled meat, no vegetables); volunteers ingesting dietary nitrosation modifiers	Urine	NAA	Completed (13, 14)
22		1982	20 M	Betel-nut chewers & eaters, controls	Urine	NAA	Completed
23	Oxford, UK (Forman)	1984	30 M	Workers in a nitrate fertilizer production plant with different exposure levels	Urine	NO_3, NAA	In progress

References: (1) Bartsch, H., Ohshima, H., Muñoz, N., Crespi, M. & Lu, S H. (1983) In: Harris, C. C. & Autrup, H. N., eds, *Human Carcinogenesis*, New York, Academic Press, pp. 833-856; (2) Bartsch, H., Ohshima, H., Muñoz, N., Crespi, M., Cassale, V., Ramazotti V., Lambert, R., Minaire, Y., Forichon, J. & Walters, C. L. (1984) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)*, Lyon, International Agency for Research on Cancer (in press); (3) Bartsch, H., Ohshima, H., Muñoz, N., Pignatelli, B., Friesen, M., O'Neill, I. K., Crespi, M. & Lu, S. H. (1983) In: Hayes, A. W., Schnell, R. C. & Miya, T. S., eds, *Developments in the Science and Practice of Toxicology*, Amsterdam, Elsevier, pp. 299-309; (4) Lu, S. H., Bartsch, H. & Ohshima, H. (1984) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)*, Lyon, International Agency for Research on Cancer (in press); (5) Ohshima, H., Pignatelli, B. & Bartsch, H. (1983a) In: Magee, P. N., ed, *Nitrosamines and Human Cancer (Banbury Report No. 12)*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 297-317; (6) Ohshima, H. & Bartsch, H. (1981) *Cancer Res.*, *41*, 3658-3662; (7) Ohshima, H., Béréziat, J.-C. & Bartsch, H. (1982b) In: Bartsch, H., O'Neill, I. K., Castegnaro, M. & Okada, M., eds, *N-Nitroso Compounds: Occurrence and Biological Effects (IARC Scientific Publications No. 41)*, Lyon, International Agency for Research on Cancer, pp. 397-411; (8) Ohshima, H. & Bartsch, H. (1982) In: Sugimura, T., Kondo, S. & Takebe, H., eds, *Environmental Mutagens and Carcinogens*, Tokyo, Tokyo University Press, pp. 577-585; (9) Ohshima, H. & Bartsch, H. (1981) In: Counsell, J. N. & Hornig, D. H., eds, *Vitamin C (Ascorbic Acid)*, London, Applied Science Publishers, pp. 215-224; (10) Ohshima, H., O'Neill, I. K., Friesen, M., Béréziat, J.-C. & Bartsch, H. (1984) *J. Cancer Res. clin. Oncol.* (in press); (11) Ohshima, H. & Bartsch, H. (1983) In: Stich, H., ed., *Carcinogens and Mutagens in the Environment*, Vol. II, *Naturally Occurring Compounds*, Boca Raton, FL, CRC Press, pp. 3-15; (12) Ohshima, H., O'Neill, I. K., Friesen, M., Pignatelli, B. & Bartsch, H. (1984) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)*, Lyon, International Agency for Research on Cancer (in press); (13) Stich, H. F., Ohshima, H., Pignatelli, B., Michelon, J. & Bartsch, H. (1983) *J. natl Cancer Inst., 70*, 1047-1050; (14) Stich, H. F., Dunn, B. P., Pignatelli, B., Ohshima, H. & Bartsch, H. (1984) In: O'Neill, I. K., von Borstel, R. E., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)*, Lyon, International Agency for Research on Cancer (in press)

(i) *Precancerous lesions of the stomach* (in collaboration with Professor M. Crespi, Dr V. Casale, Dr V. Ramazotti, Regina Elena Institute, Rome, DEB/81/019; Dr A. Aitio, Dr A. Lehtonen and Dr M. Inberg, Institute for Occupational Health, Helsinki and Turku University, Finland; Dr H. Tulinius and Dr T. A. Jönasson, Icelandic Cancer Registry and Saint-Joseph's Hospital Landakot, Reykjavik; Professor R. Lambert and Dr Y. Minaire, Edouard Herriot Hospital, Lyon, France; Professor H. Leclerc, INSERM, Villeneuve D'Ascq, France; Dr C. Walters, British Food Manufacturing Industries Research Association, Leatherhead, UK, DEC/81/04)

Subjects included in these studies are: patients (1) with chronic atrophic gastritis, with and without intestinal metaplasia; (2) with pernicious anaemia; (3) who have undergone partial gastrectomy; and (4) undergoing cimetidine treatment. All these subjects have an achlorhydric stomach, which may provide a suitable milieu for intragastric formation of *N*-nitroso compounds due to the presence of a large number of bacteria that convert nitrate to nitrite and possibly catalyse nitrosation in the stomach. The endpoints analysed are listed in Table 3 and include gastroscopy, collection of fasting gastric juice, histopathological evaluation of biopsy samples and the measurement of nitrosated amino acids in urine after application of the nitrosoproline (NPRO) test.

Interim results from studies 1 and 5 indicate that, after ingestion of nitrate and proline, urinary NPRO levels in patients with chronic atrophic gastritis are dependent on gastric pH; maximal yields were seen at about pH 2, with large interindividual variations in the amount of nitrosated amino acids excreted, ranging from 0 to 120 μg/day per person. Patients, as compared to healthy controls, excreted no apparent excess of NPRO. Urinary NPRO was not correlated with total intragastric *N*-nitroso compounds in any study subject, but smokers excreted more total nitrosoamino acids in their urine than did non-smokers. These data clearly indicate that endogenous nitrosation does occur in the human stomach, but its relation to the induction of upper gastrointestinal cancer remains to be proven.

Final comparison of subjects with and without precancerous lesions of the stomach is pending until more data are collected, in particular from subjects with normal stomach mucosa.

(ii) *Study in high- and low-incidence areas for gastric cancer in northern Japan* (in collaboration with Professor S. Kamiyama, Akita University, School of Medicine, Akita, Japan)

In order to study the role of endogenous nitrosation and nutritional deficiency in the etiology of stomach cancer, a pilot study (no. 6, see Table 3) was initiated in 1983. Samples of 24-h urine and blood were collected from 100 subjects living in high- (Akita) and low- (Iwate) incidence areas for stomach cancer in the northern part of Japan. Three different urine samples were collected from each subject: (1) undosed, (2) after ingestion of 100 mg proline three times a day after each meal, and (3) after ingestion of 100 mg proline three times a day together with 100 mg vitamin C. These samples are being analysed for nitrate and chloride ions excreted and for some *N*-nitrosamines, such as *N*-nitrosoproline, *N*-nitrosothiazolidine 4-carboxylic acid and *N*-nitroso-2-methylthiazolidine-4-carboxylic acid. The latter two compounds have recently been identified in human urine. Blood samples are being analysed for levels of vitamins (A, B_2 and E), trace elements (Zn, Fe, Se), uric acid, and some enzyme activities, as an index of nutritional status. In addition, dietary questionnaires were completed for each subject. Potential endogenous nitrosation in each individual is being correlated with the results of analyses of nutritional status and food habits.

(iii) *Studies in high- and low-risk areas for oesophageal and gastric cancer in the People's Republic of China* (in collaboration with Dr Li Bing and Dr Lu Shih Hsin, Cancer Institute, Beijing; Dr B. Chen, National Center for Preventive Medicine, Beijing; and Dr Campbell, Cornell University, Ithaca, USA, DEC/84/02)

In a recently completed study (no. 7, see Table 3), the excretion of urinary *N*-nitrosoamino acids by inhabitants living in high-risk (Linxian) and low-risk (Fanxian) areas for oesophageal cancer was compared. Linxian subjects excreted significantly more nitrate and *N*-nitrosoamino acids than those living in Fanxian. When Linxian subjects were given ascorbic acid, their level of urinary *N*-nitrosoamino acids were reduced to those found in Fanxian. Therefore, ascorbic acid, an efficient inhibitor of endogenous nitrosation, will now be examined in intervention trials.

The significance of these findings is being verified in on-going or planned studies (nos 8–10), which will involve different areas in the People's Republic of China. Excretion of urinary nitrosoamino acids will be correlated with mortality from gastric and oesophageal cancer in different provinces; in parallel, a number of risk factors for malignant diseases and nutritional indices will be analysed and comparisons made.

(iv) *Studies on betel-quid chewers* (in collaboration with Dr S. V. Bhide, Cancer Research Institute, Tata Memorial Center, Bombay, India; Professor U. Mohr, School of Medicine, Hanover, FRG; and Dr R. Grafstrøm, Karolinska Institute, Stockholm; DEC/84/03)

The correlation between oral cancer and chewing of betel quid (often containing tobacco) in India and other south-east Asian countries is well established[10]. In previous studies[11, 12], it has been shown that nitrosation of betel-nut-specific alkaloids, in particular arecoline, leads to the formation of nitroso compounds, of which *N*-nitroso-*N*-methylpropionitrile is carcinogenic in exper-

imental animals. The extent to which nitrosation of betel-nut constituents takes place *in vivo*, i.e., in the oral cavity of chewing subjects, has not so far been investigated. Therefore, urine and saliva samples have been collected from about 14 subjects with different chewings habits (i.e., using different ingredients in the betel quid). Subjects with no chewing habits and cigarette smokers were included. Saliva samples were analysed for nitrite, thiocyanate, tobacco-specific nitrosamines, *N*-nitrosoguvacoline and *N*-nitrosoguvacine, *N*-nitrosoproline, nicotine, cotinine and arecoline. Significant levels of *N*-nitrosoguvacoline and *N*-nitrosoguvacine were detected in several samples of saliva from betel-quid chewers using quid with and without tobacco (Table 4). In addition, high levels of tobacco-specific nitrosamines were detected in chewers of betel quid with tobacco. *N*-nitrosomethylpropionitrile was not detected in any of these samples.

The urine of these subjects did not contain significant amounts of tobacco- and betel nut-derived nitroso compounds, except *N*-nitrosoproline and one unknown nitroso compound, which was excreted at up to 1.8 μg/6-h urine; structural identification of this latter compound is under way.

To assess further the significance of *N*-nitrosated betel-nut-specific alkaloids, hamsters are being fed betel-nut powder with or without nitrite. The *N*-nitrosated betel-nut-specific alkaloids

Table 4. Mean amounts of *N*-nitrosamines and their precursors detected in saliva samples from chewers of betel quid with tobacco (BQ + T) or without tobacco (BQ − T), of tobacco chewers (T), of cigarette smokers (SM) and of non-smokers (control)

Compounds detected	A BQ + T	B BQ − T	C T	D SM	E Control
No. of samples analysed	12	12	3	15	5
pH of saliva	6.90–9.07	6.00–7.61	7.62–7.88	6.52–7.93	6.93–7.60
N-Nitrosonornicotine*	7.53	ND	33.40	ND	ND
N-Nitrosoanatabine*	4.81	ND	29.81	ND	ND
4-(*N*-Methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone*	0.34	ND	ND	ND	ND
N-Nitrosoguvacoline*	0.88	0.91	ND	ND	ND
N-Nitrosoguvacine*	4.04	3.18	ND	ND	ND
N-Nitrosoproline*	4.94	3.17	4.86	26.81	0.98
N-Nitrosodimethylamine*	0.98	ND	2.43	1.93	1.18
N-Nitrosodiethylamine*	8.84	ND	0.55	0.75	ND
Nicotine**	86.10	ND	142.69	0.45	ND
Cotinine**	2.02	ND	3.69	0.51	ND
Arecoline**	51.95	29.69	ND	ND	ND
Nitrite**	9.70	16.38	23.33	9.08	8.52
Thiocyanate**	7.47	14.08	24.48	49.41	26.43

* ng/ml
** μg/ml
ND, not detected

[10] Bhide, S. V., Shah, A. S., Nair, J. & Nagarajrao, D. (1984) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)

[11] IARC (1983) *Annual Report 1983*, Lyon, p. 43

[12] Wenke, G., Rivenson, A., Brunneman, K. D., Hoffmann, D. & Bhide, S. V. (1984) In: O'Neill, I. K., von Borstel, R. E., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence Biological Effects and Relevance to Human Cancer* (*IARC-Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)

and nitrosated mixtures of betel quid are also being tested in cultured epithelial cells from human buccal mucosa to see whether toxicity and DNA-strand breakage are induced.

(v) *Other studies on endogenous* N-*nitroso compounds*

A number of studies are in progress or being planned to examine subjects at risk for cancer of the bladder, liver and the breast (nos 12–14, Table 3), although, for the two latter sites, epidemiological hypotheses that *N*-nitroso compounds are involved as etiological agents have not been put forward.

(vi) *Studies on subjects exposed to precursors and nitrosation modifiers* (in collaboration with Dr H. Stich, University of British Columbia, Vancouver, Canada; Professor H. Leclerc and Dr P. Vincent, INSERM, Villeneuve d'Ascq, France; Professor B. Terracini and Dr P. Vineis, Institute of Anatomy and Pathology, University of Turin, Italy; Dr O. Pelkonen, Department of Pharmacology, University of Oulu, Finland; Dr D. Forman, Cancer Epidemiology and Clinical Trials Unit, University of Oxford, UK; Professor G. Descotes, Claude Bernard University and College of Industrial Chemistry, Lyon, France; and Professor R. Scriban, National College of Agriculture and Food Industries, Douai, France)

Several studies have been completed on subjects who ingested various levels of nitrate or nitrate-rich meals together with proline, with or without dietary nitrosation modifiers (studies nos 15–23, Table 3). Results allowed two major conclusions to be drawn: (1) they provided an unequivocal demonstration that *N*-nitroso compounds are formed in the human body, even after ingestion of amounts of precursors (amine, nitrate) that are considered a normal daily intake. The

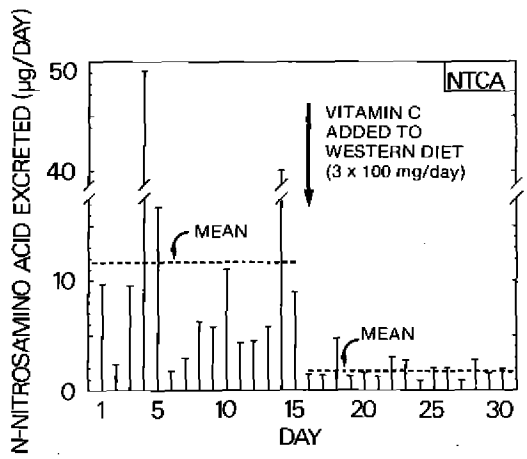

Fig. 3. Endogenous formation of *N*-nitrosothiazolidine 4-carboxylic acid in one human subject living on a Western diet and its inhibition by vitamin C. 24-h urine samples were collected each day during a 30-day period from one healthy human subject. On day 16, the diet was supplemented with 3 x 100 mg/day vitamin C (as indicated by the arrow)

amounts of nitrosated amino acids formed *in vivo* were about 16 μg/day per person when subjects were living on an uncontrolled western diet. (2) Inhibitors, like vitamins C and E and polyphenolic compounds, markedly reduce the yield of *N*-nitroso compounds formed in healthy human subjects. Vitamin C, when added to an uncontrolled western diet at a level of three times 100 mg/day, efficiently reduced the mean excretion of nitrosated amino acids in the urine (Fig. 3).

(*i*) *Characterization of biologically active substances in complex mixtures of environmental origin*

(i) *Pyrolysis products of opium and their possible role in oesophageal cancer in Iran* (Dr M. Friesen, Dr C. Malaveille, Dr I. K. O'Neill, Mrs L. Garren, Dr J. Cabral, Mrs A. Hautefeuille, Mrs D. Galendo, Dr N. Day and Dr H. Bartsch; in collaboration with Dr J. Fraisse and Dr Q. T. Pham, National Centre of Scientific Research, Vernaison, France; DEC/82/022)

The ingestion of opium pyrolysates, together with a diet deficient in riboflavin and protein and excessive consumption of hot tea, have been found to be associated with (although causality has not been established) a high incidence of oesophageal cancer in people of both sexes in a region of northeast Iran. These epidemiological results are supported by data that show a high prevalence of elevated levels (> 10 μg/ml) of morphine metabolites in the urine (indicating opium use) of both men and women in the high-risk area and a low prevalence of such elevated levels among people of both sexes in the low-risk area[13].

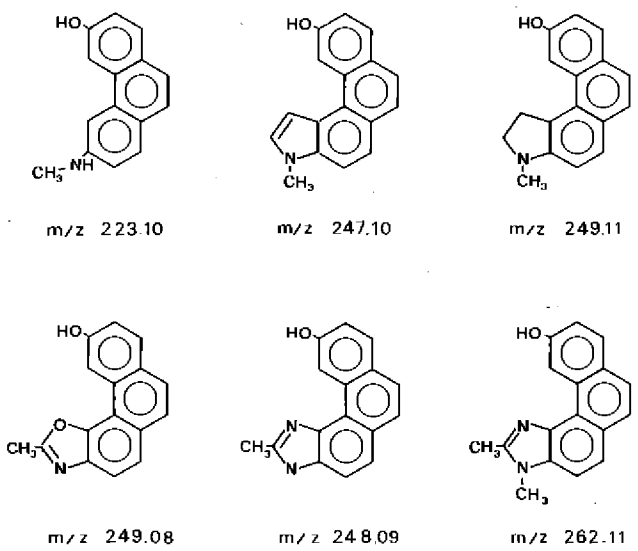

Fig. 4. Proposed structures for compounds isolated from morphine pyrolysate

[13] Day, N., Malaveille, C., Friesen, M. & Bartsch, H. (1983) In: Stich, H., ed., *Carcinogens and Mutagens in the Environment*, Vol. III, *Naturally Occurring Compounds*, Boca Raton, FL, CRC Press, pp. 59–72

Opium pipe scrapings (locally called *sukhteh*) and opium and morphine pyrolysates prepared in this laboratory have been shown to be mutagenic in *Salmonella typhimurium* after metabolic activation and to cause chromosomal damage (sister chromatid exchange) in Chinese hamster ovary cells and in human peripheral blood lymphocytes *in vitro*. Morphine pyrolysate, which accounts for a large fraction of the mutagenic activity of *sukhteh* or opium pyrolysate, produced tumours in mice after dorsal application followed by application of 12-*O*-tetradecanoyl phorbol-13-acetate[14]. Results of experiments in which these pyrolysates were tested in rodents for carcinogenic effects, using different routes of administration[15] should be available by the end of 1984.

Six of the major compounds present in morphine pyrolysate have been purified by high-performance liquid chromatography and identified by gas chromatography/mass spectrometry and Fourier transform nuclear magnetic resonance spectroscopy. The proposed structures for these compounds, all containing a substituted hydroxy-phenanthrene moiety as a common element, are shown in Figure 4. Studies to determine the individual biological activities of these compounds, their occurrence in *sukhteh* and opium pyrolysates and studies on the mechanism of their metabolic activation are in progress. The structural elucidation of a number of pyrolysis products displaying mutagenic activity also remains to be carried out.

(ii) *Ochratoxin A in foodstuffs in relation to nephropathy and bladder cancer* (Dr M. Castegnaro and Dr N. Day; in collaboration with Dr I. N. Chernozemsky and Dr T. Petkova, Institute of Oncology, Medical Academy, Sofia; and Dr J. Idle, Biological Experimental Pharmacology Department, St Mary's Hospital Medical School, London; DEC/83/11)

In view of the results obtained during the pilot study conducted in 1983, showing that ochratoxin A is present in a large proportion of food samples produced and consumed by the population in an area with high incidence of Balkan endemic nephropathy and of urinary-tract tumours[16], the study has been extended to determine whether ochratoxin A can be identified as a causal agent. It is planned to collect blood samples (5 ml) from the following groups of patients, to determine its ochratoxin A content and, at the same time, to collect food samples for analysis of ochratoxin A by immunoassay at the Agency: (1) healthy persons from families of patients with urinary-tract cancer and/or endemic nephropathy; (2) patients with cancer of the urinary tract and/or endemic nephropathy; (3) controls from two non-endemic areas; and (4) controls from two endemic areas — unaffected villages and unaffected households in affected villages. At least 30 samples from each group will be analysed.

To confirm preliminary results showing an enhanced ability of high-risk subjects in the area of Vratza to metabolize the drug debrisoquine, as compared to healthy subjects from the same villages, it is planned to collect samples of urine from drug-treated patients from the following groups: (1) healthy persons of about 30 years of age from families of patients with urinary-tract cancer and/or endemic nephropathy; (2) patients with cancer of the urinary tract; (3) patients with both cancer of the urinary tract and nephropathy; and (4) a different ethnic group living in the area

[14] IARC (1983) *Annual Report 1983*, Lyon, p. 41
[15] IARC (1983) *Annual Report 1983*, Lyon, p. 42
[16] IARC (1983) *Annual Report 1983*, Lyon, pp. 39–40

for about 25 years and not subject to these two ailments. Population groups in which the study will be performed have been selected, and sampling is under way.

The metabolism of ochratoxin A by rat strains that are slow and fast metabolizers of debrisoquine has been studied in parallel (see p. 75).

(iii) *Characterization of active principles in local plants in Pakistan* (Dr S. Riazuddin, Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan; DEC/80/001)

Five plants that are used in dried powdered form, either as insect repellants, to preserve clothing and foodstuffs or as medicinal compounds, were extracted with various solvents, and the extracted materials were tested for mutagenic activity in a bacterial test system.

Petroleum ether (boiling-point, 40–60°C) extracts of *kuth* (*Sasurea lappa*), *chraita* (*Swertia chirata*) and *ner* (*Skimmia laureola*) were active against *Salmonella typhimurium* tester strains TA98 and TA1535 in the presence of liver microsomal fractions from Aroclor-induced rats. There was no activity in tester strains TA100, TA1537 or TA1538. Similar preparations of *bachgandi* (*Acorus calamus*) and *dambre* (*Zanthoxylum alatum*) showed no activity in tester strains TA98, TA100, TA1535, TA1537 or TA1538 either in the presence or absence of liver microsomal fractions from Aroclor-induced rats.

An organic compound with a molecular composition of $C_{15}H_{18}O_2$, isolated for its activity as an insect repellant from a local plant, *Sasurea lappa*, and commonly used as an aphrodisiac, inactivated transforming DNA in a bacterial transformation system using *Haemophilus influenzae* Rd type cells as the tester strain. The inactivation of transforming DNA could not be restored by treatment with a crude protein extract isolated from adapted *Micrococcus luteus* or *Escherichia coli* cells.

(*j*) *Studies on analgesic-associated renal papillary necrosis and renal pelvic and ureteral/urothelial hyperplasia and carcinoma* (Principal investigator: Dr P. H. Bach, Robens Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, UK; DEC/83/03)

The association between analgesic- and nonsteroidal anti-inflammatory drug-related renal papillary necrosis (RPN) and upper urothelial carcinoma is well established, but may not be causal. The purpose of these investigations is to use model papillotoxic compounds as molecular probes for studying RPN and its relation to urothelial carcinoma.

The major research findings were the establishment of the validity of the acutely induced 2-bromoethanamine model for studying analgesic-associated RPN. By completing a series of investigations on the time-course changes associated with the 2-bromoethanamine model, it has become clear that the drug causes an acutely developing RPN that reflects most of the major pathological changes seen in subacute and chronic animal models and in human analgesic abusers. Studies of the effect of 2-bromoethanamine on the medullary matrix suggest that the loss of the matrix is an integral part of RPN that may be pathognomonic. Pretreating animals with single doses of several analgesics followed by 2-bromoethanamine greatly exacerbates the papillotoxic effects. A single dose of these analgesics in the absence of 2-bromoethanamine caused no morphological change in the medulla.

Work in progress includes studies of the RPN time-course, using high-resolution microscopy and multiple doses of 2-bromoethanamine, and of the long-term effects of single doses of this drug.

(*k*) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (Dr H. Vainio, Mr J. Wilbourn, Ms L. Haroun, Mrs C. Partensky and Mrs I. Peterschmitt)

(i) *Working Group meetings*

The objective of this project is to identify chemicals, groups of chemicals and exposures to complex mixtures that may present a carcinogenic risk to humans. Its implementation involves three main steps: (1) collection of all published data relevant to the assessment of the carcinogenic risk (including data on chemical production, occurrence, experimental carcinogenesis, toxicology, mutagenicity and epidemiology) for the selected chemicals or complex mixtures; (2) critical evaluation of these data by international working groups of experts in epidemiology and chemical carcinogenesis and related disciplines; and (3) publication and dissemination of the summarized data and evaluations as *IARC Monographs*. The evaluations are intended to assist national and international authorities in formulating decisions concerning preventive measures. Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. Since 1972, the US National Cancer Institute has provided financial and scientific support to this programme.

Many units within the Agency contribute to the planning and implementation of the working groups. During the last year, expertise in epidemiology was provided by Drs R. Saracci and L. Simonato; in experimental pathology, toxicology and mutagenesis by Drs R. Montesano, H. Bartsch, J. R. P. Cabral, A. Likhachev, M. Hollstein and H. Yamasaki; in analytical chemistry by Drs M. Friesen and I. K. O'Neill; in statistical aspects of data analysis by Drs J. Kaldor and J. Wahrendorf; and in editorial matters by Mrs E. Heseltine.

During the year under review, three working groups were convened in Lyon, whose deliberations and conclusions resulted in Volumes 34, 35 and 36 of the *Monographs*[17–19].

Volumes 34 and 35 are the last two of a series of four volumes in which the carcinogenicity of polynuclear aromatic compounds and exposures to complex mixtures in which these compounds are found are evaluated. The first two volumes in this series, Volumes 32 and 33, were described in last year's *Annual Report*[20]. Volume 34 covers four industries in which there are possible exposures to polynuclear aromatic compounds from coal- and petroleum-derived materials: aluminium production, coal gasification, coke production, and iron and steel founding. For two of the industries, aluminium production and iron and steel founding, the Working Group considered that the available epidemiological studies provide *limited evidence* that certain exposures within the industries are carcinogenic to humans; pitch fume was considered to be a possible causative agent in the aluminium production industry.

In the epidemiological studies reported in the early literature on the destructive distillation of coal, data on health effects due to the process of coal gasification could not be distinguished from those due to coke production. The early studies were therefore evaluated separately, and the Working Group considered that there is *sufficient evidence* that exposures to coal-tar from the

[17] IARC (1984) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 34, *Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding*, Lyon

[18] IARC (1984) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 35, *Polynuclear Aromatic Compounds, Part 4, Bitumens, Coal-Tars and Derived Products, Shale Oils, and Soots*, Lyon

[19] IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 36, *Some Allyl Compounds, Aldehydes, Epoxides, and Peroxides*, Lyon

[20] IARC (1984) *Annual Report 1983*, Lyon, pp. 44–47

destructive distillation of coal give rise to skin cancer in humans. In regard to coal gasification, the epidemiological data provide *sufficient evidence* that certain exposures in retort houses of older coal gasification plants are carcinogenic to humans, giving rise to lung cancer. The likely causative agent is coal-tar fume. Coal-tars from older gas-works have been tested by topical application, and there is *sufficient evidence* that they produce skin cancers in experimental animals. No epidemiological or experimental study was available on modern coal gasification processes. There is *sufficient evidence* that certain exposures in the coke production industry are carcinogenic to humans, giving rise to lung cancer (a possible causative agent is coal-tar fume), and *sufficient evidence* that samples of tars taken from coke ovens are carcinogenic to experimental animals.

Volume 35 is the last in the series on polynuclear aromatic compounds and comprises four monographs on complex mixtures in which these compounds occur: bitumens, coal-tars and derived products, shale oils and chimney soots from domestic and institutional sources. The

Table 5. Complex mixtures considered and evaluations made in Volume 35 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*

Complex mixture	Evidence for carcinogenicity in experimental animals
Bitumens[a]	
air-refined – extracts	sufficient
– undiluted	inadequate
cracking residue – undiluted	limited
steam-refined – extracts	sufficient
– undiluted	limited
Coal-tars and derived products	
anthracene oils	sufficient
coal-tar pitches	sufficient
coal-tars	sufficient
creosote oils	sufficient
creosotes	sufficient
Shale oils	
bitumens	sufficient
commercial blends	sufficient
crude – distillation fractions	sufficient
– low-temperature	sufficient
– high-temperature and fractions	sufficient
distillation residue	limited
oil shale – raw	limited
– spent	limited
Soots	
coal soot – dust	inadequate
– extracts	sufficient
fuel-oil soot – extracts	inadequate
heating-oil soot - extracts	limited
oil-shale soot – extracts	sufficient
wood soot – extracts	inadequate
– implants	limited

[a] Petroleum-derived

available epidemiological data provide *sufficient evidence* that coal-tar pitches and *limited evidence* that coal-tar-derived creosotes are carcinogenic to humans. There is *sufficient evidence* for the carcinogenicity of shale oils and soots to humans. No epidemiological study of workers exposed solely to bitumens was available to the Working Group. The evaluation of the experimental carcinogenicity data on these complex mixtures are given in Table 5.

Volume 36 comprises 15 monographs, on allyl compounds, aldehydes, epoxides and peroxides. The data on experimental animals were judged to provide *sufficient evidence* for the carcinogenicity of acetaldehyde and of the four epoxides considered — diglycidyl resorcinol ether (technical grade), ethylene oxide, propylene oxide and styrene oxide—and *limited evidence* for that of allyl isothiocyanate, allyl isovalerate, eugenol and hydrogen peroxide. The data were considered inadequate to evaluate the carcinogenicity of allyl alcohol, allyl chloride, acrolein, malonaldehyde, benzoyl peroxide and lauroyl peroxide. The epidemiological data provide *limited evidence* for the carcinogenicity to humans of exposure to ethylene oxide in combination with other chemicals, but *inadequate evidence* for the carcinogenicity to humans of exposure to ethylene oxide alone. Epidemiological data were either not available or inadequate to evaluate the carcinogenicity of the other compounds to humans.

(ii) *Report on a workshop to establish priorities for chemicals and mixed exposures to be evaluated in the* IARC Monographs *or to be tested in long-term carcinogenicity studies* (Mr J. Wilbourn, Ms L. Haroun and Dr H. Vainio)

In January 1984, an ad-hoc group of 21 experts from 17 countries met in Lyon to advise the IARC on priorities for chemicals and mixed exposures to be evaluated or re-evaluated in *IARC Monographs* or to be tested in long-term carcinogenicity studies. The deliberations and results of that meeting will be published in the form of an *IARC Internal Technical Report.*

Previously established criteria for selecting chemicals and exposures to complex mixtures for evaluation and for testing were reconfirmed. The group suggested 180 chemicals, groups of chemicals and exposures for evaluation or re-evaluation in future *IARC Monographs*; 110 were ranked as being of high priority and 70 of lower priority. The chemicals, groups of chemicals and exposures selected were predominantly industrial chemicals (85), drugs (29) and pesticides (20), whereas naturally occurring substances (17), complex mixtures and occupational exposures (14), food and feed additives (10) and environmental pollutants (5) formed a minority.

With regard to testing, 151 chemicals, groups of chemicals and complex mixtures were selected; 87 were ranked for high priority and 64 for lower priority. They were grouped by use or source as follows: pesticides (48), industrial chemicals (38), drugs (40), food and feed additives (8), naturally occurring substances (10) and environmental pollutants including complex mixtures (7).

It was noted that carcinogenicity studies on some of the food and feed additives, pesticides and drugs that were selected for testing may already have been carried out within industry but that the results may not have been published in the scientific literature. Publication of such data is encouraged prior to further testing being undertaken.

The list of priorities for evaluation and re-evaluation will be used in the development of future work plans for the *IARC Monographs*; and the list of priorities for testing will be circulated to institutes undertaking long-term carcinogenicity tests (see IARC *Survey of Chemicals Being Tested for Carcinogenicity*, p. 129, and international network of carcinogenicity testing, p. 124).

(*l*) *Occupational cancer review* (Dr L. Simonato, Dr R. Saracci and Mrs J. Lavallée-Hawken)

The systematic collection of published studies investigating carcinogenic risks in occupational environments has been continued, using a computerized system of bibliography. This should allow completion of an updated list of occupations and industries involving an increased risk of cancer by the end of 1984 or early 1985.

(*m*) *Use of job histories in case-control studies to detect occupational carcinogens* (Dr R. Saracci and Dr A. Walker; in collaboration with Professor O. Axelson, University Hospital, Linkoping, Sweden; Dr F. Berrino, National Cancer Institute, Milan, Italy; Dr D. Coggon, MRC Environmental Epidemiology Unit, Southampton, UK; Dr J. Fabry, Faculty of Medicine, Lyon, France; Dr M. Gerin, University of Quebec, Canada; Dr K. Kurrpa, Institute of Occupational Health, Helsinki; Dr S. Hoar, National Cancer Institute, Bethesda, USA; Dr F. Ferrario, National Cancer Institute, Milan, Italy; Dr D. Silverman, National Cancer Institute, Bethesda, USA; Dr O. Møller-Jensen, Danish Cancer Registry, Copenhagen; Ms L. Richardson, University of Quebec, Canada; Dr N. Segnan, University of Turin, Italy; Dr J. Siemiatycki, University of Quebec, Canada; Dr D. Sundin, National Institute for Occupational Safety and Health, Cincinnati, USA; and Dr P. Vineis, University of Turin, Italy)

Proponents of various methods for inferring exposure to potential carcinogens from work histories met with Agency staff in Lyon on 9–10 February 1984. Three kinds of hazard assessment were discussed in detail:

(1) risk evaluation based on job title alone, without reference to either standard or ad-hoc data on associated exposures;

(2) semi-automatic translation of job histories into exposure histories through the use of job-exposure matrices; and

(3) individualized exposure coding, in which a detailed textual work amnesis is translated into an exposure history by an industrial hygienist expert both in industrial processes in current use and in local, historical working conditions.

The group concluded that job title studies were neither sensitive nor specific, but would continue to occupy a useful place in regions in which job titles were sufficiently standardized to allow linkage between large bodies of occupational and mortality data. Job-exposure matrices could not, it was felt, be made sufficiently general to have wide applicability, because of the variation in industrial processes over regions and across time. Since the entry point into a job-exposure matrix is job title, matrix-derived exposure information may not be superior to job title data, except insofar as many job titles with similar exposure profiles can be collapsed into a manageably small number of exposure categories. Individual exposure coding is expensive and time-consuming and has been brought into large-scale, systematic operation in only one centre. Insufficient experience has accumulated to permit evaluation of its utility to date.

While improvements in systematic data collection procedures for exploratory case-control studies may have potential for the detection of previously unsuspected occupational carcinogens, there appears at present to be no system that can be put forward as an epidemiological standard.

3. SITE-ORIENTED STUDIES

(*a*) *Etiological studies on liver cancer*

(i) *Aflatoxin and hepatitis B studies in Swaziland* (Dr N. Muñoz and Dr F. X. Bosch; in collaboration with Dr F. G. Peers, Mbabane, Swaziland; UNEP/IARC FP/0107.78-03(1391)

The primary objective of this study, which developed as the result of a joint initiative of the United Nations Environment Programme and the Agency, was to assess the impact of a rural development programme (RDA) on the level of aflatoxin contamination of foodstuffs in Swaziland and to determine the prevalence of several markers of hepatitis B virus infection in the population. Data collection was completed in June 1983, and analysis has begun at the Agency. Preliminary results can be summarized as follows:

(1) *Cancer registration.* Up to June 1983, 727 cases of cancer had been registered. The crude rate for all cancers and both sexes combined is 29.4×10^5 per year. The corresponding figure for males is 26.6×10^5 per year and that for females $31.9 \times 10^5 \times$ year. Liver and oesophageal tumours are the most frequent among males: the crude annual rate for liver cancer is 5.4×10^5 and that for oesophagus, 4.7×10^5. Among women, cancer of the cervix is the dominant site, with a crude annual incidence rate of 15.3×10^5. Breast cancer is the second incident cancer, with an annual rate of 2.6×10^5, and liver cancer ranks third with a crude annual rate of 1.7×10^5.

(2) *Dietary survey.* A dietary survey of aflatoxin contamination was conducted from July 1982 to June 1983. A similar sampling system to that used in the 1972 survey was used, except that four *ndunas* were chosen rather than two for each of the 11 arable areas. 'Man-sized' portions of a main meal and of sauce were collected separately and each weighed before samples were taken for analysis. At the same time, samples of snack foods were taken from each household. Table 6 shows the proportion of positive diet samples by topographic level.

Table 6. Proportion of diet samples positive for aflatoxin by topographic level

	High veld	Middle veld	Low veld	Lubombo	Total
Total no. of samples	703	704	705	471	2583
Total no. positive	21	37	49	13	120
Percentage positive	2.99*	5.26	6.95*	2.76	4.65

* $p < 0.05$

The main source of aflatoxin is maize meal (3.41% of samples were found positive) and peanuts (21.21% of samples positive). The 'sauce' that is used almost always with the maize meal was found to be contaminated in 3.5% of cases, but this was largely due to the presence of ground peanuts. Mean levels of aflatoxin in maize meal were 163.11 ± 76.9 ng/kg of food and in peanuts, 302.5 ± 108.5 ng/kg. No significant difference was found among topographic areas.

Compared with the 1972–1973 dietary survey, these preliminary results suggest that the programme of rural development has had an impact in reducing the level of aflatoxin in human diets in two areas in which the maximum input of the programme has been three to four years and ten years, respectively.

(3) *Study of HBV markers.* Serum samples from 84 individuals, 27 of them cases of primary liver cancer, were tested for HBV markers. Diagnosis of primary liver cancer was based on a compatible clinical record and either biopsy confirmation or an α-fetoprotein level above 50 ng/ml. The prevalence of HBV markers was compared in cases and controls: Taking as baseline those patients negative for all HBV markers plus those with anti-HBs+ only, the relative risk for primary liver cancer for those with an active infection (HBsAg+ or anti-HBc+ with anti-HBs-) was 19.0 (19 cases, 5 controls; $p < 0.025$; 95% confidence limits, 2.54–149.3), and the relative risk for individuals with a past HBV infection (anti-HBs+ and anti-HBc+) was 2.1 (7 cases, 17 controls; $p < 0.10$; 95% confidence limits, 0.213–11.58). The increased risk for primary liver cancer among carriers of HBsAg and those with an active infection is well established and thus confirmed by the data from this study.

The project leader, Dr F. G. Peers, has now retired and left Swaziland, and the facilities made available for the project have been handed over to the Swazi Government. A commitment to support the Cancer Registry for a two-year period was accepted by the Agency. Scientific papers on various aspects of the project will be prepared during 1984.

(ii) *Cohort study on hepatitis B virus and liver cancer* (Dr N. Muñoz; in collaboration with Professor Phoon Wai-On, Dr Fong Ngon Phoon and Mr Wong Ah Fook, Department of Social Medicine and Public Health, University of Singapore; DEB/79/021)

A total of 7684 subjects had been admitted to this cohort up to February 1984, 6994 of whom have been tested for the various markers of hepatitis B virus. Table 7 shows the sources of the cohort members. Identification of those subjects who have developed liver cancer will commence shortly, by linking the cohort file to that of the Cancer Registry. The possibility of using the same cohort to evaluate the role of other risk factors for liver cancer, such as aflatoxin, will be explored.

(iii) *Hepatitis B virus, aflatoxin and liver cancer in the Philippines* (Dr N. Muñoz; in collaboration with Dr E. Domingo, Dr A. Lingao and Dr M. Abrigo, Department of Internal Medicine, Philippines General Hospital, Manila)

The aim of this case-control study of parents of patients with liver cancer and of parents of control patients is to determine whether subjects who have developed hepatocellular carcinoma

Table 7. Cohort study of hepatitis B virus and liver cancer

Source of cohort members	No. of specimens		HBsAg carriers	
	Collected	Tested	No.	%
Hospitals	5524	4843	604	12.47
Blood bank	1365	1365	31	2.27
Others	795	794	79	9.95
Total	7684	6994	714	10.20

(HCC) are more likely to have been infected with hepatitis B virus by their mothers than the control patients. Two controls, matched by sex and age, have been included for each case—one irrespective of serological status (control 1) and the second an asymptomatic hepatitis B surface antigen carrier (control 2). Thirty subjects with HCC, 30 non-carrier controls (control 1) and 29 asymptomatic carrier controls (control 2) with both parents alive have been identified. Blood specimens from the HCC cases, from the controls and from the parents and available siblings of cases and controls have been collected. Table 8 summarizes the latest results. The data suggest that HCC patients are more likely than controls to have been infected with HBV by their siblings and their mothers.

Table 8. Hepatitis B virus (HBV) exposure in hepatocellular carcinoma (HCC) cases, and in controls and in their parents and siblings

Group	No.	HBV exposed (%)				HBsAg + (%)			
		Cases	Mother	Father	Sibs	Cases	Mother	Father	Sibs
HCC cases	30	100.0	86.7	90.0	91.3	90.0	16.7	16.7	39.1
Control 1	30	45.8	66.7	73.3	67.6	0.0	6.7	13.3	15.7
Control 2	29	100.0	86.2	89.7	75.8	100.0	6.9	20.7	23.5

(iv) *Intervention studies using hepatitis B virus vaccine*

(1) *Intervention study in Singapore* (Dr N. Muñoz and Dr N. Day; in collaboration with Professor Oon Chong Jin, Professor Chan Soh-Ha, Dr Ewe Hui Sng and Dr Lily Chan, University of Singapore, Singapore; DEB/83/002)

Originally, this study was designed to establish a registry of 35 000 babies born before the introduction of the hepatitis B virus (HBV) vaccine, to serve as a historical control to a cohort of HBV-vaccinated children. The design of this study has been changed, since the availability of HBV vaccine in Singapore makes it now possible to vaccinate all children of HBeAg-positive mothers.

It is now proposed to constitute a control group from the older siblings of children born after the beginning of the vaccination programme. Since hepatocellular carcinoma is about five times more common among males than among females, the control group will be confined to male siblings aged less than five years. A minimum of 700 male children will be enrolled in both the control and the vaccinated cohort. Up to February 1984, 16 299 antenatal serum specimens had been collected and tested for HBV markers: 523 (3.2 %) were positive for HBsAg; 197 were positive to e antigen.

(2) *The Gambia hepatitis intervention study* (Dr N. E. Day, Dr N. Muñoz, Dr G. O'Conor and Dr M. Parkin; in collaboration with Dr R. Ryder, Tufts University School of Medicine, Boston, USA; Dr B. Greenwood and Dr H. Whittle, MRC, The Gambia; Mr P. G. Smith, London School of Hygiene and Tropical Medicine, UK)

Plans for a large-scale HBV vaccination trial in The Gambia have been developed. A meeting was held in Lyon on 20–21 May 1984, with representatives of The Gambian Ministry of Health and of the Medical Research Council's unit in The Gambia. An earlier meeting had taken place at the MRC headquarters in London on 30 March. These meetings elaborated a detailed study design, which comprises three phases:

Phase I: Mass vaccination programme. Following a period of personnel recruitment, training and piloting of HBV vaccine delivery, HBV vaccination will be incorporated progressively into the regular vaccination schedule administered by the 17 EPI (expanded programme for immunization) teams currently operating in The Gambia (the number of teams is currently being reviewed). An HBV vaccine (approved by the World Health Organization) will be introduced on a team-by-team basis at approximately three-monthly intervals, such that complete national coverage will be achieved within about four years. Nationwide HBV vaccination is expected to continue after that date. At the end of the four years over which HBV vaccination has been introduced, two groups of subjects will have been identified. Each will consist of about 60 000 children; one group will have received HBV vaccination, the other will not. Long-term follow-up of these groups for the sequelae of HBV infection, especially hepatocellular carcinoma and chronic liver disease, will enable the protective effect of vaccination against these conditions to be clearly and unambiguously assessed.

Phase II: Studies of selected cohorts. Three groups will be identified, as follows:

Cohort I will consist of 1000 infants randomly selected from those who attend the EPI but do not receive HBV vaccine, who will be followed until they reach age 10 years;

Cohort II will consist of 1000 infants randomly selected from those who attend the EPI and receive HBV vaccine, followed from the time they receive HBV vaccine for ten years; and

Cohort III will consist of four groups, to be formed of those children born in each consecutive year from the second year of the project. Each group will consist of 500 randomly selected infants who have received HBV vaccine.

Data from the clinical and laboratory surveillance of Cohorts I and II during the first ten years following vaccination will provide information that may be considered short- and medium-term endpoints of the study. Those in Cohort III will be examined only once for HBV markers following vaccination to assess the continuing immunogenicity of the vaccine throughout the study period.

Phase III: Long-term follow-up. Training programmes will be developed for hospital, clinic and other staff of the national health care system directed to the identification, characterization and recording of all cases of chronic liver disease and hepatocellular carcinoma. A cancer registry will be established in The Gambia to coordinate and facilitate this task.

This study has been designed to provide new information on the natural history of hepatitis B in a West African population, to determine the duration of HBV vaccine-induced immunity and to yield conclusive data on the efficacy of vaccination for the prevention of hepatocellular carcinoma and other chronic sequelae of hepatitis B infection.

(*b*) *Cancers of the gastrointestinal tract*

(i) *Precancerous lesions of the oesophagus in the People's Republic of China* (Dr N. Muñoz, Dr J. Wahrendorf and Dr N. E. Day; in collaboration with Dr Zheng Hong Ji, Dr Lu Jian Bang, Professor Shen Chiun, Dr Yang Kuan Re, Dr Qu Song Lang and Dr Quiao Si Je, Honan Medical College and Honan Cancer Institute, Honan, People's Republic of China; Dr Li Bing, Dr Zheng You Hui, Dr Zhang Cai-Yun, Dr Zheng Su Fang, Dr Lu Shih Hsin and Dr Liu Fu Sheng, Beijing Cancer Institute, Beijing; Professor M. Crespi and Dr A. Grassi, Regina Elena Institute, Rome; Dr D. Thurnham, Dudley Road Hospital, Clinical Investigation Unit, Birmingham, UK; and Dr M. Hambidge, Medical Center, University of Colorado, Denver, USA)

The study was initiated in September 1983 and included 610 individuals aged 35 to 64 years chosen at random from two production brigades: Dong Xiao Fung and Meng Zhuang. They were randomized into two groups, one receiving a retinol-riboflavin-zinc preparation once a week and the other a placebo. Before initiation of the treatment, a questionnaire seeking demographic data, information on smoking, drinking and dietary habits, and a 24-h recall was completed, followed by a physical examination to look for signs of vitamin A and riboflavin deficiencies, together with a collection of blood taken from each individual. The levels of β-carotene, retinol, vitamin A, riboflavin and zinc had been determined in each specimen in duplicates: one analysed in China and the other at Agency consultant laboratories. Two months after initiation of treatment, blood samples were obtained from a random sample of 100 individuals (53 from the vitamin-treated group and 47 from the placebo group) to check compliance. The results (Table 9) suggest that compliance with the treatment had been good.

Six months after initiation of the study, a follow-up examination was carried out on 607 subjects out of 610 who presented themselves. The examination included an interview, using the same questionnaire as at entry into the study, and a physical examination to look for signs of vitamin A and riboflavin deficiencies.

A review of the follow-up forms used by the 'barefoot' doctors to register the delivery of capsules indicates that each individual received the appropriate capsules each week for the first six months of the trial. Analysis of the results of the initial and follow-up investigations is in progress. The final examination will start on 20 October 1984 and will include an interview, using the same bilingual questionnaire used at the initial and follow-up interviews; a physical examination;

Table 9. Effects of treatment for micronutrient deficiencies on blood levels

Change in blood level	Retinol (%)		Riboflavin (%)		Zinc (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
More than 10% increase	72	49	80	19	30	30
Less than 10% increase	28	51	20	81	70	70

collection of blood and hair specimens for vitamin and zinc analysis; and an endoscopy, including guided cytology and biopsies.

Epidemiological intervention studies of this type require particular methodological considerations. The randomization procedure used has been that of randomized blocks. The imbalance of treatment assignments in specific strata of the study population has been compared by computer simulation with what would be achieved using other randomization procedures. The applied method compares very favourably with other, more complex methods which, for logistic reasons, would not be suitable for use in the epidemiological context of intervention trials.

(ii) *Detection of DNA alkylated bases in oesophageal tissues* (Dr D. Umbenhauer, Miss B. Chapot, Dr M. Hollstein and Dr R. Montesano; in collaboration with Dr M. Rajewsky, Institute for Cell Biology Tumour Research, University of Essen, FRG, DEC/81/03; Dr R. Saffhill, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK, DEC/83/01; and Dr S. H. Lu, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, DEC/81/02)

There is a strong correlation in studies in experimental animals between the formation and persistence of O^6-alkylguanine and the susceptibility of certain tissues to carcinogenesis by alkylating chemicals. However, the actual relevance of this modified base in the etiology of human cancer is not yet clear. In collaboration with Dr Lu, human surgical tissues have been obtained in Linxian county, People's Republic of China, an area in which there is a high risk of oesophageal cancer. There is evidence[21] that inhabitants of this area are exposed to *N*-nitroso compounds through their diet, and some *N*-nitrosamines and *N*-nitrosamine precursors have been identified.

DNA was isolated from oesophageal tumours, uninvolved oesophagus and cardiac stomach and fractionated by high-performance liquid chromatography. In this manner, the parental deoxynucleosides could be quantitated and separated from the modified nucleosides to eliminate interference in the subsequent immunoassays. In addition, O^6-methyl- and -ethyldeoxyguanosine were separated so that both modified nucleosides could be analysed in the same sample. Using a radioimmunoassay, the presence of O^6-methyldeoxyguanosine has been detected in 7 of 35 oesophagus samples and in 1 of 12 stomach samples, but in none of the tumour samples. Those samples that were positive contained in the range of 1–5 O^6-methyldeoxyguanosines per 10^7 deoxyguanosine. Experiments are now under way to determine the presence of O^6-ethyldeoxyguanosine. Determination of these alkyldeoxyguanosines in control tissues is also under way.

Since it is widely believed that the presence of O^6-alkylguanine in DNA at the time of replication is important in the initiation of carcinogenesis, the ability of a tissue to remove this premutagenic lesion may contribute to its sensitivity to carcinogenesis. Protein extracts have been prepared from the surgical specimens and from rat oesophagus and analysed for their ability to remove O^6-methyl- or ethylguanine from a DNA substrate *in vitro*. The human tissue was very efficient in removing O^6-methylguanine—approximately 10–15 times more than equivalent rat tissue. The human tumours were the most active, followed by oesophagus and then stomach, using

[21] Yang, C. S. (1984) In: O'Neill, I. K., von Borstel, R. C., Miller, C. T., Long, J. E. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)

both methylated and ethylated DNA as substrates; however, removal of the ethylated base was less efficient than that of the methyl in all tissues. This high activity of tumour tissue may explain in part the apparent lack of the premutagenic lesion in this tissue (see p. 79).

Single point mutations at critical sites in human H-*ras* and K-*ras* sequences, some of which create restriction enzyme polymorphisms, can activate these oncogenes[22]. This discovery offers a biochemical method for examining the mechanisms by which transforming *ras* alleles in human and animal tumour tissues have acquired malignant properties[23]. AG → C mutation in human *K-ras* that creates an additional Sac I restriction site in codon 12 was responsible for *ras* activation in two human tumour cell lines[22]. We are screening the DNA isolated from oesophageal tumours and adjacent tissue for Sac I polymorphism to examine further the association of this mutation with the development of human cancer.

(iii) *Precancerous lesions of the oral mucosa and oesophagus in Uzbekistan (USSR)* (Dr D. G. Zaridze and Miss M. Blettner; in collaboration with Professor N. N. Trapeznikov, Professor B. K. Poddubni, Dr J. P. Kuvshinov, Dr B. I. Poljakov, Dr E. Matiakin, Dr V. I. Rottenberg and Dr S. I. Parshikova, All-Union Cancer Research Centre of the USSR Academy of Medical Sciences, Moscow; Dr M. P. Rosin and Dr H. F. Stich, Environmental Carcinogenesis Unit, British Columbia Cancer Research Center, Vancouver, BC, Canada; and Dr D. Thurnham, Dudley Road Hospital, Clinical Investigation Unit, Birmingham, UK)

This study in an expansion of a local screening programme in an area with a high incidence of oral cancer and a moderately high incidence of oesophageal cancer (Narpai Region of Samarkand Oblast).

The aims of the study include:

(1) determination of the frequency of precancerous lesions of the mouth and oesophagus in an area with a high incidence of oral and oesophageal cancer;

(2) investigation of the possible relationship between *nass* quid chewing and cigarette smoking, and the prevalence of oral and oesophageal precancerous lesions;

(3) investigation of the role of vitamin A, β-carotene and riboflavin deficiency in the etiology of precancerous lesions and cancer of the mouth and oesophagus; and

(4) determination of the effect of vitamin supplementation on precancerous lesions of the oral and oesophageal mucosa.

Survey phase: During 1983, of 2150 males in the 55–69 age group, resident in one local authority district, who were invited to attend a medical examination by local nurses, 1505 showed up (compliance rate, approximately 70%). In addition, 61 men under the age of 55 and over the age of 70 came for a medical check-up. For all 1566 men, questionnaires were completed on sociodemographic characteristics, use of *nass*, cigarette smoking, alcohol consumption, dietary habits, medical history and family history of cancer. Oral examination was performed on all 1566 men, and oesophagogastroscopy was performed on 1344. Samples for cytological and histological

[22] Santos, E., Martin-Zanca, D., Reddy, P., Pierotti, M. A., Della Porta, G. & Barbacid, M. (1984) Malignant activation of a K-*ras* oncogene in lung carcinoma but not in normal tissue of the same patient. *Science*, **223**, 661

[23] Notario, V. Sukumar, S., Santos, E. & Barbacid, M. (1984) In: Vande Woude, G. F. Levine, A. J., Topp, W. C. & Watson, J. D., eds, *Cancer Cells*, 2, *Oncogenes and Viral Genes*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory

investigation were obtained from oral and oesophageal lesions, and photographs were taken. In addition, oral and oesophageal smears were taken for the detection of micronuclei, since it has been shown that the frequency of micronucleated cell formation is much higher in those who chew tobacco and betel nut, i.e., persons at high risk of oral cancer[24].

Of the total of 1569 men interviewed, 636 (41%) reported chewing *nass* quid (a mixture of tobacco, ash, cotton oil and lime); 259 men (17%) were cigarette smokers; and 736 men (47%) stated that they drink alcoholic beverages. Medical history of upper gastrointestinal tract diseases was reported by 282 men (18%), and symptoms related to the latter were reported by 499 men (32%). Family history of upper gastrointestinal tract cancer was reported by 143 men (9%).

Angular stomatitis, a disorder suggested as being a symptom of riboflavin deficiency, was observed in 332 of the men examined (21%). The precancerous oral lesions, leukoplakia and preleukoplakia, were found in 144 (75%) and 47 (25%) men, respectively. Cancer of the mouth was reported in three cases: two in the floor of the mouth, and one in the lower alveolar ridge.

A diagnosis of chronic oesophagitis, based on both endoscopical and histological examination, was made in 807 of the men examined (60%). Dysplasia was diagnosed in 4.1% of those with oesophagitis. Squamous-cell carcinoma of the oesophagus was diagnosed in six cases: four in the lower third of the oesophagus and two in the middle third. Adenocarcinoma of the stomach was diagnosed in six subjects.

In an initial attempt to analyse the relationship between the use of *nass*, cigarettes and alcohol and the risk of oral leukoplakia and chronic oesophagitis, hierarchies of models were fitted using GLIM-3[25]. The best fitting model found to explain the data was one involving the main effects of *nass* and smoking plus an interaction term. It was not necessary to include a term for alcohol use, since this factor did not appear to exert any influence on the probability of oral leukoplakia once the effects of *nass* and smoking had been allowed for. The relative risks obtained under this model are presented in Table 10. Risks in present *nass* users who are non-smokers and present smokers who are non-*nass* users are essentially similar; so too is the risk in those who previously chewed *nass* and smoked. The risk is especially elevated among those who presently smoke and chew *nass*.

The best fitting model obtained for oesophagitis included the main effects for smoking and alcohol consumption and an interaction term. There appeared to be no effect of *nass* use on incidence of oesophagitis. The association, as measured by the overall improvement in the fit of the model, did not appear to be as strong between these factors and oesophagitis as the previous

Table 10. Calculated relative risks, based on a statistical model, of oral leukoplakia according to smoking and *nass* use

	Non-smoker	Ex-smoker	Present smoker
Non-*nass* user	1.0	1.7	7.7
Ex-*nass* user	1.3[a]	7.1	0.0[a]
Present *nass* user	5.6	2.4[a]	12.4

[a] Unreliable due to small numbers of patients in these cells

[24] Stich, H. F., Stich W. & Parida, B. B. (1982) *Cancer Lett.*, 17, 125–134

[25] Baker, R. J. & Nelder, Y. A. (1978) *Generalised Linear Interactive Modelling (Release 3)*, Numerical Algorithms Group, Oxford

association between smoking, *nass* and leukoplakia, although the risk among current smokers and drinkers was elevated (1.8).

An elevated frequency of micronucleated cells was found in the oral mucosa of persons chewing *nass* (1.6–5.8%), and in the oesophageal mucosa of persons with chronic oesophagitis who were *nass* chewers (2.3–5.2%). Controls (non-smokers and non-chewers) had a frequency of micronucleated cell formation ranging from 0.0–0.8%. Persons who chewed *nass* had an elevated frequency of micronucleus formation, independently of the presence of oral leukoplakia.

Blood levels of riboflavin, retinol and carotene were measured in 322 men. Riboflavin status was normal in only 14% of the subjects, and above normal in the remainder; plasma retinol concentrations were low (below 20 μg/100 ml) in only 4% of the men, and two men had a value of less than 10 μg/100 ml, showing a biochemical deficiency; in 66% of the subjects, plasma carotene concentrations showed low values (below 40 μg/100 ml), and 35% had a value of less than 20 μg/100 ml, indicating biochemical deficiency.

Intervention phase: The high prevalence of oral and oesophageal precancerous conditions and the observed deficiencies of riboflavin, carotene and vitamin A in the surveyed population, as well as evidence for a possible protective effect of these substances in carcinogenesis[26–28], provide both an opportunity and a justification for an international trial, with the regression of observed precancerous lesions as the endpoint of the study. A randomized trial to this end will be carried out by our group. All eligible persons with oral leukoplakia and oesophagitis (800) will be allocated randomly to four treatment groups receiving vitamin A, β-carotene, riboflavin and placebo. One year after initiation of treatment, a second examination, exactly the same as the first, will be performed. Six months after initiation of treatment, oral examinations will be performed, and scrapings will be taken from the oral mucosa for the micronucleus test. The effect of treatment on the frequency of the formation of micronuclei should, in principle, become detectable in a much shorter time-span than any effect that might be detected by routine cytology and histology. The persons in the trial will be under constant close surveillance by local doctors and nurses, and this should ensure a high compliance rate.

The results of the intervention will be assessed as follows: (1) oral examination before, during and after treatment; (2) endoscopical investigation before and after treatment; (3) histological diagnosis before and after treatment; and (4) analysis of blood levels for vitamin A, β-carotene and riboflavin before, during and after treatment.

(iv) *Stomach cancer*

(1) *Cohort study on chronic atrophic gastritis and intestinal metaplasia in Slovenia, Yugoslavia* (Dr N. Muñoz; in collaboration with Dr I. Matko, Gastroenterology Clinic of the University Clinical Centre of Ljubljana, Yugoslavia)

This study is being extended to include about 1500 subjects, all of whom underwent gastroscopic examination at the Gastroenterology Clinic of Ljubljana between 1970 and 1975 and in whom intestinal metaplasia was diagnosed. The intestinal metaplasia will be classified into three types according to the histochemical characteristics of the mucin, and the risk of developing gastric cancer will be determined by linking the cohort to the cancer registry files.

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[26] Peto, R., Doll, R., Buckley, J. D. & Sporn, M. B. (1981) *Nature*, **290**, 201–208

[27] Sporn, M. B. & Roberts, A. B. (1983) *Cancer Res.*, **43**, 3034–3040

[28] Newborne, P. M. (1984) In: *Proceedings of Society of Toxicology, 23rd Annual Meeting, Atlanta, Georgia*, Abstract No. 425

(2) *Prevalence of precancerous lesions of the stomach in Jiaoxian, People's Republic of China* (Dr N. Muñoz; in collaboration with Dr Li Bing, Dr Zheng You Hui, Dr Wang Kao Ching and Dr Lu Shin Hsin, Beijing Cancer Institute, Beijing; Dr Chou Hui Min, Quingdao Medical College, Shandong; Dr Yang Min Lu, Chang-Wei Medical College, Shandong; and Dr Cao Shou Wei, Medical Research Institute of Shandong, People's Republic of China)

No correlation was found between blood levels of β-carotene, retinol, riboflavin and zinc, and the presence or absence of chronic atrophic gastritis or its extent. The results are summarized in Table 11.

Table 11. Gastric pathology and vitamin levels

	Normal	Superficial gastritis	Chronic atrophic gastritis		
			Mild	Moderate	Severe
MALES					
No. of subjects	3	22	12	12	3
Mean age (range)	36.7 (24.0–61.0)	40.0 (22.0–63.0)	40.9 (21.0–63.0)	46.1 (26.0–60.0)	48.0 (38.0–58.0)
Mean β-carotene (±SD)	64.3 (±16.3)	86.1 (±43.0)	96.7 (±38.6)	96.6 (±45.8)	97.1 (±48.5)
Mean retinol (±SD)	17.2 (±10.5)	20.0 (±9.0)	22.2 (±7.0)	26.8 (±13.0)	29.1 (±8.9)
Mean riboflavin (±SD)	1.52 (±0.26)	1.51 (±0.17)	1.49 (±0.16)	1.43 (±0.15)	1.38 (±0.05)
Mean zinc (±SD)					
FEMALES					
No. of subjects	1	7	13	21	4
Mean age (range)	36.5	41.6	42.6	47.6	50.3
Mean β-carotene (±SD)	90.1 (±0)	74.9 (±34.1)	66.9 (±34.2)	70.6 (±48.9)	81.2 (±52.3)
Mean retinol (±SD)	4.0 (±0)	19.7 (±9.8)	19.8 (±10.1)	19.3 (±9.1)	16.9 (±5.2)
Mean riboflavin (±SD)	1.72 (±0)	1.53 (±0.15)	1.55 (±0.16)	1.48 (±0.16)	1.43 (±0.26)
mean zinc (±SD)					

(v) *Large-bowel pathology in autopsy series* (Dr D. G. Zaridze and Dr J. Estève; in collaboration with Dr N. M. Gibbs, St Luke's Hospital, Guildford, Surrey, UK; Dr J. Simpson, Dr S. Ewen and Dr J. Clark, Department of Pathology, University of Aberdeen, Scotland, UK; Dr H. Stalsberg and Dr J. Eide, Institute of Medical Biology, University of Tromsø, Norway; Dr G. Koskela and Dr Y. Collan, Department of Pathology, University of Kuopio, Finland; and Dr O. Møller Jensen, Danish Cancer Registry, Copenhagen)

Autopsy material was collected from consecutive autopsies in three centres situated in areas with contrasting incidence rates of large-bowel cancer (Table 12): the Department of Pathology of

Table 12. Incidence[a] of colo-rectal cancer in the three countries of the study

	North-east Scotland		Norway		Finland	
	M	F	M	F	M	F
Colon (153)	22.7	22.4	14.3	14.5	8.3	9.4
Rectum (154)	15.9	9.0	11.7	8.0	8.7	6.6

[a] World age-standardized rate

the University of Aberdeen (Scotland), the Department of Pathology of the Institute of Medical Biology of the University of Tromsø (Norway), and the Department of Pathology of the University of Kuopio (Finland). All autopsies performed during the period 1976–1979 were included in the study until there were a total of 25 cases in each sex and age group (20–54; 55–64; 65–74; 75+). In Tromsø, the number of autopsies included in the study was 280, and the sex and age distribution differed somewhat from that in Aberdeen and Kuopio (Table 13).

Table 13. Distribution of autopsies by region, sex and age and percentage of autopsies with at least one polypoid lesion

Region	Age (years)			
	20–54	55–64	65–74	75+
Aberdeen				
Male	25[a] (56%)[b]	25 (44%)	25 (88%)	25 (92%)
Female	25 (48%)	25 (64%)	25 (68%)	25 (76%)
Tromsø				
Male	33 (39%)	36 (44%)	55 (65%)	47 (68%)
Female	19 (47%)	13 (38%)	28 (29%)	49 (61%)
Kuopio				
Male	25 (28%)	24 (50%)	25 (48%)	25 (52%)
Female	25 (24%)	24 (25%)	26 (50%)	26 (42%)

[a] Number of autopsies
[b] Percentage of autopsies with polypoid lesions

A macroscopic examination of each bowel was carried out and the diagnosis and location of every lesion recorded. After fixation, lesions and their locations were mapped and recorded. Polypoid lesions were removed, embedded in paraffin, cut into sagittal sections and stained with haematoxylin and eosin. Sections were examined by one or more pathologist(s) from the given participating centre. Histological classification was done according to the ICD. In addition, blind histological evaluation was performed on 150 randomly drawn slides (50 from each centre),

resulting in inter-observer disagreement for 63% of the lesions examined. Because of this striking disagreement, it was decided to perform a blind histological evaluation of all the polypoid lesions of the large bowel registered in the three participating centres. This revealed a discrepancy between the first and the second histological readings. The lowest consistency of histological evaluation between first and second examination was observed for the histological diagnosis 'adenomatous polyp'. Disagreement between the two readings for the diagnosis of 'hyperplastic polyp' and 'other polypoid lesion' was less frequent.

The results of the analysis presented below are based on a third blind evaluation carried out by a consultant pathologist. A total of 1147 polypoid lesions were identified in 680 autopsies. The distribution of autopsies with at least one polypoid lesion is presented in Table 13. The prevalence of all polypoid lesions, as well as adenomatous polyps, was highest in Aberdeen; relative to Aberdeen, the odds ratios for Tromsø and Kuopio for all polypoid lesions were 0.46 and 0.31, and for adenomatous polyps 0.65 and 0.20, respectively. The prevalence of all polypoid lesions and adenomatous polyps was higher in males, the odds ratio being 0.66 and 0.72 for all polypoid lesions and adenomatous polyps, respectively. The prevalence of all polypoid lesions and adenomatous polyps increases linearly with age, odds ratios for adenomatous polyps relative to the age group 20–54 being 1.79, 3.41 and 5.42 for age groups 55–64, 65–74 and 75+. The proportion of autopsies with other polypoid lesions only, including hyperplastic polyps, was constant and did not vary with sex and age, while the regional variation was of borderline significance and was a result of their low prevalence in Tromsø.

The results to date support the hypothesis that adenomatous polyps are precursors of large-bowel cancer.

(*c*) *Dutch-Japanese case-control study of prostatic cancer* (Dr D. G. Zaridze; in collaboration with Professor F. H. Schröder, Dr F. J. W. ten Kate and Dr F. H. de Jong, Erasmus University, Rotterdam, The Netherlands, DEB/81/042; Dr R. Hayes, Study Centre of Social Oncology, Dutch Cancer Foundation, Rotterdam, The Netherlands; Professor O. Yoshida, Professor K. Okada, Dr K. Oishi and Dr H. Yamabe, Kyoto University, Kyoto, Japan; and Dr Y. Ohno, Nagoya University, Nagoya, Japan)

This study was designed to assess the role of diet and hormonal status on the etiology of focal (latent) and invasive prostatic cancer[29]. In view of the difference in the incidence of prostatic cancer between The Netherlands and Japan, a difference in the weight of the suspected risk factors between these two countries is anticipated. In addition, the study will provide data that should make it possible to examine inter-country correlations between the incidence of prostatic cancer, and nutritional as well as other lifestyle and hormonal variables.

Progress over the past year has consisted in continuation of data collection. Biochemical analysis of collected blood samples is underway for levels of vitamin A, vitamin E and carotene, steroid hormones and trace elements.

[29] IARC (1983) *Annual Report 1982*, Lyon, p. 42

(d) Descriptive epidemiology of selected sites of cancer

This element of the descriptive epidemiology programme draws together information about various cancer sites and seeks to uncover new facets of their behaviour and distribution, to give insight into possible etiology.

(i) *International study of childhood cancer* (Dr D. M. Parkin and Miss S. Whelan; in collaboration with Dr G. Draper, University of Oxford Childhood Cancer Research Group, UK)

The *Cancer Incidence in Five Continents* series presents data derived from registries in many parts of the world by tumour site in five-year age groups. This format is a limitation in the study of the important group of cancers occurring during childhood, for which categorization by histological type is much more relevant. The Descriptive Epidemiology Programme has therefore decided, following a meeting of a steering group in Seattle in September 1982[30], to coordinate a study of such tumours during the interval between the publication of Volumes IV and V of *Cancer Incidence in Five Continents* (see p. 21). Eighty population-based cancer registries, childhood cancer registries and laboratories of pathology throughout the world, known to have data on a relatively large number of childhood tumours, have been approached to see if they are willing to participate. The objective is to produce a reference volume containing incidence rates of cancer in childhood for as many different parts of the world as possible. The time period on which the comparison will be based is the decade 1970–1979, or as near to that as possible.

Information will be requested on individual cases of childhood cancer (aged 0–14 years), to include the site and histology of the tumour (with a verbal description of the diagnosis, if possible, as well as ICD-O or other histology code) and basis of diagnosis. All centres will be asked for a description of the area from which the registered cases were drawn, including, for population-based cancer registries, data on the size of the child population for the years in which the cases were registered.

Table 14. Approximate number and continent of origin of data on cutaneous, internal and ocular malignant melanoma

	No. of collaborating centres	No. of malignant melanomas		
		Skin	Internal	Eye
Africa	1	10	–	–
America	13	9 000	–	50
Asia	3	3 000	–	–
Europe	15	7 300	200	1 400
Oceania	5	2 000	–	50
Total	37	21 310	200	1 500

The data from this study will be collected during 1984 and 1985, analysed and tabulated during 1985 and published in 1985–1986.

[30] IARC (1983) *Annual Report 1983*, Lyon, p. 59

(ii) *Malignant melanoma* (Dr C. S. Muir and Mrs J. Nectoux; in collaboration with Dr E. van der Esch, The Netherlands Cancer Institute, Amsterdam, DEB/83/005)

Data on malignant melanoma collected previously from 37 cancer registries (Table 14) will be analysed to ascertain whether the patterns are consistent with the hypothesis that the disease is associated with direct exposure to solar radiation. Information on the much rarer ocular and visceral malignant melanomas has also been received from several centres. A few areas have supplied long series of ocular melanomas which will permit examination of time trends. Should the rates for ocular melanoma not follow the increase generally observed for cutaneous melanomas, this would suggest other risk factors than increased exposure to the sun.

A study on changes in diagnostic criteria for pigmented skin lesions is meant to evaluate whether the increase in the incidence of malignant melanoma could be due, at least in part, to secular changes in diagnostic criteria. Among the 17 pathological laboratories that had tentatively agreed to participate in the enquiry, 12 are in a position to supply the required data for 1930, 1955 and 1980. From the material that has been received, however, it appears that the number of benign lesions in 1930 is generally very small. For most collaborators, therefore, the scope will be restricted to examination of the 1955 and 1980 material, although two laboratories—in Norway (Dr T. Larsen, Rikshopitalet, Oslo) and in Australia (Dr W. B. Essex, Alfred Hospital, Prahran, Victoria)—have supplied a sufficient number of cases for 1935. Sets of slides have now been received from five laboratories: once material is received from the other collaborators, a sample of the pooled material will be sent to each collaborator for 'blind' evaluation.

(e) *Multinational study on the epidemiology of lymphoid neoplasia* (Dr G. T. O'Conor and Dr C. S. Muir; in collaboration with Professor J. Costa, Institute of Pathology, University of Lausanne, CHUV, Lausanne, Switzerland (DEB/84/02) and participating centres)

It has become increasingly evident that there are important geographic and ethnic differences in the incidence, age distribution and clinical course of lymphoid leukaemia and lymphomas, which may have etiological significance. Recognizing the need for a better definition and epidemiological characterization of the separate biological entities within this group of neoplasms, a two-year feasibility study has been initiated.

A planning session was held at the IARC on 13–14 June 1983, and the principal goals and objectives of the study were agreed upon:

(1) to describe more accurately the geographic, demographic and clinical variations in subtypes of malignant lymphomas and lymphoid leukaemias;

(2) to stimulate, encourage and assist in the implementation of coordinated epidemiological and laboratory studies designed to test hypotheses related to etiology of lymphomas and lymphoid leukaemias; and

(3) to use the results to encourage the more effective treatment and management of lymphomas and lymphoid leukaemias.

It was agreed that there was a need for a reference laboratory that would also serve as a repository for storage of submitted specimens. The Institute of Pathology at the University of Lausanne, under the direction of Professor José Costa was selected, and a Collaborative Research

Agreement was negotiated with the Agency. The ISREC (Institut Suisse de Recherches Expérimentales sur le Cancer) and the Ludwig Foundation Cancer Institute are affiliated with the University and have special expertise and interest in immunological research; they have agreed to provide consultation and other assistance to the project.

A preliminary plan of work was developed and contact made with a number of centres throughout the world. A description of the study and the general requirements for participation were provided. Completion of a form describing the centre, the facilities and identification of key staff was requested as well as unstained slides or blocks from 15 recent and consecutive admissions to the affiliated hospital(s). On the basis of the responses, previous experience and site visits, a selection of participating centres, associate centres and potential centres was made. Site visits were made subsequently to Cairo, Egypt; Riyadh, Kingdom of Saudi Arabia; New Delhi, India; Rawalpindi, Pakistan; Budapest and Pecs, Hungary; Cologne, Federal Republic of Germany; and Lima, Peru. Visits to Rabat, Morocco and to associate centres in Japan are planned in 1984, and several centres in Africa are under review.

Data and specimen collection began on 1 January 1984. Review and processing of materials received in Lyon and Lausanne is in progress.

4. NUTRITION AND CANCER

(*a*) *Case-control study of adenomatous polyps of the large bowel* (Dr D. G. Zaridze and Dr E. Riboli; in collaboration with Professor M. Crespi, Regina Elena Institute, Rome, DEB/81/040; and Dr M. Hill, Public Health Laboratory Services, Centre for Applied Research, Salisbury, UK, DEB/81/041)

According to the study plan[31], a food frequency questionnaire and a seven-day diet diary have been developed, and a pilot study on 35 subjects has been carried out. The data from the pilot study are presently being analysed in order to evaluate the reliability of the estimates of food consumption. About 30 biological specimens of bowel mucosa have been sent to the Sloan-Kettering Cancer Center (New York, USA) for investigation of cell kinetics. The study itself is scheduled to start in October 1984 and will be based on 100 cases of adenomatous polyps (50 with severe dysplasia and 50 with mild dysplasia) and 100 controls (50 with abnormal cell kinetics and 50 with normal cell kinetics), matched by age, sex and date of first presentation at hospital.

(*b*) *Prospective study on diet and related factors in human cancer* (Dr D. G. Zaridze, Dr E. Riboli and Dr R. Saracci; in collaboration with Professor N. Sternby, Department of Pathology, Dr F. Lindgärde, Department of Medicine and Dr B. Åkesson, Department of Clinical Chemistry, Lund University, Malmö, Sweden; and Dr E. Callmer, Department of Medical Nutrition, Huddinge University Hospital, Huddinge, Sweden)

The proposal for a prospective study in Malmö (Sweden)[32] was reviewed and discussed in depth by an ad-hoc committee of the Swedish Medical Research Council, together with the Swedish scientists involved in the planning of the study and representatives of the Agency. It was agreed first to set up a methodological study, the main aims of which fall into two categories:

[31] IARC (1983) *Annual Report 1982*, Lyon, p. 63
[32] IARC (1983) *Annual Report 1982*, Lyon, p. 64

(1) *Generally related to dietary intake assessment methodology*

(a) Long-term (one-year) in-depth characterization of the dietary habits of a population sample, to provide information on day-to-day variations, seasonal variations and changes in food habits over time. Such data are at present lacking for Sweden and are generally scanty.

(b) Exploration, by repeated measurements, of the relation between dietary assessment and biochemical indices of nutrient intake.

(c) Comparison of results obtained during a period of weighed recording and during a period of estimated recording in the same individuals.

(2) *Primarily related to the design of a prospective study on dietary factors and cancer*

(a) Characterization of the validity and reliability of dietary assessment methods suitable for use in large population samples.

(b) Determination of variations in food consumption and nutrient intake in a representative sample of the Malmö population.

(c) Accurate estimation of adherence and drop-out rates, in addition to dietary assessment requirements in terms of time, manpower and logistic organization.

The methodological study will be set up in Malmö in the Section of Preventive Medicine of the Department of Medicine. A random sample of the Malmö population, consisting of 400 men and women in the age group 50–69, will be invited to attend a general health screening and to take part in the methodological study. Subjects will be enrolled in the study in September 1984 and followed for 12 months. The subjects will be randomized into six study groups, each group characterized by a different combination of four methods for estimating diet: (1) short food frequency questionnaire, (2) long food frequency questionnaire, (3) combination of long food frequency questionnaire with two-weeks' menu, (4) three-day food weighing and recording repeated six times over 12 months. In addition, samples of urine and blood will be collected, and routine biochemical parameters as well as total 24-h urine nitrogen, plasma retinol, plasma α-tocopherol, ascorbic acid, and fatty acid composition and plasma lecithin will be measured.

An additional component of the methodological study will be an investigation of methods of storage of biological material and their effects on biochemical determinations.

(*c*) *Cancer of the gastrointestinal tract in Belgium* (Dr A. J. Tuyns; in collaboration with Mrs L. Ravet-Ramioul, Laboratory of Epidemiology, School of Public Health, Brussels, DEB/78/014; and with a group of cardiologists; supported by the Belgian Fund for Scientific Research)

This study originated from the observation that mortality rates from gastric cancer were much higher and those from rectal cancer slightly higher in the Flemish than in the Walloon part of the country. As diet is known to be different in the two communities, particularly with regard to fat consumption, a case-control study was set up within the scope of a larger study on diet and health (EIAS: Enquête Interuniversitaire sur l'Alimentation et la Santé), which also includes investigations on cardiovascular diseases.

The interviewing of cases and of population controls has now been terminated in the two provinces under study, namely in Oost-Vlaanderen and in Liège. A first evaluation of the material available has been made[33]. The numbers of cases and of controls available appear in Table 15. This distribution of cases by site confirms the higher proportion of stomach cancers in the Flemish province, while colon cancer appears relatively more frequent in Liège; these observations are in line with the earlier findings on mortality that led to the study.

Table 15. Cancer of the digestive tract in Belgium. Numbers of controls and cases interviewed[a]

Subjects	Oost-Vlaanderen		Liège	
	No.	% of total	No.	% of total
Oesophageal cancer	43	4.1	38	5.3
Stomach cancer	295	28.1	160	22.1
Colon cancer	396	37.8	308	42.6
Rectal cancer	314	30.0	217	30.0
Total cases	1048	100.0	723	100.0
Population controls	2230		1305	

[a] From EIAS (1984) *Ann. Arch. Belges Méd. Soc.* (in press)

The controls were a representative rectangular sample of the population. Of the 5000 people (3000 in Oost-Vlaanderen and 2000 in Liège) in the original sample, 527 could not be interviewed for various reasons (not traced, deceased, physically or mentally handicapped, included by error), and 938 refused to be interviewed. The 3535 persons actually interviewed represent 70.7% of the original population sample; the crude response rate was higher in Oost-Vlaanderen (74%) than in Liège (65%).

The material is now being verified and analyses started.

(*d*) *Cancer of the large bowel in southern Europe*

(*i*) *In Marseilles* (Miss N. Charnay, Dr N. E. Day and Dr E. Riboli; in collaboration with Dr G. Macquart-Moulin and Dr J. Cornée, Unité de Recherches de Pathologie Digestive, INSERM U-31, Marseille, France)

A case-control study of large-bowel cancer was carried out in Marseilles, and a preliminary analysis published[34]. The biostatistics group at the Agency was approached for assistance in a more refined analysis, which is now almost complete. The major findings are strong protective effects related to high consumption of vegetables and to high intake of potassium.

[33] Tuyns, A. J., Péquignot, G. & Hu, M. X. (1983) *Rev. Epidemiol. Santé publ.*, 31, 179–197

[34] Macquart-Moulin, G., Durbec, J.-P., Cornée, J., Berthezene, P. & Southgate, D. A. T. (1983). *Gastroenterol. clin. Biol.*, 7, 277–286

(ii) *In Majorca* (Dr X. Bosch, Dr N. E. Day and Dr N. Muñoz; in collaboration with Dr E. Benito and Dr A. Obrador, Grup d'Estudi del Cancer Colo-rectal, Mallorca, Spain)

Interest in Spain has been aroused by apparently higher rates for colo-rectal cancer in Majorca than in the rest of the country, and a study group was established to investigate the finding in greater depth. The first step was the establishment of cancer registration. The group has now decided to proceed with a case-control study, aimed primarily at diet, and for this purpose contacted the Unit of Biostatistics and Field Studies to assist in the design, planning and analysis of the study. A small planning meeting was held at the Agency in February 1984, with Professor D. Trichopoulos present as an Agency consultant. A detailed study design was drawn up. The dietary questionnaire is being finalized in Majorca, and the training of interviewers is in progress.

(*e*) *Studies on alcohol and cancer*

Under this title, a large programme has been conducted over recent years by the Agency, mainly in Brittany and Normandy (France), extended later to other regions. One of the most interesting aspects of the role of alcohol concerns its interaction with other risk factors, which led to a study of the combined effects of such factors as tobacco and, more recently, diet.

(i) *Oesophageal and other cancers in Normandy* (Dr A. J. Tuyns, Dr J. Estève and Mrs A. Arslan; in collaboration with Dr A. Péquignot, Nutrition Section, INSERM, Le Vésinet, France)

A detailed description of drinking habits in Normandy by sex, age, urban-rural dwellers has now been published, taking into account the type of beverage and the daily consumption[35]. This is complemented by a calculation of lifetime exposure in order to take into account past consumption[36]; it was found that people tend to drink less when they get older and reach the age when they develop cancer. This correction is of course essential and must be taken into account in the evaluation of risk, as it is for tobacco. This preparatory study will lead to a further verification of whether certain alcoholic beverages entail greater risk than others, as was suggested in a previous article[37].

The first analyses of the Normandy material confirmed the predominant role played by alcohol in oesophageal cancer, in combination with tobacco, according to a multiplicative model, as already described for the material from Ille-et-Vilaine. The apparent independence of each factor is not easily compatible with the concept that tobacco would contribute the carcinogen, while alcohol would only enhance the risk of cancer. In an attempt to verify whether this theory would apply to a human population, a study was made of non-drinking smokers and non-smoking drinkers. The effect of tobacco came out clearly in males but not in the smaller group of females with oesophageal cancer, none of whom ever smoked. In contrast, the effect of alcohol in the absence of tobacco was much clearer, with a dose-response effect, both in females and in males. This seems to indicate that alcohol by itself may be more important than hitherto believed[38].

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[35] Tuyns, A. J., Péquignot, G. & Hu, M. X. (1983) *Rev. Epidemiol. Santé publ.*, **31**, 179–197
[36] Tuyns, A. J. & Estève, J. (1983) *Rev. Epidemiol. Santé publ.*, **31**, 487–488
[37] Tuyns, A. J., Péquignot, G. & Abbatucci, J. S. (1979) *Int. J. Cancer*, **23**, 443–448
[38] Tuyns, A. J. (1983) *Int. J. Cancer*, **34**, 443–444

Vitamin C is known to have a protective effect in cases of *N*-nitrosamine-induced cancer in animals. When checking on the intake of citrus fruit and juices by patients and controls in Calvados, it was found that patients consume less of these foods than controls; this protective effect was present even after correction for alcohol intake[39]. Whether this protection is due to vitamin C contained in citrus fruit must be verified further; an effect due to the product by itself, independently of its vitamin C content, cannot be excluded at this stage.

In the course of an analysis of the effect of salt on gastrointestinal cancer, an excess risk was found for oesophageal cancer as well as for cancer of the stomach and of other segments of the digestive tract. After adjustment for alcohol, this disappeared, although a minor effect still remained for cancer of the stomach[40].

Risks of oesophageal cancer related to alcohol consumption appear to be of the same order of magnitude in males and in females for comparable daily intake[38]. This is not the case for ascitic cirrhosis. Within the scope of the set of studies carried out in Calvados on the role of alcohol, patients with this disease were interviewed in the same way as cancer patients and compared to population controls. The analysis showed a dose-response effect in both sexes, but the slope of the risk curve was much steeper for females than for males[41], thus indicating that the female liver is more susceptible to alcohol, in contrast to what was observed for oesophageal cancer.

A further analysis was aimed at determining whether any particular beverage might be more cirrhogenic than others. It was found that any alcoholic beverage, whatever its concentration of alcohol, is cirrhogenic; what matters is the actual amount of ethanol consumed. There is, however, an excess risk for beer, a finding that deserves verification in population groups with a more homogeneous beer consumption pattern[42].

(ii) *Laryngeal and pharyngeal cancer in south-western Europe* (Dr A. J. Tuyns, Dr J. Estève, Dr E. Riboli and Mrs A. Arslan; in collaboration with Dr A. Zubiri, Cancer Registry of Zaragoza, Spain; Dr A. del Moral, Health Department of Navarra, Pamplona, Spain; Dr B. Terracini, Institute of Pathology, University of Turin, Italy; Dr F. Berrino, National Cancer Institute, Milan, Italy; Mr L. Raymond, Geneva Cancer Registry, Switzerland; and Dr H. Sancho-Garnier and Dr E. Benhamou, Gustave Roussy Institute, Villejuif, France)

These cancers are known to be related to consumption of alcohol and tobacco; they are highly prevalent in France, Spain and Italy and in the French-speaking part of Switzerland. As part of the extensive research programme on alcohol, a case-control study has been carried out in seven regions within these countries.

In Calvados, where this study first started, a preliminary analysis has been undertaken to determine the relative importance of alcohol and tobacco for the various cancer sites examined. Both are risk factors for all sites but the influence of alcohol predominates for oropharyngeal and for oesophageal cancer, while the role of tobacco appears to be greater for that of the larynx and hypopharynx[43].

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[39] Tuyns, A. J. (1983) *Nutr. Cancer*, **5**, 195–200
[40] Tuyns, A. J. (1983) *Nutr. Cancer*, **5**, 92–95
[41] Tuyns, A. J., Péquignot, G. & Estève, J. (1984) *Int. J. Epidemiol.*, **13**, 53–57
[42] Tuyns, A. J., Estève, J. & Péquignot, G. (1984) *Br. J. Addict.* (in press)
[43] Tuyns, A. J. & Blanchet, F. (1984) (submitted for publication)

Analysis of the case-control data will be completed before Spring 1985 for the nutritional aspects and for alcohol and tobacco exposures. The data related to occupation will be analysed later.

Clinical data on 1160 cases of laryngeal and hypopharyngeal cancers have been sent to Geneva for review, and 792 have been given a diagnosis by Dr W. Lehmann; the distribution of these cases according to the main sub-sites is given in Table 16. The different distribution in various areas and the distribution of larynx *versus* pharynx cancer in Zaragoza are notable. These results indicate that analysis of the whole set of data will clarify the association between exposure and sub-site.

Table 16. Distribution of laryngeal and hypopharyngeal cancers by main sub-site according to geographical area

Sub-site		Geneva	Turin	Varese	Caen	Pamplona	Zarragosa
Supraglottis (161.1)	No.	42	77	50	33	53	79
	% total larynx	48.2	59.2	60.2	58.9	88.3	62.2
Glottis (161.0)	No.	38	45	29	16	6	42
	% total larynx	43.7	34.6	34.9	28.6	10.0	33.1
Other larynx	No.	7	8	4	7	1	6
	% total larynx	8.1	6.2	4.9	12.5	1.7	4.7
Total larynx	No.	87	130	83	56	60	127
	% total	72.5	83.9	79.0	32.6	69.0	83.0
Pyriform sinus (148.1)	No.	20	10	15	84	23	14
	% total hypopharynx	60.6	40.0	68.2	72.4	85.2	53.8
Other hypopharynx	No.	13	15	7	32	4	12
	% total hypopharynx	39.4	60.0	31.8	27.6	14.8	46.2
Total hypopharynx	No.	33	25	22	116	27	26
	% total	27.5	16.1	21.0	67.4	31.0	17.0
Total		120	155	105	172	87	153

Preliminary analyses have been performed on the population control groups. In that related to occupation in Calvados, which has been reviewed by the group in Milan, each occupation has been given a score for exposure to asbestos, chromium, nickel, hydrocarbons, wood, dust, fumes and solvents.

The association of alcohol and tobacco consumption with socio-economic status and with exposure has been evaluated at the Agency to determine whether these factors confound associations with industrial exposures, as has often been stated. The association with socio-economic status was confirmed; it is shown in Table 17 using average consumption as a crude index. The difference in tobacco consumption is due to different proportions of non-smokers (44% among independent farmers, 9% among unskilled manual workers and agricultural workers).

No significant association with exposure was found, either for tobacco or alcohol, with the important exception of dust: a greater proportion of heavy drinkers was found among those who have a high probability of being exposed to dust; the mean consumption of alcohol was 59.4 g among the 31 classified in this category compared to 37.6 g among the 78 nonexposed to dust.

Table 17. Mean consumption of alcohol and tobacco (g/day) in relation to socio-economic status

		Salaried agricultural worker	Independent farmer	Unskilled manual worker	Skilled manual worker	Craftsman	Employee	Managerial staff	Others
MEN	Alcohol	67.5	45.7	67.0	44.7	47.4	41.9	33.0	47.8
	Tobacco	14.2	8.2	13.1	13.4	13.7	14.2	13.5	12.3
	No. of sub.	13	32	43	100	33	41	36	18
WOMEN	Alcohol	11.7	14.3	10.4	13.5	16.3	9.8	11.0	14.0
	Tobacco	0	1.3	2.5	3.1	1.0	2.4	5.3	3.1
	No. of sub.	6	31	67	56	24	42	35	14

A preliminary analysis of the available data from Geneva and Caen, together with data from Turin, has made it possible to evaluate the relation between type of tobacco smoked and risk of laryngeal cancer, as well as risk of cancer at other sites. This work was presented at the meeting on *N*-nitroso compounds in Banff, Canada[44].

(*f*) *Breast cancer in Iceland* (Dr N. Day; in collaboration with Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik)

With the financial support of the American Institute for Cancer Research, work is in progress to exploit the data obtained from a large cardiovascular study in Iceland for investigation of cancer, particularly breast cancer. Many of the factors included in the cardiovascular study were aimed at assessing nutritional status in a variety of ways, although specific dietary information was not sought, and the major interest is investigation of a possible relationship between these nutritional markers and risk for cancer.

The first step envisaged in the study was to link the cohort enrolled in the cardiovascular study (some 18 000 individuals) to the Icelandic Cancer Registry, a linkage that has now been updated to December 1982. A total of 818 cancers have been identified that occurred after entry into the cardiovascular cohort.

The second step is to examine the relationship between cancer at each site and the factors of interest, in a simple univariate manner. The factors that have been included to date are serum cholesterol, serum triglycerides, uric acid, height, weight, indices of obesity (Brocca and Quetelet index), lean body mass, body surface, serum creatinine, total bilirubin, blood pressure (systolic and diastolic), smoking history and several measures of skinfold thickness and of the skeleton. These

[44] Estève, J., Tuyns, A. J., Raymond, L. & Vineis, P. (1984) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds., *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)

analyses have now been carried out for the following: cancer at all sites and cancer of the oesophagus, stomach, colon, rectum, pancreas, lung, breast, corpus uteri, cervix uteri, ovary, prostate, kidney, bladder, skin (other than melanoma), brain and thyroid and non-Hodgkin's lymphoma and leukaemia. These analyses are being extended to include all sites for which more than three cases were observed.

The expected relationships, e.g., between smoking and cancers of the lung and bladder and between some measures of obesity and cancer of the breast, have emerged. Work is progressing on the relationship between weight change and risk for breast cancer, using the information obtained during the second and third visits made by women to the cardiovascular study.

There are, in addition, some unexpected results, which are currently being examined in greater detail. These include associations between high blood pressure and renal cancer; high weight and cancer of the brain (males); height rather than weight for endometrial cancer; low weight, but no height, for lung cancer (particularly strong in females); and high serum creatinine levels and cancer of the colon (particularly strong in males).

No association has been seen between serum levels of uric acid and either all cancers or any particular cancer. Uric acid has been proposed as a protective agent by some experimental investigators.

A publication is in preparation on the results so far obtained by the univariate analyses.

(g) *Case-control and population studies in Athens* (Dr N. Day; in collaboration with Professor D. Trichopoulos and Dr A. Tzonou, University of Athens)

Statistical support has been provided for a number of studies carried out by the department of epidemiology at the University of Athens. These include case-control studies of cancer of the ovary and of diverticulosis, and a population study investigating the effect of air pollution on general mortality. The study of diverticulosis used the same dietary questionnaire as that used in the study of large-bowel cancer reported last year[45]. It is noteworthy that cereal fibre, unrelated to risk for large-bowel cancer in Athens, demonstrated an appreciable protective effect for diverticulosis.

5. GENETICS AND CANCER (Dr G. Lenoir and Mr F. Pelloquin; in collaboration with Professor J. Dausset, Institute for Research on Blood Disorders, Paris; and Mrs C. Junien, Molecular Pathology Institute, Paris)

A new project is being implemented to evaluate whether genetic predisposing conditions can be identified in cancers arising within the general population. The proposed approach is to do linkage studies in multiple-case families by analysing the genetic make-up of individuals, using highly polymorphic DNA markers. The first step is to establish a collection of lymphoblastoid cell lines—as a source of constitutional DNA—from members of families within which multiple cases of cancer have arisen. This is being implemented for breast cancer, nasopharyngeal carcinoma and retinoblastoma.

A large bank of lymphoblastoid cell lines from 'normal families' is also in the process of being established, and will be used for genetic studies (large pedigrees) in collaboration with Professor

[45] IARC (1983) *Annual Report 1983*, Lyon, p. 63

Dausset. This material could be used as controls and for studies on transmission of DNA sequences known to play a role in oncogenesis.

A study was also performed on a series of patients with aniridia—Wilms' tumour association in order to understand better the role of the deletion on chromosome 11, known to be a critical risk factor for Wilms' tumour. The study provided a better chromosomal map of this region[46].

6. ROLE OF VIRUSES IN THE ETIOLOGY OF HUMAN CANCER

The main objective of this programme is to evaluate, using laboratory investigations linked to epidemiological studies, the role of viruses in the etiology of human cancer. The model of cancer chosen is Burkitt's lymphoma (BL), a cancer known to show great geographic variations in its incidence and to be associated with the Epstein-Barr virus (EBV).

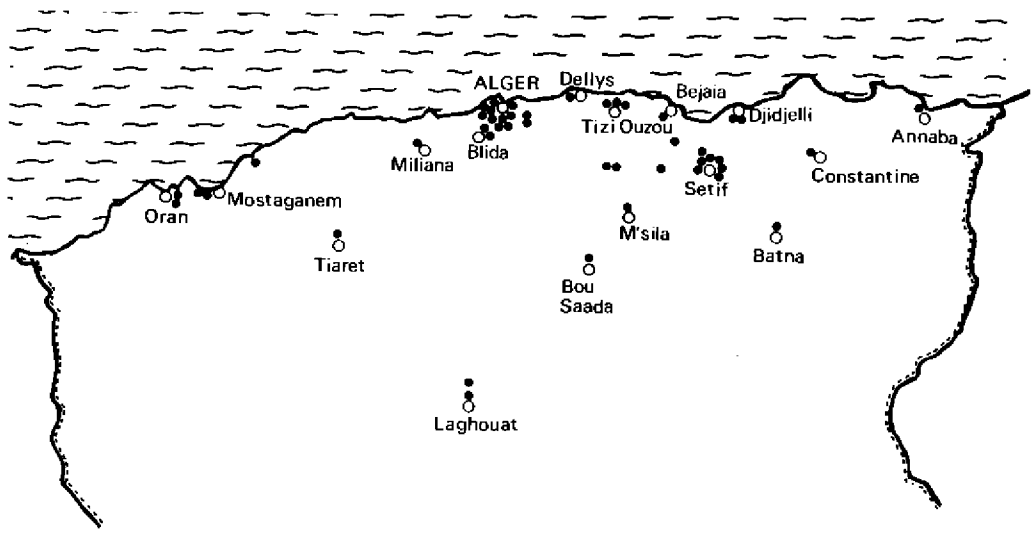

Fig. 5. Origin of Burkitt's lymphoma patients from Mediterranean areas of Algeria

(a) *Studies on Burkitt's lymphoma in central Africa*

Most of the studies are now terminated and two final reports were published recently[47,48].

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[46] Huerre, C., Despoisse, S., Gilgenkrantz, S., Lenoir, G. M. & Junien, C. (1983) *Nature*, **305**, 638–641

[47] Geser, A., de-Thé, G., Lenoir, G., Day, N. E. & Williams, E. H. (1982) *Int. J. Cancer*, **29**, 397–400

[48] Geser, A., Lenoir, G. M., Andersson-Anvret, M., Bornkamm, G., Klein, G., Williams, E. H., Wright, D. H. & de-Thé, G. (1983) *Eur. J. Cancer clin. Oncol.*, **10**, 1393–1404

(*b*) *Studies on Burkitt-type lymphoma in North Africa* (Dr G. Lenoir; in collaboration with Dr M. Aboulola, CHU Mustapha, Alger, Algeria, DEC/82/15; and Dr T. Philip, Centre Léon-Bérard, Lyon, France)

Algeria has always been considered a low-incidence area for BL. Our study, based on an analysis of 49 cases (Fig. 5), indicated that the clinical presentation of the disease in Algeria is comparable with that observed in the USA and Europe. However, when the EBV-BL association is evaluated by detecting viral markers within the malignant cells, the great majority of Algerian BL cases (over 88%) are found to be EBV-associated, as in high-incidence areas of central Africa. This suggests that the association may be related to socio-economic status and thus to age at primary infection[49]. The age distribution shows a peak between four and five years of age, and the sex ratio is (M:F) 2.26:1.

Attempts to collect more cases in order better to define the incidence of this cancer in north Africa are being made through the collaboration with Professor Aboulola.

(*c*) *Studies on Burkitt-type lymphomas in France* (Dr G. Lenoir; in collaboration with Dr T. Philip, Centre Léon-Bérard, Lyon, France)

The studies conducted in the past permitted a better clinical and pathological characterization of the disease in a low-incidence area[50]. Virological investigations have now shown that less than 20% of the tumours are EBV-associated, and that some of the rare EBV-associated lymphomas might follow infectious mononucleosis or Hodgkin's disease. More than 40 EBV-positive cases have now been identified, and the risk factors linked to viral infection in this group of patients will be evaluated in a retrospective analysis.

(*d*) *International Symposium on Burkitt's Lymphoma: A Human Cancer Model* (Organized by Dr G. Lenoir, Dr G. T. O'Conor and Dr C. Olweny (WHO Consultant) and supported in part by the Association pour le développement de la recherche sur le cancer (France) and the General Motors Cancer Research Foundation (USA))

This Symposium, convened in Lyon from 6–9 December 1983, was organized by the Agency to:

(1) review present knowledge on the etiology, clinical features and treatment of Burkitt's lymphoma in various parts of the world;

and

(2) define and stimulate new prospects for future research.

Clinical and laboratory scientists and epidemiologists were thus brought together in order to review the disease in its entirety. The subjects covered included a historical perspective, the morphological, immunological and cytogenetic definitions of the tumour, epidemiology, etiology

[49] Ladjaj, Y., Philip, T., Lenoir, G. M., Tazerout, F. Z., Bendisari, K., Boukheloua, R., Biron, P., Brunat-Mentigny, M. & Aboulola, M. (1984) *Br. J. Cancer*, **49**, 503–512

[50] Philip, T., Lenoir, G. M., Bryon, P. A., Gérard-Marchant, R., Souillet, G., Philippe, N., Freycon, F. & Brunat-Mentigny, M. (1982) *Br. J. Cancer*, **45**, 670–678

and therapy. Similarities and differences in the clinical and laboratory manifestations of BL in endemic and non-endemic regions were discussed in detail, with particular reference to the etiologic and pathogenic implications. Recent developments in molecular biology, which have provided important insights into mechanisms of malignant transformation at the subcellular level, were highlighted. Also emphasized were advances in clinical management, which have paralleled those of basic laboratory investigations so that well over 50% of cases can now be considered curable with multi-modality therapy.

The proceedings of this Symposium[51] represent a comprehensive 'state-of-the-art' reference source for this tumour, which has indeed proved to be one of the best models for the investigation of human cancer.

(*e*) *Interactions between chronic infection by duck hepatitis B virus and aflatoxin B_1 in the induction of hepatocarcinoma* (Dr J. R. P. Cabral and Dr L. Tomatis; in collaboration with Dr C. Trepo, Laboratoire des Hépatites, INSERM U45, Lyon, France; DEC/83/12)

Studies have been initiated to investigate the interaction between viral factors and aflatoxin B_1 in the etiology of hepatocarcinomas. Groups of Peking ducks (*Anas domesticus*) infected or not with duck hepatitis B virus (DHBV) will be given different doses of aflatoxin B_1. Adequate groups of controls will be available. The immediate scope of these investigations is to determine whether the addition of both DHBV and aflatoxin B_1 can induce hepatocarcinomas in the liver of the ducks.

7. BIOCHEMICAL, METABOLIC AND CYTOGENETIC PARAMETERS AS INDICATORS OF INDIVIDUAL SUSCEPTIBILITY TO CHEMICALLY-INDUCED CANCER

(*a*) *Biochemical and cytogenetic parameters as indicators of individual susceptibility to* N-*nitroso compound-induced cancer in rodents* (Dr A. Aitio[52], Miss A.-M. Camus, Dr J. R. P. Cabral, Dr J. Wahrendorf, Miss B. Balkau, Mrs E. Robert and Mrs D. Galendo; in collaboration with Dr M. Sorsa, Dr H. Norppa, Dr K. Hemminki and Miss H. Lax, Institute of Occupational Health, Helsinki)

A number of cytogenetic and metabolic parameters that may determine differences in individual susceptibility to chemically-induced cancer are being investigated. Outbred rats were dosed with *N*-nitrosodiethylamine, and another group was given *N*-ethyl-*N*-nitrosourea[53]. Changes in biochemical markers during and after carcinogen administration will be correlated with the presence or absence of tumors and with the latency period. All experimental measurements have been completed, and final evaluatin of the study awaits histopathological examination of the animals.

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[51] Lenoir, G., O'Conor, G. T. & Olweny, C., eds (1984) *Burkitt's Lymphoma: A Human Cancer Model* (*IARC Scientific Publications* No. 60), Lyon, International Agency for Research on Cancer (in press)

[52] Present address: Institute of Occupational Health, Helsinki

[53] IARC (1983) *Annual Report 1983*, Lyon, p. 71

The outcome of the study is expected to shed some light on the validity for predicting tumour susceptibility of cytogenetic and metabolic parameters, several of which are used for biological monitoring of human subjects exposed to carcinogens/mutagens.

(*b*) *Studies on benzol[a]pyrene metabolism in surgical lung tissue and mucosa specimens from lung-cancer and cancer-free patients* (Dr E. Hietanen, Dr A. Aitio, Miss A. M. Camus, Dr R. Saracci and Dr H. Bartsch; in collaboration with Professor C. Giuntini, National Research Council, University of Pisa, Italy; and Dr H. V. Gelboin, National Cancer Institute, Bethesda, MD, USA)

Enzyme activities related to the metabolic activation of carcinogens (benzol[*a*]pyrene hydroxylation and ethoxycoumarin *O*-deethylation) and to the inactivation of reactive intermediates (epoxide hydration, glutathione *S*-conjugation, glucuronide conjugation and glutathione contents) are being determined in lung tissue specimens from patients with lung cancer and other pulmonary diseases. The role of individual cytochrome P-450 isozyme species will be tested utilizing monoclonal antibodies. Activities in bronchial and parenchymal specimens are being compared. Mutagenicity, mediated by these lung specimens[54] will be related to the enzyme activities. All the data obtained *in vitro* will be related to information on the living habits of patients, their occupation, results of pulmonary function tests and diseases of the lungs. The study is in progress, and the experimental part is expected to be finished in 1984.

(*c*) *Studies on cytochrome P-450s*

(i) *Studies on the catalytic properties of different cytochrome P-450 isozymes using monoclonal antibodies* (Dr E. Hietanen, Mr C. Malaveille, Dr H. Bartsch, Mr J.-C. Béréziat and Mme G. Brun; in collaboration with Dr H. V. Gelboin, National Institutes of Health, Bethesda, MD, USA)

The cytochrome P-450-dependent mixed-function oxidase system catalyses the oxidation of drugs, carcinogens and numerous endogenous compounds. Enzyme purification, kinetic, genetic, inhibitor and immunological studies have shown the existence of various cytochrome P-450 isozymes (cyt P-450s), which differ in their physico-chemical properties, substrate and inducer specificities and product regio-specificities. Monoclonal antibodies (MABs) against cyt P-450s, which interfere with the enzyme activity, are a useful tool to determine the role of different cyt P-450s in drug and carcinogen metabolism[55].

To evaluate further the usefulness of such MABs in defining the substrate specificity of cyt P-450s, the modifying effect of two types of MAB were investigated (1) on liver S9-mediated mutagenicity of aflatoxin B_1 (AFB), benzo[*a*]pyrene 7,8-dihydrodiol (BP 7,8-diol), 2-acetylaminofluorene (AAF) and *N*-nitrosomorpholine (NMOR) in *Salmonella typhimurium* strains; and (2) on the activity in liver S9 of benzo[*a*]pyrene hydroxylase (AHH), ethoxycoumarin *O*-deethylase (ECDE), ethoxyresorufin *O*-deethylase (ERDE), aminopyrine *N*-demethylase (APDM) and testosterone 6β-, 7α- and 16α-hydroxylase (6β-H; T7α-H; T16α-H).

[54] De Flora, S., Bennicelli, C., Zanacchi, P., Camoirano, A., Petrucelli, S. & Giuntini, C. (1984) *Mutat. Res.*, **139**, 9–14

[55] Fujino, T., Park, S. S., West, D. Z. & Gelboin, H. V. (1982) *Proc. natl Acad. Sci. USA*, **79**, 3682–3686

Liver S9 was prepared from untreated (C), 3-methylcholanthrene (MC)-, phenobarbitone (PB)-, and pregnenolone 16α-carbonitrile (PCN)-treated C57 B1/6 (B6) and DBA/2 (D2) mice. The MABs were prepared by the hybridoma technique, against the major hepatic microsomal cytochrome P-450 isozymes induced in rats by MC (MAB-MC; clone:1-7-1p848-5p6) and PB (MAB-PB; clone:2-66-3.1-15p10p10).

MAB-MC inhibited (≥50%) in S9 assays: (1) mutagenicity (B6-C and B6-MC); BP 7,8-diol mutagenicity (B6-MC and B6-PCN); (3) ERDE activity (B6-C, B6-MC, D2-C, D2-MC and D2-PB); (4) AHH activity (B6-MC); (5) ECDE activity (B6-C, B6-MC); and (6) T6βH (B6-MC) and T7αH activity (B6-MC, B6-PCN). MAB-PB inhibited (≥50%) in S9 assays: (1) the mutagenicity of AFB (B6-C, B6-PB, D2-PB and B6-PCN); (2) APDM activity (B6-PB); and (3) T6βH activity (B6-PB), T7αH activity (B6-MC, B6-PB, B6-PCN) and T16αH activity (B6-PB). MAB-MC did not inhibit the S9-mediated mutagenicity of NMOR; but, surprisingly, MAB-PB increased its mutagenic effect by two- to six-fold. All the other mutagenic activities and metabolic reactions tested were not, or only moderately, inhibited (≥25%—<50 inhibition) by MAB-MC or MAB-PB.

Thus, these MABs appear to be useful tools for determining the role of MC- and PB-type isozymes in drug and carcinogen metabolism (only for inhibition ≥ 50%). In the case of certain S9, our data indicate a relationship between structural features (existence of specific antigenic determinants) and the catalytic activities of cyt P-450 isozymes; however, P-450s that do not have antigenic determinants recognized by our MABs may perform the same metabolic reactions, with overlapping substrate specificities[56].

The use of MABs to characterize the cyt P-450s responsible for the activation of carcinogens in individual human subjects might eventually be employed to predict the harmful effects of toxic compounds to the body or specific organs when its cytochrome isozyme pattern is known and compared to that of the isozyme(s) responsible for the metabolic activation of the xenobiotics.

(ii) *Purification of cytochrome P-450 that catalyses demethylation of* N-*nitrosodimethylamine and preparation of its antibody* (Dr E. Hietanen and Miss A.-M. Camus; in collaboration with Professor M. Lang, Department of Pharmacology and Toxicology, University of Kuopio, Finland; DEC/83/04)

The cytochrome P-450-catalysed *N*-demethylation reaction is an essential step in the activation of many *N*-nitroso compounds to ultimate carcinogens. Research related to this reaction has been hampered by the insensitivity of the methodology presently available. *N*-Nitroso compounds exert their carcinogenicity in many extrahepatic tissues of experimental animals and possibly man (oesophagus, stomach, colon, pancreas and brain); in some of these tissues, the presence of *N*-demethylase activity has not been demonstrated.

The aims of the study are to develop sensitive methods for measuring enzyme activities responsible for the metabolism of *N*-nitroso compounds. First, *N*-nitrosodimethylamine (NDMA) *N*-demethylase activity will be characterized, and then the cytochrome P-450 species responsible for this reaction will be purified and characterized. Second, an antibody towards this cytochrome P-450 isozyme will be produced and immunoassays developed.

[56] Hietanen, E., Malaveille, C., Bartsch, H., Béréziat, J.-C., Brun, G., Park, S. S. & Gelboin, H. V. (1984) (in preparation)

After preliminary purification steps, microsomal enzyme activity was compared in different rat and mouse strains both in controls and after pyrazole petreatment. Further purification is in progress.

In control microsomes, usually at least two forms ('high' and 'low' affinity) of NDMA-demethylase activities are found; while in pyrazole-induced animals only one high affinity ('low' K_m) form is present. In partially purified preparations, another fraction with relatively high NDMA-demethylase activity ('low' K_m) was found, which, on the basis of preliminary studies, appears to be a new type of cytochrome P-450. The low-affinity form of NDMA-demethylase activity is found in all fractions containing cytochrome P-450 haemoprotein. Further purification and characterization of this enzyme is in progress.

The genetic effects of NDMA were studied using the Ames test (with preincubation) and microsomes from Wistar and BD9 rats. In both strains of rat, pyrazole treatment increased the mutagenicity of NDMA, whereas the mutagenicity of benzo[*a*]pyrene (used as a reference compound) was not affected by pyrazole. This study demonstrates the specificity of pyrazole as an activator of NDMA metabolism in rat liver.

(*d*) *Hepatic drug metabolism and liver microsome-mediated mutagenicity of carcinogens in rat strains characterized as slow and fast metabolizers of debrisoquine* (Mr C. Malaveille, Dr E. Hietanen, Miss A. M. Camus, Mr J.-C. Bérézíat and Mrs G. Brun; in collaboration with Dr J. C. Idle and Dr J. C. Ritchie, St Mary's Hospital Medical School, London)

Hydroxylation of debrisoquine (an anti-hypertensive drug) *in vivo* has been proposed as a probe to assess individual drug handling capacity and to classify human subjects into slow and fast metabolizers[57]. To study further this genetic polymorphism in animals, DA and Lewis rat strains (slow and fast metabolizers) were used; these strains showed remarkably different toxicological responses to aflatoxin B_1, the Lewis rats being more sensitive[58].

We therefore assayed a number of hepatic microsomal enzyme activities (see above) and hepatic 9000 × *g* supernatant-mediated mutagenesis in female DA and Lewis rats. The differences found in cytochrome P-450 contents and monooxygenase activities, however, were only 30–40%, except for the total testosterone hydroxylation, which was 50% lower in the livers of DA rats than in Lewis rats. Using liver supernatant fractions from Lewis and from DA rats, the mutagenicity of *N*-nitrosomorpholine, 2-acetylaminofluorene and benzo[*a*]pyrene 7,8-diol was not different, but alfatoxin B_1 was four times more efficient as a promutagen when activated by liver from Lewis rats. The data thus suggest the existence of a specific, minor cytochrome P-450 isozyme responsible for the 4-hydroxylation of debrisoquine[59]. Studies are in progress to characterize further similarities and differences in the properties of mixed-function oxidase systems of 3-methylcholanthrene- and phenobarbital-treated DA and Lewis rats. Monoclonal antibodies against cytochrome P-450 isozymes will be used to determine the type of isozymes.

[57] Ritchie, J. C. & Idle, J. R. (1982) In: Bartsch, H. & Armstrong, B., eds, *Host Factors in Human Carcinogenesis* (*IARC Scientific Publications* No. 39), Lyon, International Agency for Research on Cancer, pp. 391–394

[58] Al-Dabbagh, S. G., Idle, J. R. & Smith, R. L. (1981) *J. Pharm. Pharmacol.*, 33, 161–164

[59] Hietanen, E., Malaveille, C., Camus, A.-M., Bérézíat, J.-C., Brun, G., Idle, J. R., Ritchie, J. C. & Bartsch, H. (1983) *Abstract Proceedings of Meeting on Cancer and Genetics, June 1983, Tromsø, Norway*

(*e*) *Metabolism of ochratoxin A* (Dr A. Hietanen, Dr M. Castegnaro and Miss J. Michelon)

To study whether the oxidative metabolism of ochratoxin A and of debrisoquine (a probe drug) is under similar genetic control, the latter drug is being used as a model for studying genetic polymorphism in man and in animals. Ochratoxin metabolism is being studied in rat strains that are fast and slow metabolizers of debrisoquine to see whether this drug minimizes the metabolism of ochratoxin A (see also above). A method using extraction into methanol/chloroform and reverse-phase high-performance liquid chromatography has been set up to analyse both ochratoxin A and its metabolites in rat urine.

(*f*) *Effect of dietary lipids on lipid peroxidation/foreign compound metabolism and their role in tumour initiation/progression* (Dr E. Hietanen, Dr V. Kobljakov, Mlle V. Bussacchini, Mr J.-C. Béréziat and Miss A. M. Camus)

Dietary components have been attributed a significant role in the development of cancers in man[60,61]. The action of xenobiotics entering the body as food contaminants and the modulation of cancer induction by nutrients must be considered; whether nutrients act as tumur 'promoters' or whether they modulate the initiation process is still unresolved. Many epidemiological studies in which dietary fat and cholesterol intake have been examined in relation to cancer incidence or mortality have shown a relation between dietary lipids and the risks of breast, colon and lung cancers[62,63].

Although experimental studies have established a link between dietary lipids, especially polyunsaturated fats, and chemically induced cancer[64,65], little is known about the underlying mechanism(s). In order to examine some of the hypotheses that have been proposed[66], long-term dietary experiments have been started in rats fed a 30% lipid diet containing polyunsaturated fatty acids; another group is kept on an equicaloric low-fat diet from weaning onwards. All rats were first given *N*-nitrosodiethylamine (3 mg/kg per day on five days a week for 10 weeks). During the course of the study, subgroups were killed for analysis of glutathione, glutathione metabolizing enzymes and carcinogen and other xenobiotic metabolizing enzymes in the liver and extrahepatic tissues. Furthermore, lipid peroxidation is measured in tissues by malondialdehyde determination and chemiluminescence techniques. At the end of the study, histopathological examinations will be made, and any differences in tumour yield between the groups will be noted.

Non-invasive methods are used to monitor a group of rats kept to the end of the study: urine is collected for measurement of thioethers, and at the end of the study exhaled ethane and pentane will be determined as indices of lipid peroxidation in the body. Lipid and enzyme parameters and lipid peroxidation and glutathione metabolizing enzyme activities will be measured in blood. Finally, analyses are made (1), on a group basis, of possible changes in carcinogen/xenobiotic-metabolizing enzyme activities, in amounts of glutathione/glutathione metabolizing enzymes and of lipid peroxidation reactions in various tissues/whole animals due to dietary manipulation

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[60] Howard, J. K. (1981) *Practitioner*, **225**, 811–817
[61] Wynder, E. L. (1976) *Fed. Proc.*, **35**, 1309–1315
[62] Carrol, K. K. (1980) *J. environ. Pathol. Toxicol.*, **3**, 252–271
[63] Hinds, M. W., Kolonel, L. N., Lee, J. & Hantin, J. H. (1983) *Am. J. clin. Nutr.*, **37**, 192–193
[64] Reddy, B. S., Watanabe, K. & Weisburger, J. H. (1980) *Bull. N. Y. Acad. Med.*, **56**, 673–696
[65] Weisburger, J. H., Reddy, B. S., Hill, P., Cohen, L. A. & Wynder, E. L. (1980) *Bull. N. Y. Acad. Med.*, **56**, 673–696
[66] IARC (1983) *Annual Report 1983*, Lyon, p. 73

and/or carcinogen administration; and (2), on an individual basis, the same parameters and their changes will be correlated with the presence/absence of tumours and with organ site.

In another experiment, the lipid content of the diet will be varied from 2 to 25%, and the degree of saturation will be varied from saturated to highly polyunsaturated fats. The data will be evaluated on a group and on an individual basis to determine the relationship between these biochemical parameters with tumur formation. Such markers, should they be found, will then be explored in human studies.

(*g*) *Effect of enzyme inhibitors/inducers on rat liver* N-*demethylase* (Dr E. Hietanen and Dr V. A. Kobljakov)

N-Demethylation by a cytochrome P-450-dependent enzyme(s) is a necessary step in the activation of many carcinogens, such as *N*-nitroso compounds, hydrazines and *N,N*-dimethylaminoarenes. To characterize this enzyme(s) further, *N*-demethylation of aminopyrine (AP), *N*-nitrosodimethylamine (NDMA) and 1,2-dimethylhydrazine (DMH) was studied in liver microsomes following pretreatment of rats with various drugs that change the cytochrome P-450 isoenzyme composition. Pyrazole (Py) increased the *N*-demethylation of DMH by 170% and of NDMA by 120% above the control values, but not the demethylation of AP. Phenobarbitone (PB) increased the demethylation of AP by 100% and that of DMH by 80%, but slightly depressed that of NDMA. In Py-induced liver microsomes, *N*-demethylation of AP, DMH and NDMA was not affected by methyrapone (1 mmol/1), but AP and NDMA demethylation was inhibited in microsomes from PB-treated liver. SKF 525A (1 mmol/1) inhibited the *N*-demethylation of AP, irrespective of inducer treatment, by 30-40%, but it had no effect on the NDMA demethylation.

Formaldehyde formation in the presence of both AP and DMH by PB-treated liver microsomes was higher than in the presence of one of the substrates alone. This increase may be due to additional formation of formaldehyde from AP in the presence of DMH[67] and suggests that DMH inhibits the 'non-formaldehyde' pathway of oxidation of AP, thus facilitating the oxidation of AP *via* enhanced formaldehyde formation. Taken together, the different effects of inducers and inhibitors of *N*-demethylation suggest that this reaction is catalysed by various forms of cytochrome P-450.

(*h*) *Activation of chemical carcinogens by embryonal tumours at various stages of development* (Principal investigator: Dr V. Khudoley, Petrov Institut of Oncology, Leningrad, USSR, DEC/83/05)

The aims of this on-going study are to elucidate (1) the ability of various rat embryonal tissues at different stages of development to activate a number of representative carcinogens into mutagens; (2) the inducibility of drug-metabolizing enzymes in embryonal tissues; and (3) the metabolic activation capacity of carcinogens by organ and tissue preparation from pregnant animals.

[67] Kobljakov, V. & Hietanen, E. (1984) *Abstracts of the 9th European Workshop on Drug Metabolism, Pont-à-Mousson, France, 11–15 June 1984*

II. STUDIES ON MECHANISMS OF CARCINOGENESIS

1. STUDIES ON DNA REPAIR AND METABOLISM OF CARCINOGENS

(a) *Modulation of DNA repair in parenchymal and non-parenchymal rat liver cells* (Dr A. Likhachev, Dr R. Montesano, Mrs G. Planche-Martel and Miss O. Deblock)

Previous studies[1] have shown that chronic treatment of rats with *N*-nitrosodimethylamine (NDMA) results in increased repair of O^6-methylguanine in liver DNA. The aim of the present studies was to determine if this increased repair was confined to one or more cell population (parenchymal *versus* nonparenchymal) of the liver. In-vivo alkylation studies in these two cell populations, separated by elutriation centrifugation, show that increased removal of this alkylated

Table 18. Alkylated purines in parenchymal and non-parenchymal cells of liver after a single dose of ^{14}C-*N*-nitrosodimethylamine (NDMA) (2 mg/kg) to BD rats pretreated (2 mg/kg x 3 weeks) or not with NDMA

Cell type	Time (h) after ^{14}C-NDMA	O^6-/*N*7-methylguanine ratio	
		Pretreated	Control
Parenchymal	2	0.023	0.065
	6	0.013	0.062
	12	0.011	0.050
Nonparenchymal	2	0.094	0.083
	6	0.087	0.10
	12	0.089	0.10

base (decrease in O^6-/N7-methylguanine ratio, Table 18) occurs in parenchymal but not in non-parenchymal cells as compared to control rats receiving a single dose of NDMA. In-vitro measurements of O^6-methylguanine transferase activity, using alkylated DNA as substrate, also show a higher activity of this repair 'enzyme' in parenchymal cells. DNA synthesis, as determined by ^{3}H-thymidine incorporation, was considerably increased in nonparenchymal cells but not in parenchymal cells following chronic treatment with NDMA. These findings indicate that the low repair of O^6-methylguanine and the high level of DNA synthesis in nonparenchymal cells correlates well with the induction of haemangiosarcomas in BD rats by chronic administration of NDMA.

[1] Montesano, R., Brésil, H., Planche-Martel, G., Margison, G. P. & Pegg, A. E. (1983) *Cancer Res.*, **43**, 5808–5814

(*b*) *Effects of age on DNA methylation and repair in rats exposed to alkylating agents* (Dr A. Likhachev and Miss O. Deblock; in collaboration with Dr A. Anisimov, Dr A. Ovsyannikov and Dr M. Korsakov, N.N. Petrov Research Institute of Oncology, Leningrad, USSR)

Of the various DNA adducts produced by methylating agents, O^4-methylthymidine appears to be of biological importance in carcinogenesis and mutagenesis, since, like O^6-methylguanine, this adduct also miscodes during DNA synthesis. The aim of these studies is to identify and determine the levels in various organs of different species of the enzyme responsible for the repair of O^4-methylthymidine.

The capacity of various rat embryonal tissues to repair O^6-methylguanine (O^6-meG) formed in DNA after transplacental administration of *N*-methyl-*N*-nitrosourea (MNU) was found to be considerably lower than in corresponding tissues of young adult animals[2]. Most tissues of young adult animals had a higher capacity to repair O^6-meG than those of old rats, except for the liver, where repair proceeded more efficiently in older rats[3]. Persistence of DNA methylated purines in various tissues was non-uniform in young (three-month-old) and older (14-month-old) rats exposed to MNU. Maximal efficiency of rat liver extracts to remove O^6-meG from methylated DNA was found in those from animals aged 1 and 12 months, whereas those from rats aged 3 and 22 months had considerably lesser efficiency. The DNA content was higher in the liver tissue of aged animals.

(*c*) O^6-*Alkylguanine DNA transferase activity in human, monkey and rat liver* (Dr J. Hall, Miss H. Brésil and Dr R. Montesano)

Previous studies[4] have shown that in in-vitro assays using methylated DNA substrates human and rat liver fractions were able to catalyse the repair of O^6-methylguanine (O^6-meG). These studies have been extended to include monkey liver fractions and the repair of O^6-ethylguanine (O^6-etG) from DNA[5] (Fig. 6). Human and monkey liver fractions have similar capacities for the repair of O^6-meG and are eight to ten times more active than rat liver fractions. The rate of repair is dependent on the degree of modification of the DNA substrate and the protein concentration used. The reaction involves transfer of the alkyl group from guanine in the DNA substrate to a cysteine residue in the protein, with a concomitant loss of activity in a mechanism similar to that described for other mammalian and bacterial systems. Liver extracts from all the species examined show a lower capacity to repair O^6-etG than O^6-meG. In-vitro metabolic studies, using liver slices, have shown that all three species are capable of metabolizing *N*-nitrosodimethylamine (NDMA) but that the activity in monkey liver is considerably lower than that in human and rat liver. The lack of evidence of a carcinogenic effect of NDMA in monkey liver could be correlated to this low capacity to metabolize NDMA and the high O^6-alkylguanine transferase levels in this organ.

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[2] Likhachev, A. J., Alexandrov, V. A., Anisimov, V. N., Bespalov, V. G., Korsakov, M. V., Ovsyannikov, A. I., Popovic, I. G., Napalkov, N. P. & Tomatis, L. (1983) *Int. J. Cancer*, **31**, 779–784

[3] Likhachev, A. J., Ohshima, H., Anisimov, V. N., Ovsyannikov, A. I., Revskoy, S. Y., Keefer, L. K. & Reist, E. J. (1983) *Carcinogenesis*, **4**, 967–973

[4] Pegg, A. E., Roberfroid, M., von Bahr, C., Foote, R. S., Mitra, S., Brésil, H., Likhachev, A. & Montesano, R. (1982) *Proc. natl Acad. Sci. USA*, **79**, 5162–5165

[5] Hall, J., Brésil, H. & Montesano, R. (1984) *Carcinogenesis* (in press)

(*d*) *Repair of* O^4*-methylthymidine residues in DNA by mammalian liver extracts* (Dr R. Becker and Dr R. Montesano)

Double-stranded poly-[d(A-T).d(A-T)], methylated *in vitro* by reaction with radiolabelled *N*-methyl-*N*-nitrosourea, was used as a substrate to assay the capacity of mammalian liver extracts to repair another miscoding DNA adduct, O^4-methylthymidine. Following incubation at 37°C with substrate (containing 65 fmol O^4-methylthymidine) and heat-inactivated or monkey liver extracts,

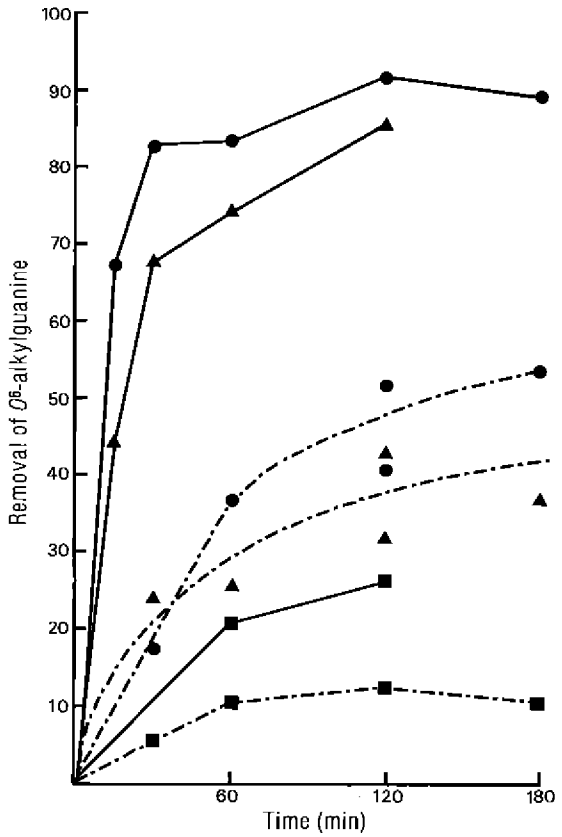

Fig. 6. Percentage removal by human (●), monkey (▲) and rat (■) liver extracts of O^6-methyl- (–) and O^6-ethylguanine (–·–) from alkylated DNA (150 µg) containing 0.30-0.39 pmol (1070-1385 dpm) O^6-methylguanine or 0.42 pmol (2180 dpm) O^6-ethylguanine

the extent of O^4-methylthymidine repair was measured by analysis of deoxynucleoside digests and taken as the difference between the amount of O^4-methylthymidine in control and active preparations. The amount of O^4-methylthymidine repaired by monkey liver extracts was proportional to

the amount of protein added, up to a protein concentration of about 5 mg/ml, and kinetic analysis of O^4-methylthymidine repair as a function of incubation time revealed that the reaction reached a plateau by 2 h. This repair activity could not be accounted for by contaminating nucleases since the amount of 3-methylthymidine recovered was always greater than 90%, even though O^4-methylthymidine content had declined to as little as 25% of control values. Furthermore, monkey liver extracts incubated with DNA containing ^{3}H-thymidine catalysed the release of less than 1% of the radioactivity present in the substrate. O^4-Methylthymine, the free base, was not detected in ethanol-soluble supernatants, indicating that the mechanism of repair of O^4-methylthymidine does not involve a DNA glycosylase. Thus, the mechanism of repair of O^4-methylthymidine resembles that of O^6-methylguanine, and appears to be similar to that found in bacteria[6,7]. Preliminary experiments with extracts from human, monkey, partially hepatectomized rat and untreated rat liver demonstrated that all species have activity that leads to a decrease in the amount of O^4-methylthymidine remaining in the substrate after incubation *in vitro*, as compared to control assays; further, the order of activity parallels that found for O^6-methylguanine DNA-methyltransferase activity, with human and monkey liver most active, partially hepatectomized rat liver intermediate, and rat liver least active.

(*e*) *Activation of styrene in Friend erythroleukaemia cells* (H. Yamasaki, H. Vainio and N. Martel; in collaboration with Dr H. Norppa, Institute of Occupational Health, Helsinki; and Dr G. Belvedere, Pharmacological Research Institute Mario Negri, Milan, Italy)

Recent studies suggest that styrene can be activated in the presence of haemoglobin as well as by conventional microsomal fractions[8]. In the lymphocyte culture system, erythrocytes are essential for the induction of sister chromatid exchanges by styrene[9]. In an attempt to develop a biological system in which both activation of styrene and the biological activity of its metabolites can be detected, we used cultured Friend erythroleukaemia cells, which start to synthesize haemoglobin when various differentiation inducers, such as hexamethylene bisacetamide (HMBA), are added. Styrene was found to be metabolized only when incubated with differentiating (HMBA-induced) cells.

Experiments to study the effect of styrene on sister chromatid exchange in differentiated and undifferentiated cells have been carried out and the results are now being analysed.

2. BIOLOGICAL CONSEQUENCES OF CARCINOGEN-DNA ADDUCTS (Mr A. Barbin and Mr J. C. Béréziat; in collaboration with Dr R. J. Laib, Institute of Pharmacology, Toxicology Unit, University of Mainz, FRG; Professor M. F. Rajewsky, Institute for Cell Biology, University of Essen, FRG; Professor G. Michel, Université Claude-Bernard, Lyon, France; and Dr M. Radman, Department of Molecular Biology, Free University of Brussels, Rhode-St-Genèse, Belgium)

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[6] McCarthy, T. V., Karran, P. & Lindahl, T. (1984) *EMBO J.*, **3**, 545–550
[7] Ahmed, Z. & Laval, J. (1984) *Biochem. biophys. Res. Commun.*, **120**, 1–8
[8] Belvedere, G. & Tursi, F. (1981) *Res. Commun. Chem. Pathol. Pharmacol.*, **33**, 273–282
[9] Norppa, H., Vainio, H. & Sorsa, M. (1983) *Cancer Res.*, **43**, 3579–3582

The mutagenicity and carcinogenicity of vinyl chloride results from the reaction of metabolites, especially chloroethylene oxide (CEO), with DNA[10,11]. CEO can yield chloroacetaldehyde (CAA) by thermal rearrangement or by reaction with chloride ions and can be hydrolysed to glycolaldehyde. The kinetics of these reactions were studied by ^{1}H-Fourier transform nuclear magnetic resonance[14]. CEO, CAA and glycolaldehyde can bind to glutathione and to macromolecules forming mono- and cyclic adducts or crosslinks with nucleic acid bases.

The TD_{50} value of CEO (about 2)[11] and its nucleophilic selectivity ($s = 0.71$)[12] are not correlated, although a general relationship was established for other carcinogenic alkylating agents[13]. The mutagenic effectiveness (mutants per 10^8 survivors per mmol/l per h) of CEO in *Escherichia coli* is several orders of magnitude greater than that of other alkylating agents[14]. These two striking discrepancies suggest that the target site of CEO may be different from that (those) of other alkylating agents (e.g., O^6 of guanine).

Previous misincorporation assays[15-17] and studies on mutagenicity in bacteria[16,18,19] have indicated that CEO may act through a miscoding DNA lesion, possibly a cytosine adduct. Therefore, attempts were made to characterize and isolate new CEO- (or CAA-)cytidine adducts (using high-performance liquid chromatography, nuclear magnetic resonance and gas chromatography-mass spectrometry. *In vitro*, 3,N^4-ethenocytidine is the major final adduct formed from either CEO or CAA; however, the intermediates are probably different for the two compounds. It is hypothesized that, *in vivo*, CEO and CAA bind to the free amino group of cytosine in double-stranded DNA and that the secondary structure of DNA prevents the formation of 3,N^4-ethenocytosine; instead, another stable miscoding adduct may be formed.

Studies are in progress to prepare monoclonal antibodies against 1,N^6-ethenoadeoxyadenosine and 3,N^4-ethenodeoxycytidine. Attempts are being made to immunize rodents with synthetic polynucleotides.

3. MECHANISMS OF TUMOUR PROMOTION

(a) *Characterization of human placental factors that modulate specific binding of phorbol esters and protein kinase C activity* (Dr H. Yamasaki, Miss E. Hamel and Miss N. Martel; in collaboration with Dr J. L. Tayot, Institut Mérieux, Marcy-l'Etoile, France)

Recent studies on the mechanisms of action of phorbol esters suggest that their primary action is on the cellular membrane, and a class of specific binding sites for the tumour-promoting phorbol esters has indeed been found in a variety of cells[20]. More recent studies have suggested that these binding sites are identical with a novel protein kinase, protein kinase C[21]. We are looking for factors

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[10] Barbin, A., Brésil, H., Croisy, A., Jacquignon, P., Malaveille, C., Montesano, R. & Bartsch, H. (1975) *Biochem. biophys. Res. Commun.*, **67**, 596–603

[11] Zajdela, F., Croisy, A., Barbin, A., Malaveille, C., Tomatis, L. & Bartsch, H. (1980) *Cancer Res.*, **40**, 352–356

[12] Barbin, A., Bérézíat, J. C., Croisy, A., O'Neill, I. K. & Bartsch, H. (in preparation)

[13] Bartsch, H., Terracini, B., Malaveille, C., Tomatis, L., Wahrendorf, J., Brun, G. & Dodet, B. (1983) *Mutat. Res.*, **110**, 181–219

[14] Hussain, S. & Osterman-Golkar, S. (1976) *Chem.-biol. Interactions*, **12**, 265–267

[15] Barbin, A., Bartsch, H., Lecomte, P. & Radman, M. (1981) *Nucleic Acids Res.*, **9**, 375–387

[16] Barbin, A., Laib, R. & Bartsch, H. (1984) *Mutat. Res.*, **130**, 165–166

[17] Barbin, A., Laib, R. & Bartsch, H. (submitted for publication)

[18] Barbin, A., Perrard, M. H., Besson, F., Bérézíat, J. C., Michel, G. & Bartsch, H. (in preparation)

[19] Barbin, A., Toman, Z., Dambly, C., Radman, M. & Bartsch, H. (in preparation)

that modulate specific binding of phorbol esters and/or protein kinase C activity. We reported previously that a phorbol ester binding inhibitory factor (PEBIF), can inhibit the binding of

Table 19. Effect of tumour promotion inhibitors on TPA inhibition of communication between BALB/c 3T3 cells[a]

Addition to culture medium	No. of dye-coupled cells per injection	Inhibition (%)
Experiment I[b]		
None	30.1 ± 4.5	–
TPA, 100 ng/ml	8.8 ± 5.8	70.1
Dexamethasone, 1 mmol/l	27.2 ± 5.7	9.6
TPA + dexamethasone	22.5 ± 4.3	25.2
Fluocinolone aceonide, 1 µg/ml	28.7 ± 5.4	4.7
TPA + fluocinolone acetonide	24.6 ± 5.6	18.3
Retinoic acid, 1 mmol/l	44.1 ± 9.0	−46.5
TPA + retinoic acid	39.1 ± 7.5	−29.9
Experiment II[c]		
None	33.5 ± 3.5	–
TPA, 100 ng/ml	4.9 ± 3.2	83.4
dbcAMP, 1 mmol/l	76.4 ± 9.8	−128.1
TPA + dbcAMP	70.8 ± 10.1	−111.3
Caffeine, 1 mmol/l	36.5 ± 6.2	−8.9
TPA + caffeine	6.3 ± 3.1	81.2
dbcAMP + caffeine	84.5 ± 5.5	−152.2
TPA + dbcAMP + caffeine	84.2 ± 6.2	−151.3

[a] From Yamasaki, H., Enomoto, T., Hamel, E. & Kanno, Y. (1984) In: *Proceedings of the 14th Princess Takamatsu Symposium: Cellular Interactions by Environmental Promoters*, Tokyo, University Park Press (in press)

[b] BALB/c 3T3 cells were cultured with the indicated chemicals for 3 weeks; culture medium and chemicals were changed twice a week.

[c] Cells were cultured with the indicated chemicals for 6 h before assay of intercellular communication.

^{3}H-phorbol 12,13-dibutyrate on different types of cell, and the factor was partially purified (133-fold) from an extract of human placenta[22]. When partially purified PEBIF fraction was added to protein kinase C (from mouse brain) in an assay mixture, dose-dependent activation of kinase activity was observed. This stimulating activity was strictly calcium-dependent and could be precipitated by 80% ethanol without loss; it can be separated from PEBIF activity by gel filtration. Further studies are now in progress. It was further found that PEBIF only slightly inhibits phosphatidylserine- and diolein-stimulated C kinase activity.

[20] Blumberg, P. M., Delclos, K. B., Dunphy, W. G. & Jaken, S. (1982) In: Hecker, E., Fusenig, N. E., Kunz, W., Marks, F. & Thielmann, H. W., eds, *Cocarcinogenesis and Biological Effects of Tumor Promoters*, New York, Raven Press, pp. 519–535

[21] Nishizuka, Y. (1984) *Nature*, **308**, 693–698

[22] Hamel, E., Martel, N., Tayot, J. L. & Yamasaki, H. (1984) *Carcinogenesis*, **5**, 15–21

(*b*) *Inhibition of gap-junctional communication by tumour-promoting phorbol esters and protection by compounds that inhibit tumour promotion* (Mr T. Enomoto and Dr H. Yamasaki)

Using a dye-transfer method[23,24], we are continuing to study the mechanism by which tumour promoting phorbol esters inhibit gap-junctional intercellular communication. Examination of structure-activity relationships of phorbol esters and related compounds show a good correlation between their promoting activity on mouse skin and their inhibitory effect on intercellular communication[24]. The inhibition appears to be mediated through phorbol ester receptors, since the extent of inhibition of the specific binding of ^{3}H-phorbol 12,13-dibutyrate to BALB/c 3T3 cells parallels that of intercellular communication by various phorbol ester derivatives[24].

We have also tested the effect on inhibition by 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) of dye transfer of chemicals that have been reported to have anti-tumour promotion activity on mouse skin. cAMP, retinoic acid and glucocorticoids all protect against the inhibition by TPA of intercellular communication (Table 19). These results, together with other related findings (see p. 87), provide evidence that blocked cellular communication may play an important role in carcinogenesis, especially in tumour promotion.

(*c*) *Modulation of gene expression by tumour promoters* (Dr H. Yamasaki, Dr M. Hollstein and Miss N. Martel)

After phorbol esters have bound to their specific receptors—probably protein kinase C—they modulate gene expression (cell differentiation) of various types of cultured cells[25]. The relationship between phorbol ester binding and modulation of gene expression was studied in detail using a Friend erythroleukaemia cell line as a model system. Our results suggest that TPA can suppress globin gene expression continuously, even though the number of its receptors is decreased significantly, due to down regulation[26].

The effect of TPA on inhibition of globin gene expression and terminal cell differentiation is reversible for a long time. Since globin mRNA is not detected as long as TPA is present in the culture medium, we assume that TPA action takes place around the time of transcription[26]. We are now trying to determine the molecular mechanism by which specific gene expression is modulated by a phorbol ester. Our activities include a study of the effect of TPA on the level of methylation of cytosines in specific genes involved in erythroid differentiation, e.g., globin gene, *erb* B gene.

(*d*) *Comparative study of a complete tumour promoter and a second-stage tumour promoter on cultured cells* (Dr H. Yamasaki, Miss N. Martel, Ms A. M. Aguelon-Pegouries and Mr T. Enomoto; in collaboration with Dr G. Furstenberger and Dr F. Marks, German Cancer Research Center, Heidelberg, FRG)

Recently, the process of skin tumour promotion was shown to be subdivided into at least two stages: stage I, consisting of short-term (one to four times) application of TPA; and stage II,

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[23] IARC (1983) *Annual Report 1983*, Lyon, p. 81

[24] Enomoto, T., Martel, N., Kanno, K. & Yamasaki, H. (1984) *J. cell. Physiol.* (in press)

[25] Yamasaki, H. (1984) In: Slaga, T. J., ed. *Mechanisms of Tumor Promotion*, Vol. IV, Boca Raton, FL, CRC Press Inc., pp. 1–26

[26] Yamasaki, H., Martel, N., Fusco, A. & Ostertag, W. (1984) *Proc. natl Acad. Sci. USA*, **81**, 2075–2079

consisting of long-term treatment with mezerein[27] or, more efficiently, the semi-synthetic phorbol ester 12-*O*-retinoyl phorbol 13-acetate (RPA)[28]. By itself, RPA has almost no tumour-promoting effect (like short-term TPA treatment) but is almost as powerful an irritant skin mitogen as TPA[28]. By comparing the responses evoked by TPA and by RPA in biological systems other than skin, it may be possible to distinguish effects related to stage I of promotion from those related to stage II, i.e., due most probaly to the pleiotropic activities of a phorbol ester. This study was undertaken to compare the effects of TPA with those of RPA on differentiation of Friend erythroleukaemia cells (FELC), intercellular communication between BALB/c 3T3 cells and two-stage transformation of BALB/c 3T3 cells.

The doses of TPA and RPA necessary to inhibit the specific binding of ^{3}H-phorbol 12,13-dibutyrate (^{3}HPDBu) to BALB/c 3T3 cells (50% inhibition doses, ID_{50}: 8–13 ng/ml) were very similar; however, RPA was less potent than TPA in inhibiting ^{3}HPDBu binding to FELC. Intercellular communication between BALB/c 3T3 cells, measured by transfer of microinjected fluorescent dye (Lucifer Yellow), was inhibited by RPA as well as by TPA; TPA was about five times more potent than RPA. RPA also inhibited FELC differentiation induced by hexamethylene bisacetamide but not the differentiation of a TPA-resistant clone. The dose-responses of these two compounds in inhibiting differentiation of TPA-sensitive and -resistant FELC were very similar. When TPA and RPA were compared for their activity in promoting in-vitro cell transformation of BALB/c 3T3 cells initiated with 2-methylcholanthrene (0.1 μg/ml), both RPA and TPA significantly increased the yield of morphologically transformed foci. These results suggest that RPA and TPA share some common in-vitro biological effects, which may be related to the second stage of skin tumour promotion. These in-vitro studies do not allow us to delineate the effect of a second-stage tumour promoter from that of complete tumour promoters such as TPA.

(*e*) *In-vivo two-stage carcinogenesis* (Dr H. Yamasaki, Dr J. R. P. Cabral, Mrs D. Galendo and Dr L. Tomatis)

As reported last year[29], no promoting activity of TPA was found on skin or internal organs of C57BL/6 mice using a transplacental initiation (benzo[*a*]pyrene)-postnatal promotion protocol. Since C57BL/6 mice are relatively resistant to initiation-promotion tumorigenesis, a new set of experiments with CD-1 mice was designed.

When CD-1 mice were initiated transplacentally with benzo[*a*]pyrene and the newborn mice treated with TPA by skin painting, a significant increase in the skin papilloma yield was observed (Fig. 7). Non-promoted newborn mice had no skin papillomas. Twice weekly applications of TPA to uninitiated mice also produced papillomas but to a lesser extent than in initiated mice. These results suggest that 'initiated cells' can be produced transplacentally and that these cells can be 'promoted' postnatally. Our results also indicate that CD-1 mice are more susceptible than C57BL/6 mice to the induction of skin tumours with the protocol used. The experiment is still under way to examine possible promotion of tumours in internal organs.

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[27] Slaga, T. J., Fisher, S. M., Nelson, K. & Gleason, G. L. (1980) *Proc. natl Acad. Sci. USA*, **77**, 659–663
[28] Furstenberger, G., Berry, D. L., Sorg, B. & Marks, F. (1981) *Proc. natl Acad. Sci. USA*, **78**, 7722–7726
[29] IARC (1983) *Annual Report 1983*, Lyon, p. 86

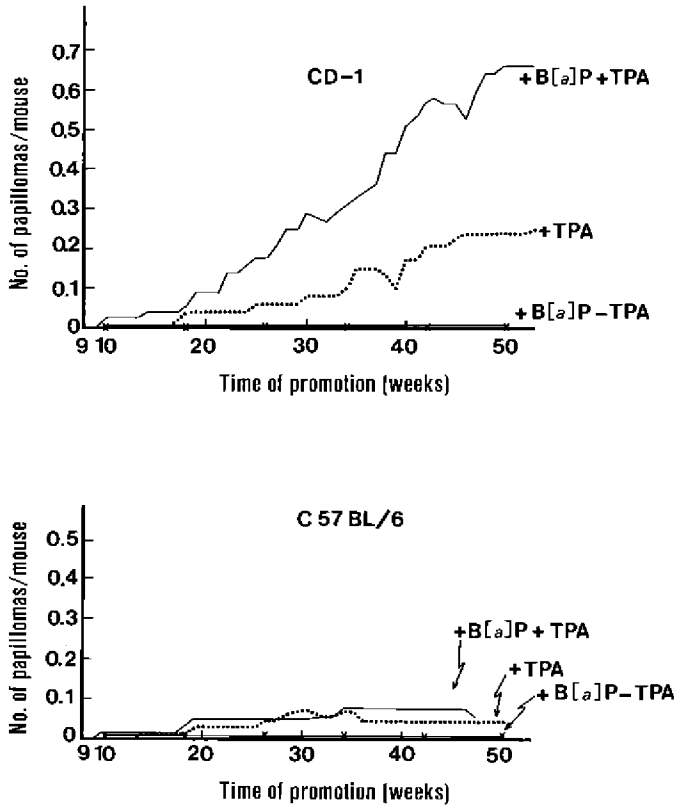


Fig. 7. In-vivo two-stage carcinogenesis: ●, prenatal olive oil + postnatal TPA; ○, prenatal benzo[*a*]pyrene + postnatal TPA; ×, prenatal benzo[*a*] pyrene + postnatal acetone

(*f*) *Quantitative effects of tumour initiators and promoters* (Dr H. Yamasaki, Dr J. R. P. Cabral, Dr N. E. Day, Dr J. Wahrendorf and Mrs D. Galendo; in collaboration with Dr I. Chouroulinkov, Institute of Scientific Research on Cancer, Villejuif, France)

A study on the quantitative effects of tumour initiators and promoters is being continued in C57BL/6 and CD-1 mice. In C57BL/6 mice, the effect of a single application of various doses of benzo[*a*]pyrene, i.e., 0.05, 0.5, 5, 20, 50, 100 and 300 μg/mouse, with and without subsequent treatment, with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), was studied. This experiment is now terminated, and the results are being analysed statistically.

In the experiment with CD-1 mice, the dose of benzo[*a*]pyrene that acted as an initiating agent was fixed at 50 μg, and different doses of TPA were applied at different intervals of time. The

Table 20. Experimental protocol to study the effect of time-interval of application on dose-response to a tumour promoter

Frequency of TPA application [a]	TPA, µg/application/0.1 ml acetone					
	0.1	0.2	0.4	0.8	1.6	3.2
Once in 16 days (1/2)			70	60	50	40
Once in 8 days (1)		70	60	50	40	30
Once in 4 days (2)	70	60	50	40	30	30
Every other day (4)	60	50	40	30	30[b]	
Every day (8)	50	40	30[b]	30[b]		

[a] In parentheses, number of mice used
[b] With control group (no benzo[*a*]pyrene)

experimental protocol is illustrated in Table 20. Results after 32 weeks of TPA application indicate that the dose-response to TPA is clearly dependent on the frequency of its application. The experiment will be completed and the data analysed at the end of 1984.

4. CHEMICAL CARCINOGENESIS AND MUTAGENESIS IN CULTURED CELLS

(*a*) *Mutagenesis and transformation in BALB/c 3T3 cells* (Dr H. Yamasaki, Mrs C. Piccoli and Dr K. Fujie; in collaboration with Dr T. Kakunaga, National Cancer Institute, Bethesda, MD, USA)

Development of a system in which mutation and transformation can be measured in BALB/c 3T3 cells continues.

Diethylstilboestrol (DES) has been reported to induce morphological transformation, but not mutation, in cultured Syrian hamster cells[30]. We have tested DES for its mutagenic activity in BALB/c 3T3 cells using ouabain resistance as a marker. Up to 10 µg/ml of DES, there was no increase in the number of ouabain-resistant cells, nor was it active in freshly isolated primary rat hepatocytes. In a concurrent study of cell transformation, we found a borderline positive result. Further experiments on the effect of DES on cell transformation are being carried out.

Benzene, a human carcinogen, has been shown to be clastogenic in many systems but not mutagenic to bacteria or mammalian cells[31]. We are studying the effect of benzene on mutation and transformation of BALB/c 3T3 cells. Our preliminary results suggest that it has a weak transforming activity.

(*b*) *Role of blocked intercellular communication in BALB/c 3T3 cell transformation* (Mr T. Enomoto and Dr H. Yamasaki)

In order to study the possible role of intercellular communication in in-vitro cell transformation, the communicating capacity of BALB/c 3T3 cells transformed by 20-methylcholanthrene was investigated using a dye transfer method. Morphologically transformed foci, detectable four to

[30] Barrett, J. C., Wong, A. & Mc Lachlan, J. A. (1981) *Science*, **212**, 1402–1403
[31] IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 4, Lyon

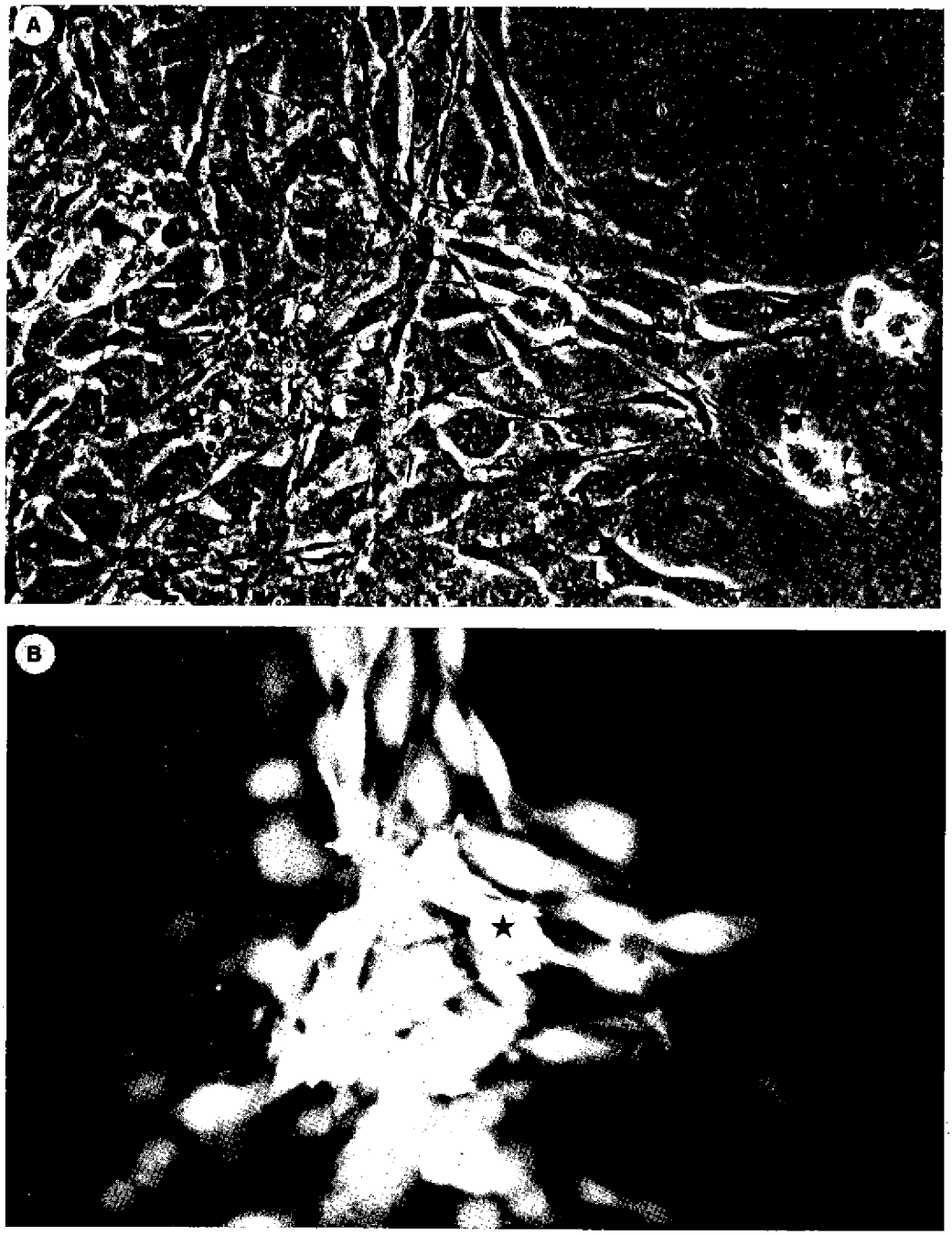
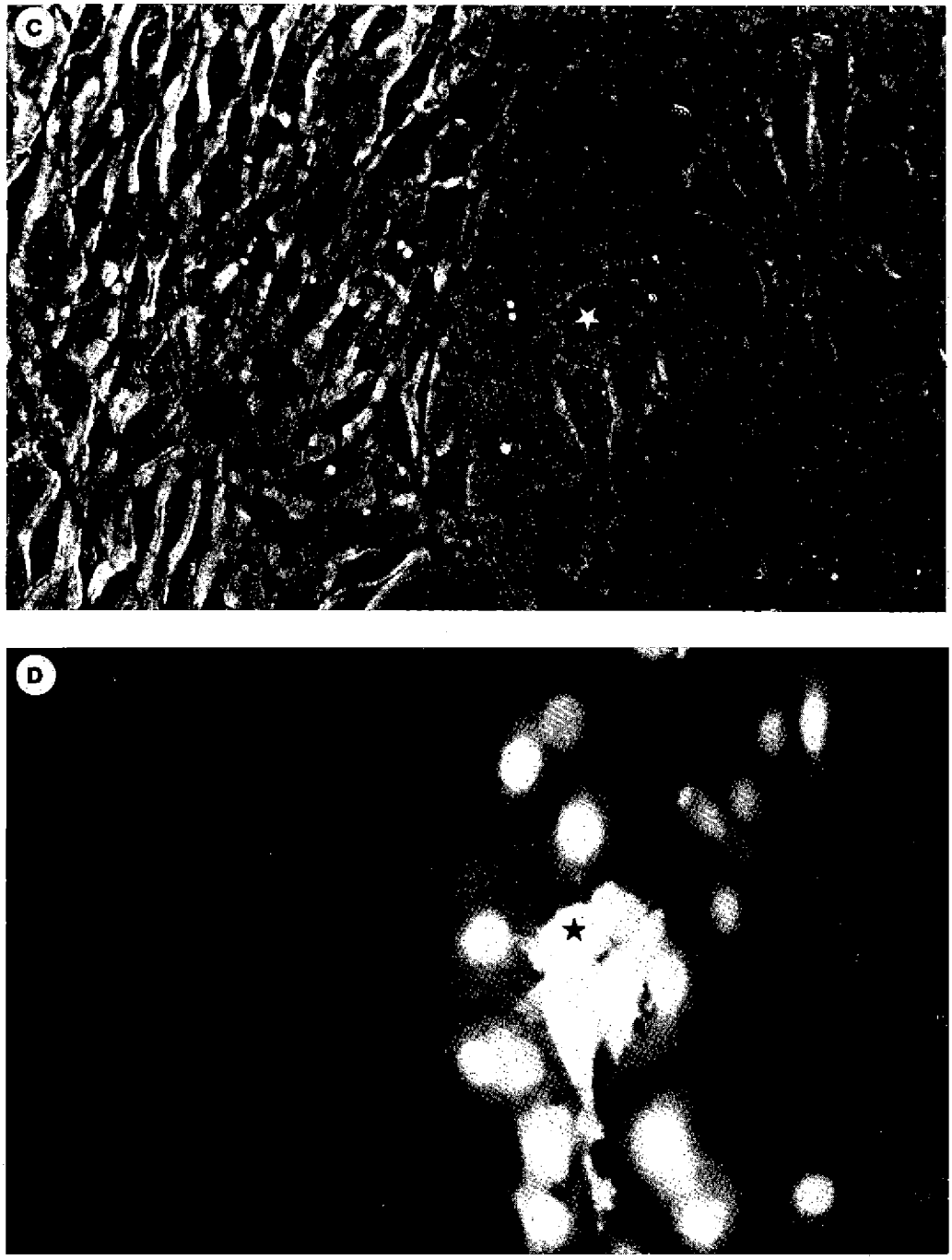


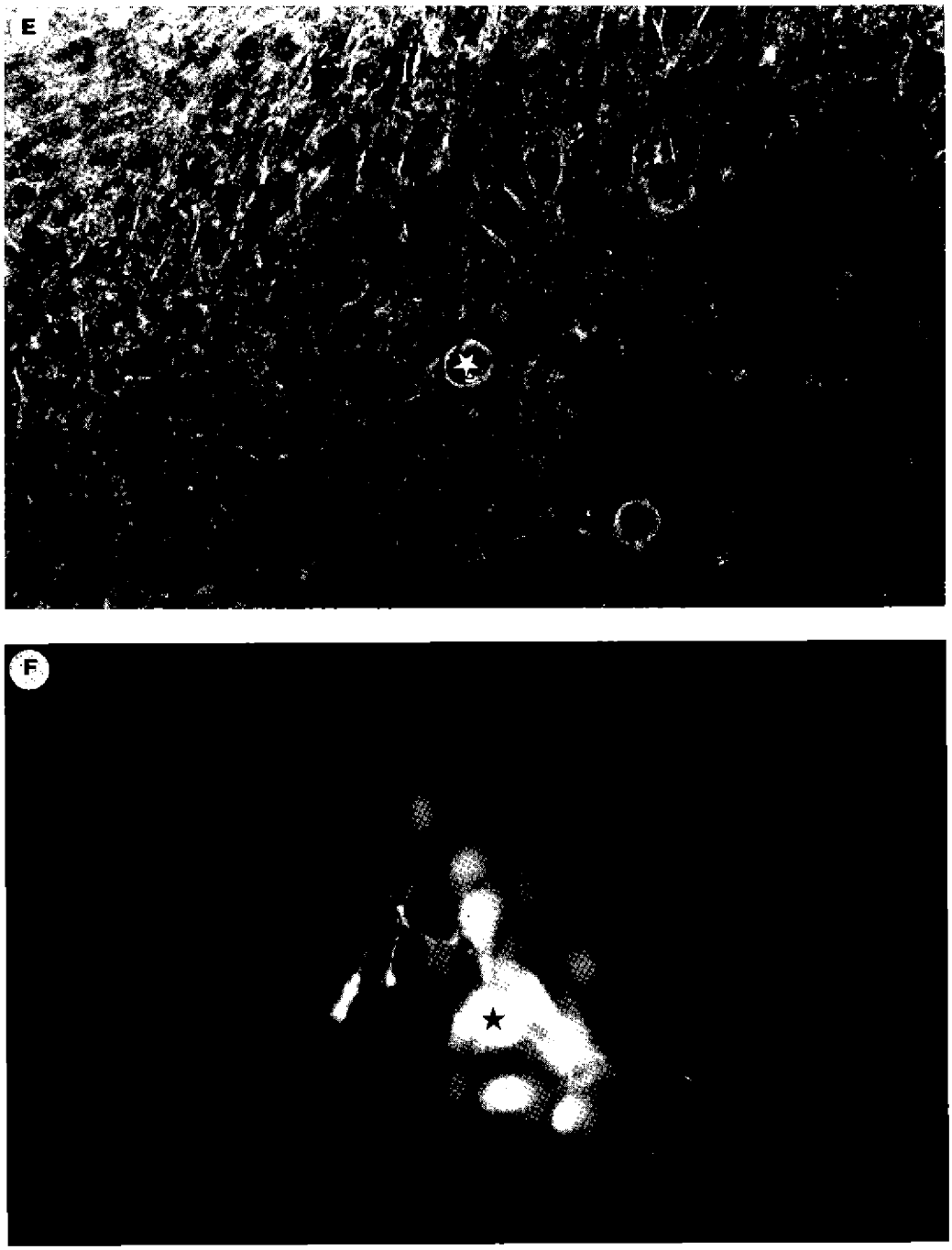
Fig. 8. Patterns of dye transfer in 20-methylcholanthrene (MCA)-induced transformed foci of BALB/c 3T3 cells and surrounding non-transformed counterparts

Transformed foci obtained five weeks after MCA treatment were used for the measurement of dye transfer. A transformed or non-transformed cell was injected with fluorescent Lucifer Yellow CH dye and was microphotographed 10 min later. Cells into which the dye was injected are indicated by ★.

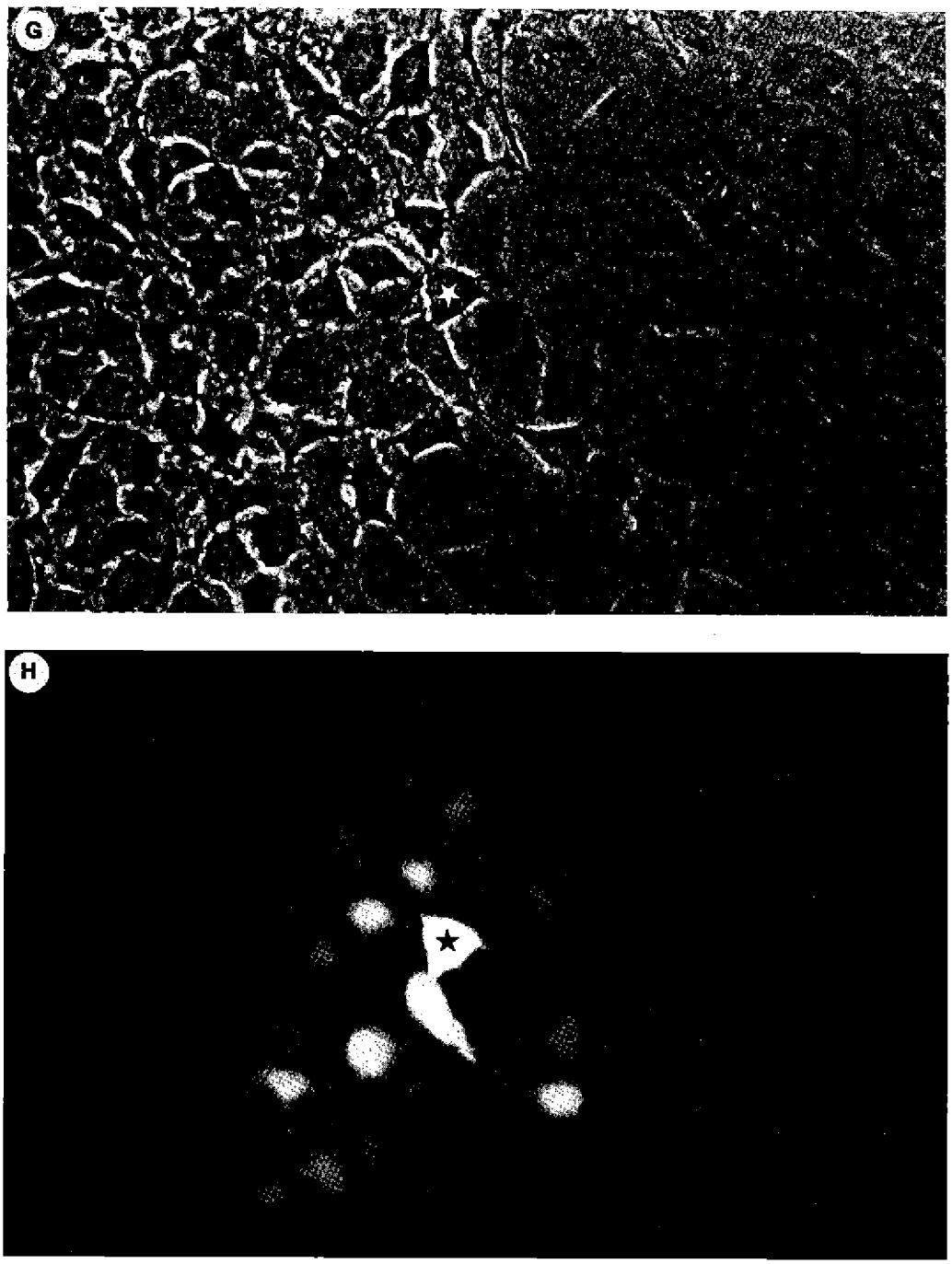
a, b: Dye transfer in a type-III transformed focus. Note that dye transfer is limited to the transformed focus.



c, d: Dye was injected into a non-transformed cell located close to a transformed focus. Note that dye transfer is limited to the non-transformed cells.



e, f: Micrograph of the centre of a type-III transformed focus. Dye transfer is observed among multi-layered cells.



g, h: Dye transfer in a type-I transformed focus. Note that dye is transferred into surrounding non-transformed cells as well as into neighbouring transformed cells.

five weeks after treatment with 20-methylcholanthrene (1.0 μg/ml), are clearly distinguishable under the phase-contrast microscope from surrounding non-transformed monolayer cells; therefore, a tracer dye can be injected into individual cells and gap-junctional communication between and among transformed and non-transformed cells be studied directly.

When fluorescent Lucifer Yellow CH was microinjected into a cell within a transformed focus, the dye was transferred to other transformed cells but not to cells in the adjacent non-transformed area, although they were in physical contact (Fig. 8). Similarly, dye injected into a non-transformed cell was transferred to neighbouring non-transformed cells but not to cells in an adjacent transformed focus. These results indicate that when BALB/c 3T3 cells are transformed by 20-methylcholanthrene, they can no longer communicate with surrounding normal cells, although they maintain the ability to communicate with other transformed cells in the focus. Quantitative data on the capacity of cells of types I and III transformed foci to transfer dye are summarized in Table 21. Unlike type-III transformed foci, cells in type-I foci can communicate with surrounding normal cells.

Table 21. Dye transfer among transformed and adjacent non-transformed BALB/c 3T3 cells

Lucifer Yellow CH solution was microinjected into a single cell (donor cell) at the periphery of transformed foci (types III or I) that were very close to surrounding non-transformed cells (see Fig. 7a, b) or into a single non-transformed cell that was near transformed foci (see Fig. 7c, d).

Donor cell	Recipient cell (No. of dye-coupled cells/injection) [a]	
	Non-transformed	Transformed
Transformed type III		
transformed cell (n = 56) [b]	1.8 ± 1.2	34.2 ± 8.9
surrounding non-transformed cell (n = 32)	24.2 ± 9.9	1.2 ± 1.0
Transformed type I		
transformed cell (n = 25)	10.6 ± 4.0	16.5 ± 5.2
surrounding non-transformed cell (n = 20)	17.3 ± 3.5	8.5 ± 3.4

[a] Mean ± SD

[b] Number of injections in transformed and non-transformed areas

These results suggest that loss of the ability to communicate with surrounding non-transformed cells may be one of the important determinants of induction and expression of final malignant transformation.

(*c*) *Characterization of transformation-sensitive and -resistant BALB/c 3T3 cell lines in terms of multi-stage carcinogenesis* (Dr H. Yamasaki, Mr T. Enomoto and Miss N. Martel; in collaboration with Dr Y. Kanno and Dr Y. Shiba, Hiroshima University, Hiroshima, Japan; and Dr T. Kakunaga, National Cancer Institute, Bethesda, MD, USA)

Variants of BALB/c 3T3 cells with different susceptibilities to transformation by ultraviolet irradiation and by benzo[*a*]pyrene have been isolated and characterized previously by Dr Kakunaga's group. Those studies showed that a highly susceptible clonal cell line (A31-1-13) and a resistant cell line (A31-1-8) were similarly sensitive to mutation by ultraviolet irradiation and in the extent to which covalent DNA adducts of benzo[*a*]pyrene were formed and removed, suggesting that they differ in a function related to a later stage (promotion) rather than to an initial phase of cell transformation.

When the effects on these cell lines of phorbol ester tumour promoters were studied, we found that they had a similar number of phorbol ester receptors and responded similarly to TPA stimulation of 2-deoxyglucose uptake. When the effect of TPA on intercellular communication was measured electrophysiologically or by a dye transfer method, the two cell lines respondend similarly. Moreover, although these cell lines show different susceptibilities to 20-methlycholanthrene-induced cell transformation, both responded to TPA in its enhancement of the transformation.

These results indicate that A31-1-8 and A31-1-13 clonal cells respond to a similar extent to exogenously added tumour-promoting agents. Therefore, these cells have a similar ability to express several phenotypes that are considered to be related to the promotion phase of cell transformation. We therefore considered the possibility that these two clonal cell lines have different intrinsic capacities to express some transformation-related phenotypes. Thus, we cultured the cells under conditions similar to those in which cell transformation occurs, i.e., long-term culture at confluence, and intercellular communication capacity was measured by a dye transfer method.

The results are shown in Figure 9. The communication abilities of these cell lines were similar when they were in a growing phase. When they reached confluence, however, they showed quite different communicating abilities: A31-1-8 cells exhibited a high capacity for cell communication when in confluence, whereas A31-1-13 cells showed a markedly lower capacity to communicate soon after they had reached confluence, which remained lower for four weeks. This difference may partially explain their different sensitivities to transformation. If blockage of cell communication is involved in the promotion phase of cell transformation, our results suggest that highly transformation-sensitive clonal cells have a higher intrinsic ability to promote (express) transformed phenotypes.

(*d*) *Mutagenesis of a bacterial gene, ECogpt, in human cells* (Ms C. Drevon; in collaboration with Dr C. F. Arlett, Dr J. F. Burke and Dr M. R. James, MRC Cell Mutation Unit, University of Sussex, Falmer, Brighton, UK; DEC/82/021)

The project to study alterations induced by ultraviolet and X-rays in the structure of a small bacterial gene that has been introduced into human cells is being continued. To address this problem, human fibroblasts deficient in HGPRT were transfected with a SV40 pBR322 recombinant plasmid which contains the *Escherichia coli* sequence, Ecogpt, coding for XPRT, the bacterial analogue of the mammalian enzyme of the transfected genes. Six out of six gpt^+ clones,

when plated in 6-thioguanine medium, reverted to the gpt− phenotype at a frequency of 1–5%. Southern blot phenotype analysis of the DNA of ten revertant clones showed that the reversion to the gpt− phenotype was the result of deletion of the *gpt* gene. Such a high reversion frequency does not allow mutagenesis experiments to be performed. This problem could perhaps be obviated by the use of a double vector containing two selectable markers. The maintenance of selective pressure

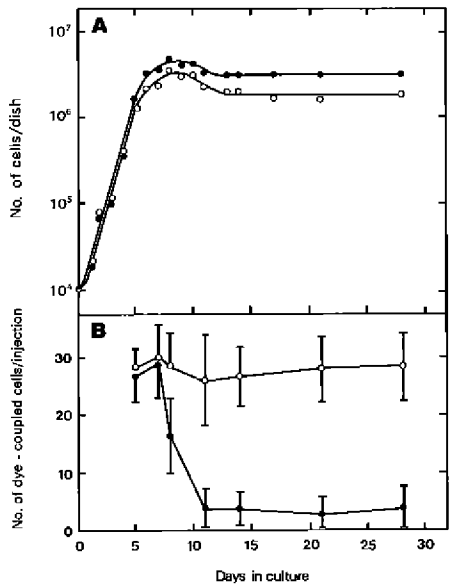


Fig. 9. Comparison of growth rate and intercellular communication capacity of clone A31-1-8 and A31-1-13 BALB/c 3T3 cells.
A, growth curve; B, intercellular communication measured by dye transfer method. At the indicated times of culture, Lucifer Yellow solution was microinjected into individual cells using an Olympus injectoscope, and the number of fluorescent cells was counted 10 min later under a fluorescence microscope. Each point represents the mean value ± standard deviation from 43 to 90 independent injections. o, A31-1-8 cells; •, A31-1-13 cells

on one of the markers during the whole course of the experiment having a stabilizing effect on the transfected genes, the reversion rate would be expected to be lower. A double vector containing the *gpt* gene and a *neo* gene (conferring resistance to Kanamycin in bacteria and G418 in eukaryotic cells) has been constructed by ligation of the two vectors, pSV2 gpt and pSV2 neo and has been transfected into normal and A-T human skin fibroblasts. The stability of the gpt+ clones grown in the presence of G418 is presently under investigation.

Among the clones analysed by Southern blot analysis, one has been found to have a high copy number of the *gpt* gene. Southern blot analysis of the non-digested DNA showed that the *gpt* copies were extrachromosomal. Work is going on to determine if the extrachromosomal DNA originates from an integrated copy of SV2 gpt, or is exclusively episomal.

(*e*) *Enhancement of chemically induced transformation in BALB/c 3T3 cells by an active form of vitamin D_3, 1,25-dihydroxyvitamin D_3* (Dr T. Kuroki, Institute of Medical Science, University of Tokyo; DEC/79/006)

1,25-Dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] is a hormonally active form of vitamin D_3 which regulates calcium levels in blood. It is formed from vitamin D_3 by sequential hydroxylation first in the liver at the 25-position and then in the kidney at the 1-position. Recently, the receptor protein for 1,25$(OH)_2D_3$ has been found in a wide variety of organs and cells, including intestines, bone, parathyroid, skin, and some cultured cell lines, suggesting that the physiological role of this vitamin is not limited to calcium homeostasis but could extend to other functions. We reported previously that 1,25$(OH)_2D_3$ stimulates the differentiation of epidermal keratinocytes[32] and myeloid leukaemia cells[33]. Interestingly, these effects of 1,25$(OH)_2D_3$ are very similar to those of 12-*O*-tetradecanoylphorbol-13-acetate (TPA), a tumour promoter, and this prompted us to examine the possible promoting effect of 1,25$(OH)_2D_3$[34].

Treatment of cells with 20-methylcholanthrene alone at 1 μg/ml for 72 h produced about one transformed focus per 10 dishes with a frequency of 0.18 per 10^3 survivors. Subsequent incubation of these cells with 0.05–10 ng/ml 1,25$(OH)_2D_3$ for two weeks markedly increased the transformation in a dose-dependent manner: a seven-fold increase was observed at a concentration of 1 ng/ml (2.4×10^{-9}M) and a 15-fold increase at a concentration of 10 ng/ml. 1,25$(OH)_2D_3$ alone did not induce transformation or cytotoxicity. The enhancement was probably mediated by a cytosol receptor for 1,25$(OH)_2D_3$, which has an equilibrium constant of 28.4 pM and a maximum binding of 32.6 fmol/mg protein.

1,25$(OH)_2D_3$ is an essential nutrient, and its physiological level in plasma is 0.05 ng/ml (1.2×10^{-10}M). This study indicates that 1,25$(OH)_2D_3$ may be a natural modulator of growth and differentiation of cells and of the promotion of certain types of tumours.

(*f*) *Cellular and biochemical markers of neoplastic transformation of epithelial cells in culture* (Dr J. M. Vasiliev, Cancer Research Center of the USSR Academy of Medical Sciences, Moscow; DEC/79/010)

Work has concentrated on the production and characterization of a series of monoclonal antibodies against epithelium-specific components of intermediate filaments (prekeratins) and extracellular matrix (laminin and entactin). About 20 clones have been obtained and are being characterized by immunofluorescence on frozen tissue sections and by immunoblotting.

A new method of visualizing focal cell-substrate contacts, using a monoclonal antibody against a 80-kD serum protein tightly bound to the substrate, was developed. It was shown that marginal focal contacts were present in non-tumorigenic IAR cells, but absent from tumorigenic cells. Thus, alteration of cell-substrate interaction in epithelial cell system seems to accompany transformation, as in fibroblasts.

Analysis by means of four different markers of two tumours produced in rats after inoculation of clone C2 IAR 6–1 RT 7 cells has confirmed the diagnosis of these tumours as sarcoma-like

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[32] Hosomi, J., Hosoi, J., Abe, E., Suda, T. & Kuroki, T. (1983) *Endocrinology*, **113**, 1950–1957

[33] Abe, E., Miyaura, C., Sakagami, H., Takeda, M., Konno, K., Yamazaki, T., Yoshiki, S. & Suda, T. (1981) *Proc. natl Acad. Sci. USA*, **78**, 4990–4994

[34] Kuroki, T., Sasaki, K., Chida, K., Abe, E. & Suda, T. (1983) *Gann*, **74**, 611–614

anaplastic neoplasms. It is planned to apply marker analysis to different tumours caused by inoculation of IAR cells. New types of monoclonal antibodies will be used for this purpose.

(*g*) *Dependence of tumour growth rate and metastatic potential on type of carcinogenic agent* (Dr S. Plesnicar and Dr G. Sersa, Institute of Oncology and Faculty of Medicine, Ljubljana, Yugoslavia; DEC/83/002)

Experiments are being carried out to determine the growth rates of primary mammary gland tumours and their pulmonary metastases in CBA mice. Cells from the mammary tumour are injected intravenously, and the growth rate of the pulmonary metastases is compared with the growth rate of the primary tumour.

1,2-Dimethylbenz[*a*]anthracene was applied topically to the mammary gland of CBA mice by directly dusting glands exposed surgically. The first tumour appeared after 64 days; the arithmetic mean doubling time was six days. Histology revealed squamous-cell carcinomas. Pulmonary metastases were induced by intravenous injection of these tumour cells. In order to test the applicability of this technique, 5×10^5 tumour cells obtained from a subcutaneous fibrosarcoma were injected. The growth rate of the pulmonary metastases was similar to that of the primary tumour, when similar volumes were compared. The time lapse between the injection of fibrosarcoma cells and the appearance of pulmonary metastases was calculated to be 1.7 metastases per day.

(*h*) *Development of a biochemical method for quantitative measurement of genetic changes* (Dr M. Radman and Ms G. Maenhaut, Department of Molecular Biology, University Libre, Brussels; DEC/82/016)

Current methods for detecting genetic alterations suffer either from insensitivity, due to 'neutral' mutations (mutations without phenotype) in the case of forward mutation assays, or from limited specificity in the case of reversion mutation assays. The aim of these studies is to develop biochemical probes for detecting mutations in any kind of DNA, e.g., human genomes. When a mixture of homologous DNA with sequence alterations is denatured and renatured, heteroduplex DNA is formed, with diverse mispaired (substitution mutation) or unpaired (frameshift mutations and other deletions, insertions and rearrangements) bases. Proteins are being used that bind and/or cut mispaired or unpaired bases, as well as chemicals (e.g., bromoacetaldehyde) that modify specifically the mispaired and unpaired bases. The repair of all possible mispaired base pairs and unpaired bases in the cI gene of phage λ has been studied. It is apparent that transition mismatches (G:T and A:C) and frameshift (-1) deletion mismatches are the most frequent polymerase errors and are also those best corrected. Transversion mismatches (in particular, G:A, C:T and C:C) are repaired depending on the neighbouring nucleotide sequence. It is concluded that mismatched base pairs can exist in two conformations: intrahelical (like G:T and A:C) and extrahelical (like some transversion mismatches and base insertion frameshift mismatches). Only intrahelical mismatches appear to be well recognized and repaired by the *Escherichia coli* methyl-directed mismatch repair system encoded by the *mut H*, *mut L*, *mut S* and *mut U* genes. Extrahelical bases were detected by specific anti-base antibodies (provided by Dr Marc Leng, Orléans, France), and S1-endonuclease by nuclear magnetic resonance or the bromoacetaldehyde reaction.

(*i*) *Workshop on the use of established cell lines for screening environmental carcinogens* (Dr H. Yamasaki; in collaboration Dr T. Kakunaga, National Cancer Institute, Bethesda, MD, USA)

A Working Group was convened to discuss molecular and cellular mechanisms of cell transformation, the biological similarity between in-vitro cell transformation and in-vivo carcinogenesis, and the feasibility of screening environmental carcinogens using in-vitro transformation assays of established cell lines. The Working Group devoted particular attention to the methodological and technical problems associated with the use of two established cell lines, BALB/c 3T3 and C3H 10T½, prepared guidelines for practical procedures in the performance of these in-vitro assays and developed standard methods for scoring morphologically transformed foci.

The proceedings of the Workshop will be published[35].

5. ROLE OF CYTOGENETIC ANOMALIES IN THE ETIOLOGY OF HUMAN CANCER

Studies of Burkitt's lymphoma (BL) have indicated that the Epstein-Barr virus (EBV) cannot be considered the sole cause of the disease. At the cellular level, chromosomal rearrangements—also detected in EBV-free BL tumours—are suspected to play a critical role in the malignant process. Over the last few years, a large part of our activity has been devoted to studying the biological significance of these chromosomal anomalies. Most of the studies were carried out on BL and on another childhood cancer, Ewing's sarcoma.

(*a*) *Cell cultures of Burkitt-type lymphoma* (Dr G. Lenoir, Dr V. Gurtsevitch, Mrs M. Vuillaume and Mrs S. Pauly; in collaboration with Dr I. Philip, Léon Bérard Centre, Lyon, France)

The majority of Burkitt-type lymphomas can be cultivated *in vitro* as continous lymphomatous cell lines, independent of the presence of the EBV genome. Moreover, normal 'non-malignant' human lymphocytes, which can be used as controls, can also be cultivated continuously *in vitro*, once they have been immortalized by EBV. Taking advantage of these two facts, a large panel of lymphoma cells and lymphoblastoid cell lines has been established at the Agency. A total of 90 BL lines were established, including 33 EBV-negative BL lines, originating from cases in Europe (mainly France), North Africa and Central Africa. This is the largest collection of malignant BL lymphoma lines presently available. The cells are being used in collaborative studies to analyse their phenotypes, genotypes and cytogenetic characteristics (see below).

Using monoclonal antibodies that recognize B-cell differentiation antigens, an attempt was made to classify the tumour lines according to their degree of maturation[36], and to correlate the phenotype of cells with the grographic origin of the patient, the presence of EBV, and the type of chromosomal translocation[37]. Tumorigenicity assays are also under way.

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[35] Kakunaga, T. & Yamasaki, H., eds (1984) *IARC Scientific Publications*, Lyon (in preparation)
[36] Favrot, M. C., Philip, I., Philip, T., Dore, J. F. & Lenoir, G. M. (1984) *Lancet*, **i**, 745–746
[37] Cohen, J. *et al.* (1984) *J. Immunol.* (submitted for publication)

To this end, 18 BL cell lines and 10 lymphoblastoid cell lines (LCL)—recently established from peripheral lymphocytes or bone-marrow cells of the same BL patients—were tested for tumorigenicity in 4-5-week-old nude mice of Swiss genetic background. One to two days before inoculation of the cells, whole -body irradiation was carried out with a dose of 450 rads. Four mice were used to evaluate the tumorigenicity of one cell line: four increasing doses of cells, ranging from 1.6×10^6 to 25×10^6, were injected under the skin of both flanks of each mouse; the mice were examined every day up to eight weeks and the size of the tumours at the injection site measured. The BL cell lines tested showed varying degrees of tumorigenicity, which were classified as high, intermediate, low and no tumorigenicity. An unexpected finding was that all 10 LCL analysed were also able to produce tumours, although most of them regressed and the latent period was usually longer than that with BL cell lines.

(*b*) *Cytogenetic investigations on lymphoid cells* (Mrs E. Mark-Vendel; in collaboration with Dr R. Berger, Institute for Research on Blood Disorders, Paris; and Dr J. Fraisse, Blood Transfusion Centre, St Etienne, France, DEC/83/09)

Initial studies indicated that in Europe and central Africa BL cells always carry one of the following translocations; t(8;14), t(8;22) or t(2;8)[38]. We extended this observation recently to cases originating from North Africa[39] (see Table 22). As in other parts of the world, all three types of translocation are observed, and all BL cases are found to have one of these anomalies.

The chromosomal anomalies involving chromosome 8 and either chromosome 2, 14 or 22 can therefore be considered characteristic features of BL, independent of the geographic origin of the patient, EBV association, or clinical presentation. A recent study indicated that additional

Table 22. Chromosomal translocations and surface immunoglobulins (Sig) in 13 Algerian Burkitt's lymphoma patients

Patient No.	Corresponding cell line (IARC/BL)	Sex/Age (years)	Sig	Translocation
1	6	M/4	μλ	t(8;14)
2	7	M/9	μκ	t(2;8)
3	8	M/3	μλ	t(8;14)
4	18	M/3	μλ	t(8;14)
5	35	M/5	μκ	t(8;14)
6	36	F/54	μκ	t(8;14)
7	52	M/4	μλ	t(8;14)
8	60	F/4	μλ	t(8;22)
9	61	M/4	μκ	t(2;8)
10	62	M/4	μκ	t(8;14)
11	65	F/3	μλ	t(8;14)
12	72	M/11	μλ	t(8;14)
13	73	M/3	μκ	t(8;14)

[a] Complex three-way translocation

[38] Bernheim, A., Berger, R. & Lenoir, G. (1981) *Cancer Genet. Cytogenet.*, 3, 307–315
[39] Mark-Vendel, E., Philip, T., Ladjaj, Y., Aboulola, M. & Lenoir, G. M. (1983) *Lancet*, ii, 788

chromosomal changes, especially those involving the long arm of chromosome 1, are also observed at a relatively high frequency[40].

(*c*) *Significance of chromosomal anomalies at the molecular level* (Dr G. Lenoir; in collaboration with Dr P. Leder, Harvard Medical School, Boston, MA, USA; Dr G. Bornkamm, Institute of Virology, Hygiene Centre, Freiburg, FRG; and Dr C. Croce, Wistar Institute, Philadelphia, PA, USA)

Chromosomes 14, 2 and 22 have been shown recently to carry genes for immunoglobulin heavy chains and for light chains kappa and lambda, respectively. Our study on the correlation between Ig light chain expression and variant translocation in BL[41] strongly suggests that malignant transformation may result from transposition of a segment of chromosome 8 (8q24) to an active region of an Ig-locus-carrying chromosome. This situation is very similar to that observed in mouse plasmacytoma and suggests that BL can be used as a human model for studying the role of genetic transposition in carcinogenesis.

The initial study, performed in Dr Leder's laboratory, indicated that the segment of chromosome 8 involved in the translocation carries a cellular oncogene designated as 'myc'[42]. In most BL cell lines,this gene is rearranged following the translocation.

The rearrangements of the oncogenes are not due to prolonged in-vitro cultivation of the malignant cells. As indicated in Figure 10, the gene rearrangements are observed in cell lines as well as in the initial tumour samples. In the t(8;14) translocation, the *myc* oncogene moves from chromosome 8 to the Ig (H) locus on chromosome 14[43]. However, in the variant translocations, *myc* remains on chromosome 8, and lambda or kappa genes are translocated from chromosome 22 or 2 to chromosome 8[44–46].

The molecular significance of these rearrangements has been the subject of extensive studies by several groups during the last months, and a review was published recently[47]. The studies suggest that subtle alteration of the expression of the translocated c-*myc* is characterized by a shift in promoter utilization and an apparent insensitivity to the regulation that inactivates the normal c-*myc* allele within the same cells[48]. The coding region of the translocated c-*myc* is unchanged, but somatic mutations that may be important in the deregulation process are observed in putative control regions[43, 48]. The collection of BL cell lines established at the Agency laboratory has a critical role in the various studies carried out by the collaborating laboratories in the etiopathogenesis of BL.

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[40] Bernheim, A., Berger, R. & Lenoir, G. (1983) *Cancer Genet. Cytogenet.*, **8**, 223–229

[41] Lenoir, G. M., Preud'homme, J. L., Bernheim, A. & Berger, R. (1982) *Nature*, **298**, 474–476

[42] Taub, R., Kirsch, I., Morton, C., Lenoir, G., Swan, D., Tronick, S., Aaronson, S. & Leder, P. (1982) *Proc. natl Acad. Sci. USA*, **79**, 7837–7841

[43] Battey, J., Moulding, C., Taub, R., Murphy, W., Stewart, T., Potter, H., Lenoir, G. & Leder, P. (1983) *Cell*, **34**, 779–787

[44] Hollis, G. F., Mitchell, K. F., Battey, J., Potter, H., Taub, R., Lenoir, G. M. & Leder, P. (1984) *Nature*, **307**, 752–755

[45] Croce, C. M., Thierfelder, W., Erikson, J., Nishikura, K., Finan, J., Lenoir, G. M. & Nowell, P. C. (1983) *Proc. natl Acad. Sci. USA*, **80**, 6922–6926

[46] Erikson, J., Nishikura, K., Ar-Rushdi, A., Finan, J., Emanuel, B., Lenoir, G., Nowell, P. C. & Croce, C. M. (1983) *Proc. natl Acad. Sci. USA*, **80**, 7581–7585

[47] Leder, P., Battey, J., Lenoir, G., Moulding, C., Murphy, W., Potter, H., Stewart, T. & Taub, R. (1983) *Science*, **222**, 765–771

[48] Taub, R., Moulding, C., Battey, J., Murphy, W., Vasicek, T., Lenoir, G. M. & Leder, P. (1984) *Cell*, **36**, 339–348

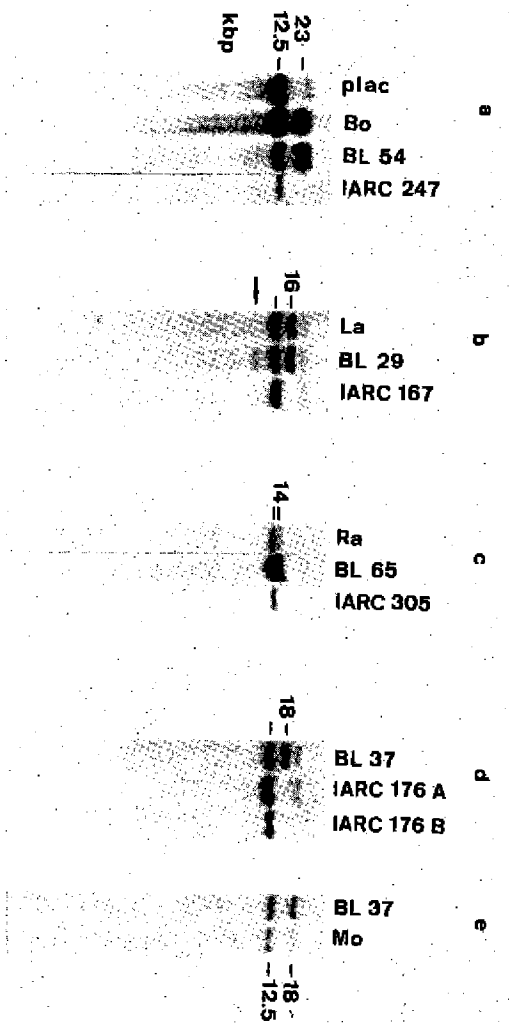

Fig. 10. Autoradiogram of nitrocellulose filters containing EcoRI digested DNAs of different origin after hybridization with a ^{32}P-labelled probe of the cloned second human c-*myc* exon (1.5 kb SacI). The DNAs originated from tumour biopsies, tumour cell lines (BL) and EBV-immortalized lymphoblastoid cell lines (IARC) from four patients (a, b, c and d-e). The DNA of the biopsy and tumour line from the fourth patient were compared on a separate gel (e). Human placental DNA served as control in (a). The arrow points to the faint additional band observed in BL 29.

(*d*) *Chromosomal studies on Ewing's sarcoma cells* (Dr J. M. Bechet and Dr G. Lenoir; in collaboration with Dr C. Turc, CHU Faculty of Medicine, Dijon, France; Dr T. Philip, Centre Léon Bérard, Lyon, France; and Dr G. Bornkamm, Institute of Virology, Hygiene Centre, Freiburg, FRG)

In order to investigate whether genetic transposition occurs in conditions other than haematopoietic disorders, in which several specific chromosome translocations have been observed, other childhood malignancies have been studied. Several cell lines from Ewing's sarcomas have

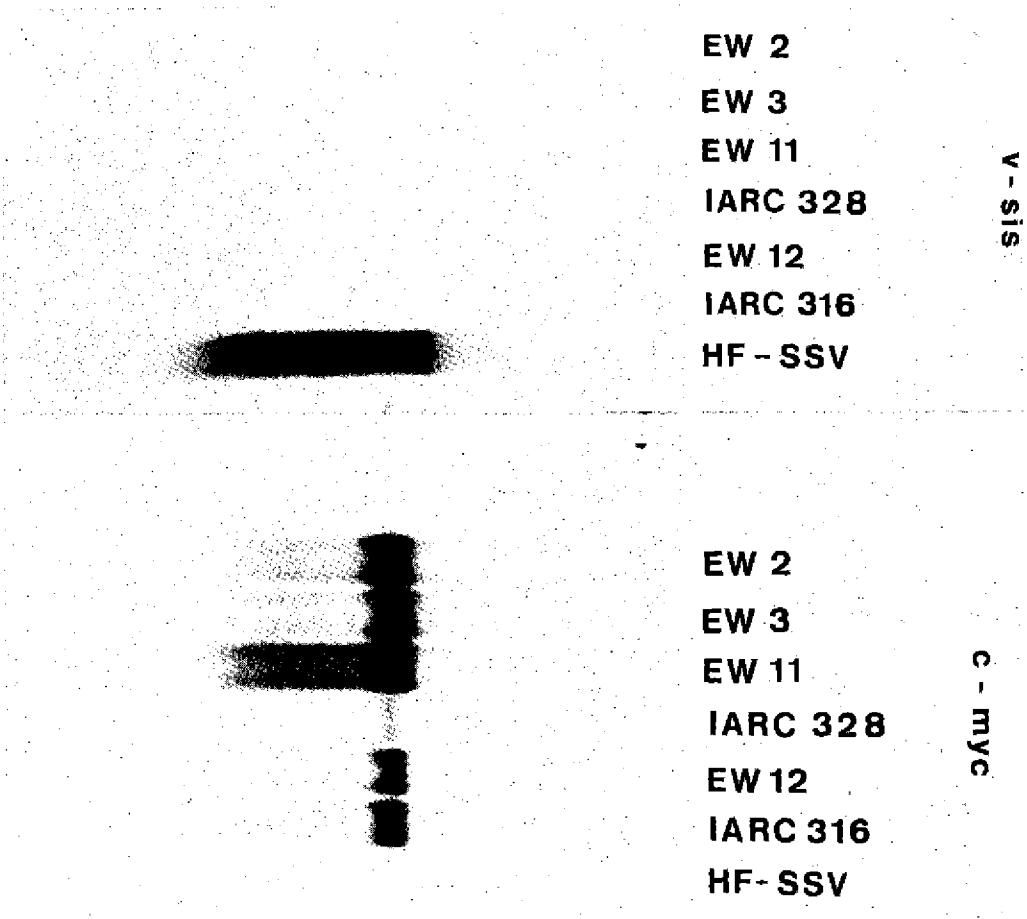

Fig. 11. Northern blot analysis polyadenylated RNA from Ewing's sarcoma cell lines. The blots were probed with ^{32}P-labelled v-*sis* DNA (left) and c-*myc* DNA (right). IARC/EW cell lines 2, 3, 7 and 11 have been described previously[49]. IARC/EW 12 is a recently established Ewing's sarcoma cell line. IARC/EW 7 was analysed in a separate experiment (not shown), with similar results. IARC/328 and 316 are lymphoblastoid cell lines established from the same patients as IARC/EW 11 and 12, respectively. HF-SSV (provided by K. von der Helm) is a marmoset cell line transformed by simian sarcoma virus that was included as a positive control for *sis* expression.

been established successfully in culture, and a translocation t(11;22) (q24;q12) appears to be a characteristic feature of the malignant cells[49,50]. Similar translocations have been observed in fresh tumour material by other workers[51].

In an investigation of the significance of these translocations, molecular studies were performed to evaluate whether the c-*sis* oncogene which normally resides on chromosome 22 (q24), is activated following the translocation. Studies by Northern blot analysis inicate that this gene is not activated in Ewing's sarcoma[52] (Fig. 11).

(*e*) *Relationship between karyotypic pattern of cancer cells and etiological factors* (Dr F. Mitelman, Department of Clinical Genetics, University of Lund, Sweden; DEC/78/13)

Detailed karyotypic data on chromosomal aberrations, as identified by banding techniques, have been collected systematically as a registry since 1980. The material has been amassed from three main sources: published cases ascertained from three computer-based literature scans, unpublished cases from the laboratory of Dr Mitelman and unpublished cases communicated by numerous colleagues all over the world. By 1980, the complexity of the information prompted adoption of computer methods for assembling, revising and indexing.

A total of more than 5000 cases is now contained in the registry. A catalogue presenting detailed karyotypic data for 3844 cases with chromosomal abnormalities has been published[53]. The computerized data are coded for a number of parameters:

- detailed morphological diagnosis, tumour site, clinical state and survival:
- karyotype, type of tissue studied, technique used for chromosome preparation and time of culture;
- mode of ascertainment, i.e., whether or not the case belongs to an unselected consecutive series of patients studied in a laboratory;
- age, sex, ethnic group and geographic region;
- previous neoplasm: morphological diagnosis, topography and type of treatment;
- hereditary disorder, including constitutional chromosomal aberrations in the patient or in relatives;
- obvious environmental or occupational exposure to potential mutagenic or carcinogenic agents.

This information can easily be retrieved and used for scientific purposes. Active workers in the field may, upon request, obtain information directly from Dr Mitelman.

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[49] Turc-Carel, C., Philip, I., Berger, M. P., Philip, T. & Lenoir G. M. (1983) *New Engl. J. Med.*, **30**, 496–498
[50] Turc-Carel, C., Philip, I., Berger, M. P., Philip, T. & Lenoir, G. M. (1984) *Cancer Genet. Cytogenet.*, **12**, 1–19
[51] Aurias, A., Rimbaut, C., Buffe, D., Dubousset, J. & Mazabraud, A. (1983) *New Engl. J. Med.*, **309**, 496
[52] Bechet, J. M., Bornkamm, G., Freese, U. K. & Lenoir, G. M. (1984) *New Engl. J. Med.*, **310**, 393
[53] Mitelman, F. (1983) *Cytogenet. Cell Genet.*, **36**, 1–515

6. PERINATAL CARCINOGENESIS

(*a*) *Tumour induction in multigeneration studies* (Dr A. Likhachev, Dr R. Becker, Dr. J. R. P. Cabral, Dr L. Tomatis and Mrs D. Galendo; in collaboration with Dr N. P. Napalkov, N. N. Petrov Research Institute of Oncology, Leningrad, USSR, DEC/81/33; and Dr B. N. Hemsworth, Life Science Laboratory, Teeside Polytechnic, Cleveland, UK, DEC/82/01)

Experiments designed to study the possibility that exposure of female rats to *N*-ethyl-*N*-nitrosourea during pregnancy results in an increased cancer risk for successive generations have now been completed.

Investigations have been initiated to study the effect of postnatal application of various modifying factors on carcinogenesis in two successive generations of rats and mice exposed transplacentally to different carcinogens. Skin applications of 12-*O*-tetradecanoylphorbol 13-acetate to the F1 and F2 descendants of female mice exposed to 7,12-dimethylbenz[*a*]anthracene during gestation resulted in the appearance of skin tumours. Administration of *N*-methyl-*N*-acteoxymethylnitrosamine to pregnant rats was followed by a low level of DNA methylation in various foetal tissues; offspring developed some malignant tumours[54]. In most F1 and F2 descendants exposed further to thyroidectomy or methylthiouracil, tumours developed in the thyroid and some other organs. Persistent oestrus induced postnatally in F1 and F2 rats exposed to 7,12-dimethylbenz[*a*]anthracene or *N*-methyl-*N*-nitrosourea during embryogenesis resulted in an increase in the carcinogenic effect of those agents.

Treatment of male rats with *N*-ethyl-*N*-nitrosourea before mating resulted in the appearance of neurogenic tumours in the progeny. An expanded study is in progress in which tumour appearance is being studied in the offspring of male rats and mice treated with *N*-ethyl- or *N*-methyl-*N*-nitrosourea and mated subsequently.

A further study is being made of a possible carcinogenic effect of the thymidine analogue 5-bromodeoxyuridine (BUdR), which produces miscoding and mutagenic effects and persists in the DNA of various rat tissues over long periods. BUdR is being given to pregnant rats, and then to their offspring during the neonatal period. Since previous experiments had shown that BUdR induces kidney lesions and ethyl methane sulphonate produces kidney tumours, combined administration of the two compounds is also being investigated. BUdR was further administered repeatedly to rats during the neonatal period, and the animals were then exposed either to monolateral nephrectomy (males) or to persistent oestrus induced by subcutaneous implantation of the ovary into the tail following bilateral ovariectomy.

Studies are currently underway to assess the potential carcinogenicity of products derived from the combustion of opium (see p. 41). In one study, morphine pyrolysate in arachis oil is being given by gavage to female BDVI rats on the 15th-19th days of pregnancy at a dose of 10 mg/kg bw.

(*b*) *Possible role of prezygotic events* (Dr R. Becker, Dr J. R. P. Cabral and Dr L. Tomatis)

Treatment of male rats before mating with *N*-ethyl-*N*-nitrosourea during periods corresponding to post-spermatogonial stages of gamete development resulted in an increased incidence

[54] Likhachev, A. J. (1984) In: Reznik-Schüller, H., ed., *Perinatal Carcinogenesis*, Boca Raton, FL, CRC Press (in press)

of neurogenic tumours in the progeny[55]. This study is being extended to determine if a similar response is produced in the progeny when the treatment-mating interval is lengthened to encompass *N*-ethyl-*N*-nitrosourea-induced heritable alterations in spermatogonia.

Covalent modification of spermatogenic cell DNA by alkylating mutagens and carcinogens such as *N*-ethyl-*N*-nitrosourea and subsequent repair, if any, of such DNA lesions, particularly *O*-alkylated base adducts, may be related to the increased incidence of nervous system tumurs seen in the progeny obtained from matings two weeks after *N*-ethyl-*N*-nitrosourea treatment of male rats[55]. Accordingly, studies are in progress to determine whether alkylation of spermatogenic cell DNA is comparable in nature and extent to that found is somatic cell DNA following treatment with *N*-ethyl-*N*-nitrosourea. DNA repair enzyme activities will be measured *in vitro* with cell-free extracts and alkylated DNA substrates. With such a system, O^6-alkylguanine DNA alkyltransferase activity has been measured in extracts from whole rat testes and single spermatogenic-cell suspensions. Fractionation of mixed single spermatogenic-cell suspensions by centrifugal elutriation, to obtain purified populations of spermatogonia, pachytene spermatocytes, early spermatids and late spermatids is being investigated. Preliminary results, utilizing extracts from fractions enriched in pachytene spermatocytes (>90% pure), early spermatids (about 60% pure) and late spermatids (about 50% pure), suggest that O^6-alkylguanine DNA alkyltransferase activity may be related to germ-cell maturation.

It has been suggested that the increase in tumour incidence in animals descended from parents exposed to mutagens prior to mating is a consequence of transmission of a cancer-predisposing genotype to the progeny. This hypothesis can be tested by comparison of relevant enzymes, such as those which might limit the carcinogenic response in descendants of mutagen-treated males and in progeny from untreated animals. Such a study is in progress, in which O^6-methylguanine-DNA-methyltransferase activity in various tissues from controls and descendants of male rats treated with *N*-ethyl-*N*-nitrosourea two weeks prior to mating will be determined. Alternatively, utilization of such molecular biological techniques as DNA transfection may prove to be a more direct means of testing this hypothesis.

7. MEETING ON AGE-RELATED FACTORS IN CARCINOGENESIS (Dr A. Likhachev and Dr. R. Montesano; in collaboration with Dr V. Anisimov and Dr N. P. Napalkov, N. N. Petrov Research Institute of Oncology, Leningrad, USSR)

A meeting was organized by the Agency and the N. N. Petrov Research Institute of Oncology, Leningrad, USSR and was held on 7–9 December 1983 in Leningrad. Various experimental and epidemiological aspects of the relation between carcinogenesis and ageing were discussed. In particular, papers were presented on the role of DNA repair, metabolism, immunological and hormonal balance in the process of carcinogenesis and ageing, and the participants were exposed to widely different schools of thought. The meeting was attented by more than 20 participants from the USSR, Europe, Japan and the USA. The proceedings are in press[56].

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[55] Tomatis, L., Cabral, J. R. P., Likhachev, A. & Ponomarkov, V. I. (1981) *Int. J. Cancer*, **28**, 475–478

[56] Likhachev, A., Anisimov, V. & Montesano, R., eds (1984) *Age-related Factors in Carcinogenesis* (*IARC Scientific Publications* No. 58), Lyon, International Agency for Research on Cancer (in press)

III. DATA COLLECTION AND RESEARCH METHODS

1. IMPROVEMENT OF EPIDEMIOLOGICAL DATA COLLECTION

(a) *Cancer registries* (Dr C. S. Muir)

Continued collaboration with cancer registries is essential for the success of the Descriptive Epidemiology Programme. Work has started on the fifth volume of the *Cancer Incidence in Five Continents* series (see p. 21), and the survey of malignant melanoma continues (see p. 61). Increasing problems of confidentiality have reinforced efforts to elaborate a code of practice for confidentiality in cancer registries (see below).

(i) *International Association of Cancer Registries* (Dr C. S. Muir, Miss S. Whelan and Mrs A. Romanoff; in collaboration with Professor Pelayo Correa, Louisiana Tumor Registry, New Orleans, LA, USA; DEB/73/16)

The Agency continues to provide a Secretariat to the Association, now comprising 162 members. Regular newsletters inform members about

- developments in cancer registration throughout the world,
- projects and meetings arising from the Association's status as a non-governmental organization in relation with WHO,
- other meetings of interest, and
- relevant literature, including abstracts of annual reports and other registry publications.

A scientific meeting of the Association was held in Heidelberg, FRG, in September 1983 and was opened by Dr H. Geissler, Federal Minister of Health. The theme of the meeting was 'Benefits of Cancer Registration to the Cancer Patient and Society', and the programme included presentations on the detection of industrial cancer risk, screening programmes and the relevance of cancer registration to the cancer patient of the future, as well as a wide range of proferred papers dealing with various aspects of registration. The participants from 19 countries were welcomed by the German Cancer Research Centre (Director, Professor H. zur Hausen), which acted as host to the meeting. Professor G. Wagner of the Institute of Information, Documentation and Statistics acted as local organizer.

The next meeting of the Association will take place in September 1984 in Fukuoka, Japan, with the assistance of a local organizing committee headed by Dr T. Shigematsu of the School of Medicine, Fukuoka University. The programme includes consideration of the role of cancer registries in cancer control programmes in five different countries, their role in etiological research and current registry problems and solutions to those problems.

The President of the Association has nominated Dr T. Mack (Los Angeles County Cancer Surveillance Program, USA) as the association representative on the Editorial Board for Volume V of *Cancer Incidence in Five Continents.*

(ii) *Cancer registration in romance-language countries* (Dr A. Tuyns, Dr J. Estève and Mrs J. Nectoux; in collaboration with Mr L. Raymond, Geneva Tumour Registry, Switzerland; and Dr E. Benhamou, Gustave Roussy Institute, Villejuif, France)

A meeting was held on Ascension Day and the day after in Madrid, at the Ministry of Health, at the invitation of Dr C. Martinez Garcia. The opening lecture, given by Dr Najera Morrondo, was on 'The epidemiological approach to the cancer problem'. Several other papers were given that illustrated the increasing activities of the members of the group in analytical epidemiology: e.g., on bladder cancer in Turin and Geneva, and on breast cancer in Spain and in Milan. Descriptive analyses of cancer incidence and various comparisons between registries were also reported. Several new registries presented their first results. The conference was closed by Professor L. Massé from Rennes. A report of the meeting will be prepared by the Agency, as in previous years, and will be available before the next meeting, which will be held in Portugal on Ascension Day 1985.

The group also showed an increasing interest in methodological problems, and a second meeting on statistical concepts in descriptive epidemiology was held at the Agency on 4–5 November 1983 to discuss the draft of a publication on that subject. This manual will include discussion of the statistical analysis of incidence rates, time trends, and survival; its intended audience will be both epidemiologists and statisticians working in cancer registries.

(iii) *Confidentiality in cancer registries* (Dr C. S. Muir and Mrs E. Démaret)

Following a survey of the legal basis of cancer registration[1], it became evident that many cancer registries would like to have an internationally accepted code of registry practice in relation to confidentiality. A working party was established in 1983 to plan an approach to the problem, comprising, in addition to Dr Muir and Mrs Démaret, Dr J. T. P. Bonte, Central Bureau of Statistics, Voorburg, The Netherlands; Dr T. Hakulinen, Finnish Cancer Registry, Helsinki; Dr W. Hunter, Commission of the European Communities, Luxembourg; and Miss G. Pinet, Health Legislation Unit of the European Regional Office of WHO, Copenhagen.

Having determined the scope of such a code, the working party approached Dr E. Pukkala of the Finnish Cancer Registry to prepare a draft. This was used at a meeting held in Lyon on 5–7 June 1984 as the basis for a draft code of practice, which has now been sent to the members of the International Association of Cancer Registries for comment before wider circulation through WHO and EEC channels.

In its current state, the draft code includes a statement on the aims of confidentiality, recognizing that a balance has to be struck between the right of privacy of an individual and his right, and that of his fellow citizens, to benefit from the knowledge of cancer causation, prevention and treatment that derives from cancer registration. The principles for the preservation of data confidentiality are stated, guidelines for the use and release of registry data proposed and a series of specific measures that may be employed to preserve confidentiality listed.

[1] IARC (1982) *IARC intern. tech. Rep. 82/003*, Lyon

(iv) *Role of the registry in cancer control* (Dr D. M. Parkin and Dr C. S. Muir; in collaboration with Dr G. Wagner, German Cancer Research Center, Heidelberg, FRG)

Following the 1983 annual meeting of the International Association of Cancer Registries, which had as its theme 'the benefits of cancer registration of the cancer patient and society'[2], it was agreed that it would be of value to publish a monograph illustrating the various ways in which data provided by cancer registries can be used in planning and evaluation of cancer control. A publication with contributions from Agency staff members and specialists experienced in these aspects of registration will appear in 1984.

(*b*) *Computers and cancer registration*

(*i*) *A microcomputer system for cancer registries* (Dr D. M. Parkin and Mr M. Smans)

Development of the software for a system of cancer registration was continued with the appointment of Mr P. Delfosse as consultant for five months in 1983–1984. A complete set of programmes has been written, using the computing language BASIC, and the system has been field-tested at the Cancer Center in Casablanca, Morocco. A description of the system (CANREG) is available[3]. A microcomputer has been purchased, with an operating system that permits a considerable extension of CANREG, and work is in progress to modify the existing programmes.

(ii) *Directory of computer resources for cancer registries* (Dr D. M. Parkin, Mrs E. Démaret, Dr C. S. Muir and Mr M. Smans; in collaboration with Mr H. R. Menck, University of Southern California, Department of Family and Preventive Medicine, Los Angeles, CA, USA)

A working group met in Lyon in June 1984 to discuss a proposal to produce a publication listing the computer software in use in cancer registries throughout the world, and publications concerning cancer registration methodology. In addition to those mentioned above, the working group comprised Dr P. Crosignani (National Institute for the Study and Treatment of Tumours, Milan, Italy) and Mr R. Skeet (South Thames Cancer Registry, UK). The need for such a publication was agreed upon, and it was decided that it should be in the form of a directory, to be updated regularly. It was agreed to produce the first volume in this series, under the principal editorship of Mr Menck, as a joint IARC/International Association of Cancer Registries (see p. 105) publication. The content and format were defined, and a questionnaire for eliciting information from contributing centres designed. Publication is projected for 1985.

(*c*) *Classification and nomenclature: standardization*

It is essential that classifications and nomenclatures change to incorporate new concepts, otherwise they fall into disuse. Those formulating classifications for international application must, however, steer a rather conservative course, as many proposed classification schemes do not

[2] IARC (1983) *Annual Report 1983*, Lyon, p. 98
[3] Parkin, D. M., Delfosse, P., Smans, M. & Muir, C. S. (1984) *IARC intern. tech. Rep. 84/001*, Lyon

stand the test of time. The section on lymphatic and haematopoietic neoplasms of the ICD-O needs revision, and preliminary discussions on appropriate methods have taken place.

(i) *Tenth Revision of the International Classification of Diseases* (Dr C. S. Muir)

Several far-reaching proposals for changes in the structure of the *International Classification of Diseases* have been mooted, which are designed to increase the number of rubrics available. Cancers that have hitherto been allotted rubrics 140–234 may be assigned C00-C99 and possibly a further 100 rubrics, D00-D99. When a definitive proposal has been made by the DES Unit of the Division of Health Statistics of WHO Headquarters, it will be circulated to cancer registries for comment.

(ii) *Multiple tumours* (Dr C. S. Muir)

Multiple malignant primary tumours may occur in one individual at the same or at different times. They may occur at the same or different sites, and any of the foregoing combinations may be of the same or different histological type. There is, however, no clear and general agreement on which grounds these cancers, the frequency of which is growing, should be denoted either as single neoplasms or separate primaries. Part of the current confusion results from a desire to deal with separate facets of the question by application of one set of rules to cover all situations, whether these pertain to calculation of incidence or survival, clinical patient care or etiological research.

While recognizing that the determination of whether two (or more) tumours in an individual are primary cancers is a medical problem, a cancer registry frequently has to decide. In order that such decisions be made in a uniform manner, a series of definitions and rules has been formulated. These are rather conservative and would tend to reduce, for the purposes of the calculation of incidence rates, the frequency with which such neoplasms are recognized. There is still debate on whether to count two malignant tumours of different histology originating in the same primary site twice (e.g., basal-cell and squamous-cell carcinoma of skin) and on how to count cancers in each breast.

Dr J. Staszewski, lately at the Gliwice Cancer Registry, Poland, has analysed replies received from 38 cancer registries following circulation of a series of proposed definitions and rules. On the basis of these responses a further series of proposals were made, which, in turn, elicited comments from 29 registries. Following circulation of the latest version of the proposed rules, cancer registries contributing their data to Volume VI of *Cancer Incidence in Five Continents* will be asked to use these rules to enhance comparability.

The cancer registration system in England and Wales uses the National Health Service register to 'flag' registered cases of cancer as a means of passive follow-up (to identify deaths and, hence, calculate survival). It is therefore possible to identify live individuals registered with two (or more) cancers. Pilot studies suggest that 61% of these represent true multiple primary malignancies (rather than duplicate registrations, etc.). The incidence of second tumours in relation to site of primary cancer, patient characteristics, etc. can thus be studied. A Research Agreement (DEB/83/24) has been established with the London School of Hygiene and Tropical Medicine (Principal investigator: Dr M. Coleman) to permit this study to be undertaken.

(*d*) *Mapping of cancer* (Mr M. Smans and Dr C. S. Muir)

Several atlases showing cancer distribution are being prepared as part of the programme for the presentation of geographic differences in cancer (see p. 21).

(i) *Mortality atlas*

Work on the mortality atlas for the countries of the European Economic Community (EEC) continues. Data at the level of departments, counties or equivalent have now been received from Belgium, Denmark, England and Wales, France, Italy, Northern Ireland, Luxembourg, The Netherlands and Scotland, and descriptive supporting material has been received from three of these countries. Due to data protection laws, the FRG has found it difficult to supply information at the level of the *kreis* (county) but can probably do so for the 31 *bezirk*. It is hoped to receive this material soon so that mapping can begin.

Following preparation of maps for selected commoner cancers, contributors will meet in Lyon to discuss interpretation and further analyses.

(ii) *Incidence atlases*

Scotland: Two draft atlases comprising over 300 maps, 50 in colour, have been produced on the Agency's computer graphics system and discussed with the Scottish Cancer Registries (Coordinator: Dr I. Kemp, Scottish Information Services Division, Edinburgh). The supporting descriptive text has been revised and draft comments on the pattern of distribution prepared.

German Democratic Republic: Agreement has now been reached with Professor S. Tanneberger (Akademie der Wissenschaften der GDR, Berlin-Buch) and Dr W. H. Mehnert (National Cancer Institute, Academy of Sciences of the GDR, Berlin-Johannisthal) on the collaborative production of a cancer incidence atlas for the German Democratic Republic. A map, by *kreis* (county), has been prepared for lung and breast cancers. These have been sent to Berlin for comment, pending receipt of the data for 1975–1979. Once these have been entered and verified, procedures similar to those used for the Scottish cancer atlas will be followed.

Other countries: Dr W. Zatonski (Institute of Oncology, Warsaw) has expressed interest in collaborative production of an updated cancer mortality atlas for Poland[4].

Professor E. Marubini and Dr C. Cislaghi (Institute of Biometry and Medical Statistics, Milan, Italy) have had preliminary discussions at the Agency with a view to collaborating in the preparation of a cancer mortality atlas for Italy, including recent data and portraying geographical differences within Italy in time trends.

(iii) *Data presentation and interpretation*

Theoretical work has been undertaken that led to the choice of a seven-class colour scale for the presentation of rates on maps. These pass from green to red through yellow: a relatively 'natural' colour scale suggesting, like traffic lights, a gradation from safety to danger. This solution will, however, pose problems for people who are red-green colour blind. When examining a map, particularly for sites with a low incidence, it may be difficult to decide by inscription whether a pattern is random or not. Statistical work is thus being undertaken with a view to proposing a measure of clustering for such maps.

(*e*) *Cancer incidence in migrants to Israel* (Dr D. M. Parkin and Miss O. Bouvy; in collaboration with Dr R. Steinitz and Dr L. Katz, Israel Center for Registration of Cancer and Allied Diseases, Jerusalem, Israel, DEB/83/19; and Dr J. Young, National Cancer Institute, Bethesda, MD, USA)

[4] Staszewski, J. (1979) *Regional Differences in Cancer Mortality in 1970–1974 in Poland*

The aim of this segment of the Descriptive Epidemiology Programme is to publish work that illustrates the uses of descriptive epidemiology in cancer, either in the generation of etiological hypotheses or in the planning and evaluation of cancer control measures.

The Israel Cancer Registry records the place of birth of all cases registered since 1960, and, for immigrants to Israel, the year of immigration. The Israel Bureau of Statistics publishes annual estimates of population by county of origin and by continent of origin; estimates are also provided by period of migration. It is thus possible to calculate incidence rates of different cancers in migrants from several countries or regions, and to examine how these rates vary with duration of residence in Israel. It is proposed to examine rates based on registrations in the period 1960–1979. These registrations are being checked against the population register of Israel to complete missing data on country of origin and period of migration. The data will be published as a monograph, in which comparisons are made of incidence rates between different migrant groups and between migrants to Israel and people in the country of origin. Incidence in relation to duration of residence in Israel will be presented, either as incidence rates or as proportional registration ratios.

(f) *Clearing-house for on-going research in cancer epidemiology* (Dr C. S. Muir, Mrs A. Nagy-Tiborcz, Mrs E. Démaret and Dr D. M Parkin; in collaboration with Professor G. Wagner and Mr K. Schlaefer, German Cancer Research Centre, Heidelberg, FRG, DEB/74/03) (Partially supported by Contract No. NO1-CO-55195 with the National Cancer Institute, USA)

The clearing-house for on-going research in cancer epidemiology was created in 1974 by the Agency and the German Cancer Research Centre, Heidelberg, FRG, and operates with partial support from the International Cancer Research Data Bank Program of the National Cancer Institute of the USA. Eight annual directories have now been published. Although the content has more than doubled since 1976, the *Directory* now seems to be tending to a 'steady-state', in that the number of new projects initiated more or less equals the number completed or abandoned. The 1984 *Directory* contains information on 1213 studies reported from 61 countries.

While there is no change in the order of the number of reports by country—USA and UK continuing to contribute most of the projects, followed by Japan and Canada—the increasing participation of other parts of the worlds is welcomed. For example, the 1984 *Directory* includes over 20 current research projects from the People's Republic of China. Another country increasing its contribution is The Netherlands. The most frequently studied cancer sites are lung, female breast, cervix uteri and liver, followed by stomach, leukaemia and childhood cancers. It is remarkable that there has been no change in the distribution of sites under study since the inception of the clearing-house.

The clearing-house *Directory* provides a separate index of chemicals to facilitate identification of studies of human chemical exposures. Since the introduction of this index in 1978, some 220 chemicals and chemical compounds have been notified as being studied. The 1984 *Directory* adds a further ten compounds. The occupational index, created in 1981, has increased continously, and in 1984 15 new occupations were added to the 130 already included. Emerging areas of interest in recent years have been, *inter alia*, protective effects of dietary items such as vitamins A and C, retinol-containing foods and fibre, and the relationship between psychological factors and cancer. Contrary to what might have been expected in view of the current emphasis on promotion in experimental carcinogenesis, few epidemiological studies were reported on this topic. The need to

incorporate new key-words may point to new areas of interest: among those added in 1984 were haemophilia, transuranic elements, fat, fruit/vegetables and protection. 'Data resource' is another increasingly used term.

The material in the clearing-house is widely used and is incorporated in the CANCERPROJ and RPROJ data bases of the International Cancer Research Data Bank Program of the USA.

2. DEVELOPMENT OF STATISTICAL METHODOLOGY

(a) *Dissemination of statistical methods for cancer research*

(i) *Analysis of Cohort Studies* (Dr N. E. Day, in collaboration with Professor N. E. Breslow, University of Washington, Seattle, WA, USA)

The planned contents were described last year[5]. Progress has continued, and the monograph should be completed by the end of 1984.

(ii) *Design and Analysis of Long-term Animal Experiments* (Dr J. Wahrendorf; in collaboration with Dr J. J. Gart and Dr R. E. Tarone, National Cancer Institute, Bethesda, MD, USA; Dr D. Krewski, Health and Welfare, Ottawa; and Mr P. N. Lee, London)

Preparation of this monograph progressed throughout the year. Meetings were held in June 1983 and April 1984 to review the manuscript, which is now undergoing final editing.

(b) *Development of statistical methodology*

(i) *Statistical methods for epidemiological studies* (Dr N. E. Day, Dr J. Wahrendorf, Dr J. M. Kaldor and Miss M. Blettner; in collaboration with Professor N. E. Breslow, University of Washington, Seattle, WA, USA; Dr C. C. Brown, National Cancer Institute, Bethesda, MD, USA; Dr D. Clayton, University of Leicester, UK; Dr L. Edler, Deutsches Krebsforschungszentrum, Heidelberg, FRG; Mr P. Smith, London School of Hygiene and Tropical Medicine, London; and Dr A. Tzonou, Universityof Athens)

Attention this year has focussed on the effects of errors in the measurement of exposure on interferences drawn from analytical epidemiological studies. Apart from leading to underestimation of the true level of risk, such misclassification can lead to an inability to control properly for confounding variables, an incorrect shape of dose-response curves[6], and a distortion of the interaction between two or more exposure variables. The extent to which these effects are produced by misclassification is being examined quantitatively. In addition, ways are being examined by which modification of study design may help to overcome these biases.

(ii) *Statistical methods for carcinogenicity studies* (Dr J. Wahrendorf)

An approach to analysing two-exposure carcinogenicity experiments has been developed for cases in which the context of observation has been recorded for the tumour of interest and in which

[5] IARC (1983) *Annual Report 1983*, Lyon, p. 104
[6] Blettner, M. & Wahrendorf, J. (1984) *Meth. Inform. Med.*, **23**, 37–40

intercurrent mortality has been adjusted for. This approach was used to analyse a study with plutonium oxide and benzo[*a*]pyrene, for which it could be shown that the joint effect is described by a multiplicative model[7].

Analysis of data from a study of 24 192 female BALB/c mice treated with 2-acetylaminofluorene at various dose levels and examined after several scheduled sacrifices has been started, to investigate the association among tumour types.

(iii) *Statistical aspects of mutagenicity experiments* (Dr J. Wahrendorf; in collaboration with Dr G. A. T. Mahon, European Economic Community, Brussels; and Dr M. Schumacher, University of Dortmund, FRG)

Non-parametric methods for the analysis of data from Ames tests have been developed further by computing simple statistical tables that allow assessment of the statistical significance of the experimental results after only elementary calculations[8].

A review of statistical issues in mutagenicity experiments, including significance testing and estimation of effect, has been initiated in order to make better quantitative evaluations of the results.

(*c*) *Quantitative cancer risk estimation* (Dr J. Kaldor and Dr N. E. Day; with the financial support of the European Economic Community)

Quantitative cancer risk estimation is the process whereby epidemiological and, possibly, laboratory data are combined to provide an estimate of the increase in cancer risk produced by exposure to a carcinogen. Epidemiological data are rarely adequate for risk estimation, mainly because of the lack of study populations exposed sufficiently long ago, or of sufficient size for an elevated risk to be detectable. Even when epidemiological data on an exposure are available, risk estimation is complicated by the need to model accurately the effect on risk of low exposure levels, and temporal factors such as age at exposure and elapsed time since exposure.

A review of the published literature on human carcinogens (as determined in *Supplement 4* to the *IARC Monographs*) revealed that, in general, while the available epidemiological data clearly indicate the carcinogenic effect of the compounds or exposures studied, reasonable data on dose are usually unavailable. An interim report was prepared[9], summarizing relevant literature for three of these exposures.

For a few human exposures, namely to tobacco, alcohol, radiation and asbestos (of which only asbestos has been considered in the *IARC Monographs* series), relatively good dose information is available. A review has been prepared[10], which summarizes the findings with regard to dose-response produced by these agents. Calculations have also been made to show the size of risk that could be detected in an epidemiological study, and the consequences of an interpolation strategy which allows for the possibility of linearity at low doses, when in fact the dose-response is flat at low doses[11].

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[7] Metivier, H., Wahrendorf, J. & Massé, R. (1984) *Br. J. Cancer* (in press)
[8] Wahrendorf, J., Mahon, G. A. T. & Schumacher, M. (1984) (submitted for publication)
[9] Report to EEC, Internal Report
[10] Day, N. E. (1984) In: Krewski, D., ed., *Toxicological Risk Assessment*, New York, CRC Press (in press)
[11] Kaldor, J. M. & Day, N. E. (1984) In: *Risk Quantitation and Regulatory Policy* (*Banbury Report*), Cold Spring Harbor, NY, Cold Spring Harbor Laboratory (in press)

In some epidemiological studies, the excess number of cancer cases observed is large enough to permit comparison of various models of risk, even though no exposure measurements are available. Workers in a South Wales nickel refinery, who have been studied previously[12], experienced a mortality rate for lung cancer five times higher than national rates, and 56 nasal cancer deaths were observed when less than one was expected. These data have been reanalysed, and it was found that quite different models were appropriate for the two cancers[13].

When no human studies are available, risk estimations must be made on the basis of animal carcinogenicity bioassays or even of in-vitro test systems. Work is continuing on the analysis of short-term test data and on the quantitative relationship between carcinogenicity and mutagenicity[14].

(*d*) *Evaluation of early detection programmes*

(*i*) *Theoretical developments* (Dr N. E. Day; in collaboration with Dr A. Sasco and Professor S. D. Walter, McMaster University, Hamilton, Ontario, Canada)

The usefulness of the case-control approach to the evaluation of screening programmes is being increasingly recognized[15, 16]. The appropriate case-control design, however, depends on the nature of the screening test, whether it is aimed primarily at precancerous lesions or at early cancer. A paper has been submitted for publication describing the alternative approach[16].

Case-control results can be used not only to assess the degree of protection afforded by the test, but also to estimate natural history parameters. The statistical methods required for this approach are being developed.

(*ii*) *Screening for cancer of the cervix*

(1) *Estimation of natural history parameters* (Dr N. E. Day, Dr D. M. Parkin, Ms S. Moss and Mrs A. Arslan; in collaboration with Professor N. W. Choi, Manitoba Cancer Treatment and Research Foundation, Canada; Dr E. A. Clarke, Ontario Cancer Treatment and Research Foundation, Toronto, Canada; Dr J. D. F. Habbema, Department of Public Health and Social Medicine, Erasmus University, Rotterdam, The Netherlands; Dr M. Hakama, The Finnish Cancer Registry, Helsinki; Dr J. E. Macgregor, Department of Pathology, University of Aberdeen, Scotland, UK; Dr K. Magnus, Norwegian Cancer Registry, Oslo; Dr B. Malker, Swedish Cancer Registry, The National Board of Health and Welfare, Stockholm; Dr O. Møller-Jensen, Danish Cancer Registry, Copenhagen; Dr F. Petterson, Department of Pathology, Radiumhemmet, Stockholm; Dr P. Poll, Pathology Department, Central Hospital, Nykøbing F., Denmark; Dr P. Prorok, Biometry Branch, National Cancer Institute, Bethesda, MD, USA; Mr L. Raymond, Geneva Tumour Registry, Switzerland; Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik)

[12] Doll, R., Morgan, L. G. & Speizer, F. E. (1970) *Br. J. Cancer*, **24**, 623–632
[13] Kaldor, J. M., Peto, J., Day, N. E., Doll, R., Herman, C. & Morgan, L. (1984) (submitted for publication)
[14] McCann, J., Horn, L. & Kaldor, J. M. (1984) *Mutat. Res.*, **134**, 1–47
[15] Morrison, A. S. (1982) *Am. J. Epidemiol.*, **115**, 6–8
[16] Weiss, N. S. (1983) *Am. J. Epidemiol.*, **118**, 457–460

A meeting was held in Copenhagen in November 1983, supported in part by the Danish Cancer Registry and the European Office of WHO, at which the majority of centres participating in the study reported their results. Work in the remaining centres is almost complete. It is intended to present a summary of the complete material at a meeting to be held in Lyon, convened jointly by the UICC and the IARC, in November 1984. The full results will be published subsequently as an Agency Scientific Publication.

A case-control approach is proving useful for the summary and unified presentation of results, even when a cohort approach was initially adopted. Some results from Aberdeen (Table 23) indicate that, in a high-quality programme, screening for cervical cancer produces few false negatives and that the duration of the pre-invasive state (carcinoma *in situ* or dysplasia) is seldom less than five years. There is, unfortunately, considerable variation among the centres, suggesting that the quality of screening rather than the natural history of the disease may be the determining factor in a programme's effectiveness.

Table 23. Screening history of cases of cervical cancer diagnosed at screening compared to matched controls (Aberdeen series)

	No previous negative	Months since last negative smear						
		0–11	12–23	24–35	36–47	48–71	72–119	120+
All cases	48	0	1	1	5	14	5	6
Controls	67	15	57	36	50	139	19	17
Rel. protection	1.0		76.4	33.7	13.1	11.4	5.0	2.7
Cases in stages IA/B only	26	0	1	3	11	4	4	
Controls	41	10	35	28	24	90	14	8
Rel. protection	1.0		35.1	19.0	8.4	5.9	3.2	1.6

(2) *Computer simulation of cervical cytology screening*

A computer model has been developed that is designed to simulate demographic events, natural disease history and screening activity in a 'realistic' population over a time period of 30 years. The model uses a micro-simulation approach, so that individual life histories and screening histories can be made dependent upon past events. These approaches provide many advantages over previously reported models, which examine the theoretical results of screening activity only in single birth cohorts, or which place restraints upon the parameters of natural history (e.g., distribution of sojourn times in preclinically detectable states) that can be incorporated. The model is able to examine complex screening policies that involve both examinations at fixed ages and/or intervals, and also 'individual' tests (e.g., during pregnancy, gynaecological examination or at family planning attendance).

The impacts of different policies that have been recommended for screening the population of England and Wales are being studied, using natural history parameters derived as described above[17].

[17] Colette, B., Rombach, J. J., Day, N. E. & de Waard, F. (1984) *Lancet*, i, 1224–1226

(iii) *Breast cancer screening* (Dr N. E. Day; in collaboration with Dr B. J. A. Collette, Preventicon, Utrecht, The Netherlands; Professor F. de Waard, National Institute of Public Health, Bilthoven, The Netherlands; Dr A. Verbeek, Nijmegen University, The Netherlands; Dr L. Tabar, Falun Hospital, Mammography Department, Falun, Sweden; Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik; and Dr S. D. Walter, McMaster University, Hamilton, Ontario, Canada)

(1) *Case-control studies* were carried out in Utrecht and Nijmegen to evaluate the effect of breast cancer screening on subsequent breast cancer mortality. The results have been published[17,18]. In Utrecht, screening involved both mammography and physical examination and was aimed at women over 50 years of age[19]. The relative risk of dying from breast cancer among screened women was 0.31 (95% confidence limits, 0.13–0.70). In Nijmegen, screening was limited to single-view mammography and included women from 35 to 65 years of age. The corresponding relative risk was 0.48 (0.23–1.00).

(2) *Natural history.* A comparison of the results from Utrecht with those from the original study in New York (the HIP study) indicates that in Utrecht, using more modern mammography techniques, the sensitivity was higher and the duration of the detectable pre-clinical phase longer. These data were presented at a UICC meeting in Venice in November 1983. A joint analysis is planned of the screening results from the two programmes in The Netherlands and the programme in Kopperberg. The latter is a randomized study.

(3) *Implications for national screening policies.* In conjunction with the Icelandic Ministry of Health, a meeeting was convened in Reykjavik, 11–12 April 1984, to review the most recent evidence on the effectiveness of breast cancer screening, in order to assist the Icelandic authorities in determining what emphasis to place on breast cancer screening in their population-based early detection programme. Participants in the meeting were: Dr S. Bjornsson, Icelandic Cancer Society, Reykjavik; Dr A. Brekkan, National Hospital, Reykjavik, Dr J. Chamberlain, Royal Marsden Hospital, Sutton, Surrey, UK; Dr B. Collette and Dr F. de Waard, Preventicon, Utrecht, The Netherlands; Dr N. E. Day, IARC; Dr G. Geirsson, Early Detection Programme, Reykjavik; Dr A. Grimsson, Ministry of Health, Reykjavik; Mr G. Hall, Ministry of Finance, Reykjavik; Dr R. Kristjansdottir, Icelandic Cancer Registry, Reykjavik; Dr S. S. Magnusson, National Hospital, Reykjavik; Professor A. B. Miller, National Cancer Institute, Toronto, Ontario, Canada; Dr O. Olafsson, Director, Medical Service, Reykjavik; Dr B. Sigfusson, Mälmo, Sweden; Dr K. Sigurdsson, Early Detection Programme, Reykjavik; Dr P. Sugurdsson, Ministry of Health, Reykjavik; Dr H. Sigvaldason, Icelandic Cancer Registry, Reykjavik; Dr G. Snaedal, Icelandic Cancer Society, Reykjavik; Dr L. Tabar, Falun Hospital, Mammography Department, Falun, Sweden; Dr M. S. Tzechkovski, WHO, Geneva; Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik.

A summary of the proceedings and recommendations are being prepared for publication.

(*e*) *Development of statistical data bases in cancer epidemiology*

(i) *International study to evaluate risks of radiation exposure in cervical cancer patients* (Dr R. Saracci, Dr G. Engholm, Dr N. E. Day, Miss M. Blettner and Miss D. Mag-

[18] Verbeek, A. L. M., Holland, R., Sturmans, F., Hendriks, J. H. C. L., Mravunac, M. & Day, N. E. (1984) *Lancet*, i, 1222–1224

[19] de Waard, F., Collette, H. J. A., Rombach, J. J., Baanders-van Halewijn, E. A. & Honing, C. (1984) *J. chron. Dis.*, 37, 1–44

nin; in collaboration with Dr P. Fraser and Mr M. Coleman, London School of Hygiene and Tropical Medicine, London, DEB/81/27; Dr O. Møller-Jensen and Dr H. H. Storm, Danish Cancer Registry, Copenhagen, DEB/81/18; Dr M. Hakama and Dr R. A. Rimpelä, Finnish Cancer Registry, Helsinki, DEB/81/29; Dr K. E. Kjørstad, Norwegian Radium Hospital and Norwegian Cancer Society, Oslo, DEB/81/30, DEB/83/04; Dr F. Pettersson, Karolinska Hospital, Stockholm and Dr B. Malker, Swedish Cancer Registry, Stockholm, DEB/81/31; Dr V. Pompe-Kirn, Cancer Registry of Slovenia, Institute of Oncology, Ljubljana, Yugoslavia, DEB/81/36; Dr A. B. Miller, National Cancer Institute of Canada, Toronto, Canada, DEB/82/03; Dr F. Berrino, National Institute for the Study and Therapy of Tumours, Milan, Italy, DEB/82/04; Dr R. Frischkorn, University Women's Clinic, Göttingen, FRG, DEB/82/05; Dr Z. Hlasivec and Dr V. Kubec, Institute of Radiotherapy, Oncological Centre, Prague, DEB/82/07; Professor D. von Fournier, University Women's Clinic, Heidelberg, FRG, DEB/82/08; Professor H. Lochmüller, University Women's Clinic, Munich, FRG, DEB/82/09; Dr E. A. Clarke, Ontario Cancer Treatment and Research Foundation, Toronto, Canada, DEB/82/11; Dr H. Kucera, Clinic of Gynaecology, University of Vienna, DEB/82/12; Professor N. W. Choi, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Canada, DEB/82/13; Dr K. Sigurdsson and Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik, DEB/83/03; Dr J. D. Boice, National Cancer Institute, Bethesda, MD, USA; Mr P. Smith, London School of Hygiene and Tropical Medicine. Supported by contract NOI-CP-11017 with the US National Cancer Institute)

The purpose of this study is to examine risks associated with exposure to low and moderate doses of ionizing radiation. Previous annual reports have described the study, which is an extension of an international study of the incidence of leukaemia following radiotherapy for cervical cancer. A large number of clinics in Europe and the USA participated in the leukaemia study, which was sponsored by the WHO. The study is carried out as follows:

(1) *Cohort study in cancer registries.* Fifteen cancer registries enrolled a total of some 180 000 cervical cancer patients in this study. The incidence of second primaries in enrolled cohorts has been compared for each site with the incidence of primary cancer in the general population. Analyses have been made by stage of cervical cancer (invasive *versus* in-situ) and treatment (irradiated or non-irradiated). The results of the study have been published in an IARC Scientific Publication[20].

(2) *Case-control studies in cancer registries and clinics.* In the cohort study, no details on whether radiotherapy was given to enrolled patients were available and only a crude classification of patients as irradiated or non-irradiated could be made. In order to describe dose relationships, case-control studies will be carried out in which radiotherapy given to each selected patient will be described in detail. A Dosimetry Committee, under Dr M. Stovall at the M. D. Anderson Hospital and Tumor Institute in Houston, Texas, USA, is currently developing methods for estimation of radiation dose to various organs on the basis of detailed patient-specific information. The cohort

[20] Day, N. E. & Boice, J. D., Jr, eds (1984) *Second Cancer in Relation to Radiation Treatment for Cervical Cancer (IARC Scientific Publications* No. 52), Lyon, International Agency for Research on Cancer

study in registries provided the frame from which to select cases and controls in registries. It also provided the basis for decisions on what second primaries to include in the case-control studies. In clinics, the follow-up carried out in the original leukaemia study has been extended close to present time. A few registries have enrolled new patient cohorts, thus considerably extending the clinic contribution. Cases have been selected from the enrolled cohorts as patients who had developed second primary cancers that met certain criteria of site and time. For each case, two controls have been selected (four for leukaemia cases) matched for year of and age at diagnosis of the cervical cancer among patients with a survival time at least as long as that of the case. The total number of cases included from centres participating in the European segment of the study is estimated to be 3000. Several centres have completed the abstraction of hospital records for selected patients, and all centres are expected to have completed data collection by the beginning of 1985.

(ii) *Second malignancies following chemotherapy for cancer* (Dr N. E. Day and Dr J. M. Kaldor; in collaboration with Dr J. Cuzick, Imperial Cancer Research Fund, London; Dr W. H. Mehnert, Cancer Registry of the German Democratic Republic, Berlin-Buch; and Dr R. Simard and Dr P. Ghadirian, Cancer Institute of Montreal, Québec, Canada)

It has been well established that chemotherapeutic agents, like radiotherapy, can induce leukaemia and possibly other tumours in treated patients. While this is obviously an undesirable outcome, it represents one of the few situations in which human exposure to carcinogenic agents can be quantified accurately.

A collaborative group, including many participants in the Agency cervical cancer radiation study, as well as representatives of other cancer registries and treatment centres in Europe, was established to pursue the study of second tumours following chemotherapy. An initial meeting was held in January 1983, at which it was agreed that the registries would tabulate observed and expected numbers of second primary tumours, following cancers of the ovary and testes and Hodgkin's disease, malignancies for which chemotherapy is widely used. A progress meeting was held in March 1984, at which some preliminary results were presented and discussed.

As expected, a number of registries (Denmark, Sweden, Norway and South Thames) reported a large excess of leukaemia in patients diagnosed with the designated first primaries (a total of 144 observed, as compared to 50.6 expected, among the four registries one year or more after diagnosis of the first primary). Excesses of solid tumours were also seen, including second primary cancers of the bladder and lung. Some of the treatment centres also reported increased numbers of leukaemia and other cancers in treated patients.

It thus appears from these initial results that registry material is sensitive enough to detect an excess cancer risk in cancer patients. In order to relate this risk directly to the administration of chemotherapy, it is necessary to abstract detailed information in order to compare the type and dose of chemical agents employed between cases diagnosed with a second primary tumour and controls diagnosed only with the same first primary as cases. A protocol and hospital record abstraction sheet for this case-control study phase is currently being prepared, and should be available by the end of 1984.

One of the participating registries (the German Democratic Republic) has already embarked on a case-control study of leukaemia as a second primary tumour following ovarian cancer. Preliminary results suggest that the relative risk of leukaemia associated with cyclophosphamide treatment is at least 20 fold.

(iii) *Feasibility of conducting a cancer epidemiology study within the framework of a cardiovascular disease project* (Dr J. Wahrendorf)

A project entitled 'Multinational Monitoring of Trends and Determinants in Cardiovascular Disease' (MONICA) is being developed at WHO Headquarters, Geneva. Part of the project, in which some 30 countries are participating, is the conduct of standardized population-based surveys on the prevalence of certain risk factors such as smoking, serum cholesterol and, more generally, dietary habits. The feasibility is being investigated of following up individuals in some areas for subsequent cancer experience through cancer registries. A multinational, population-based, prospective cohort study of this type could investigate life-style-related etiological hypotheses of cancer. Centres that are conducting their surveys in areas covered by cancer registries have been approached as to the nature of their dietary investigations: depending on local circumstances and the purpose of the investigation, a variety of methods are used to assess dietary habits. Steps were taken to ensure comparability of quantitative dietary information between centres, which would be essential for combining all surveyed populations into one cohort. Thus, a food frequency questionnaire, similar for all centres, has been proposed as a complement to 24-h recalls and three- or seven-day records. The possible size of the cohort has been estimated, and the expected numbers of cancers at major sites calculated for different durations of follow-up. A phase-by-phase development of the study is considered which would ensure thorough control of the quality of the data as well as the inclusion of several intermediate objectives, such as correlation studies of dietary habits with cancer incidence.

(iv) *Integration of clinical and epidemiological research* (Dr J. Wahrendorf and Dr A. Walker)

A great deal of the information collected on patients in clinical trials for the treatment of cancer can also be of relevance to elucidating the etiology of the disease. A critical appraisal of this aspect has been prepared, exploring clinical parameters of particular interest, outlining possible epidemiological investigation and defining logistic requirements[21].

Table 24. Sample size requirements

Correlation between true value and the measure obtained	Case-control study with one control per case (No. of cases)	Cohort study	
		Cohort size	Expected no. of cases
1.0	430	2496	100
0.9	584	3422	137
0.8	758	4466	179
0.7	1011	5984	239
0.6	1401	8321	333
0.5	2046	12192	488

[21] Wahrendorf, J. & Walker, A. M. (1984) (submitted for publication)

(*f*) *Effects of misclassification in categorical response* (Dr A. Walker and Miss M. Blettner)

Misclassification of the extent of exposure to an agent under study is a recurrent problem in epidemiological research. We have studied the extent of misclassification when individuals are sorted into ordered categories by an imperfect measure, and we have calculated the increase in study size required to counterbalance the loss of accuracy. For a typical situation (five levels of exposure; average risk, 4%; three-fold risk gradient; alpha level, 5%; power, 95%), the increasing size of studies required when the exposure measure used has less than perfect correlation with the true level of exposure are as shown in Table 24.

3. METHODS FOR DETECTING CARCINOGENS

(*a*) *Short-term tests for the detection of carcinogens/mutagens* (M. C. Malaveille and Mrs G. Brun)

New *Salmonella typhimurium* tester strains TA102 and TA104, developed by Dr B. Ames, have been shown to detect as mutagens a number of carcinogens that were not previously detected with the standard tester strains. To evaluate further the relevance of the new strains, various carcinogens (diethylstilboestrol, thiourea, 1,4-dioxane, safrole, urethane, thioacetamide, hexamethlyphosphoramide and aminotriazole), which are non-mutagenic in *Salmonella*/microsome and *Salmonella*/rat hepatocyte assays[22], using standard tester strains, were assayed. Experiments were performed using plate incorporation and liquid incubation assays in the presence and absence of a metabolic activation system. Diethylstilboestrol, safrole and hexamethylphosphoramide appeared weakly mutagenic only in TA104 in the presence of a metabolic activation system, in a liquid incubation assay. Weak direct mutagenicity was induced in TA104 and TA102 by 1,4-dioxane when tested in a plate incorporation assay. All the other compounds tested were found to be devoid of mutagenic activity. In view of the weak mutagenic response observed, however, additional experiments will be performed in order to assay the value of these new tester strains.

(*b*) *Endogenous formation and detection of carcinogens*

(i) *Studies on* N-*nitrosation catalysis by bacteria* (Miss S. Calmels, Mr H. Ohshima and Dr H. Bartsch; in collaboration with Professor A. Gounot, Université Claude Bernard, Lyon, France; Professor P. Vincent, Hôpital Croix Rousse, Lyon, France; Professor H. Leclerc, INSERM, Villeneuve d'Ascq, France; and Dr K. Suzuki and Dr T. Mitsuoka, Institute of Physical and Chemical Research, Saitama, Japan)

Since bacterial catalysis of endogenous nitrosation has been suggested to play an important role in the etiology of certain human cancers, such as cancer of the stomach[23] and urinary bladder[24], studies on the microbial formation of *N*-nitroso compounds were initiated in 1983 in our labo-

[22] IARC (1983) *Annual Report 1983*, Lyon, p. 111
[23] Correa, P., Haenszel, W., Cuello, C., Tannenbaum, S. & Archer, M. (1975) *Lancet*, **ii**, 58–59
[24] Hawksworth, G. M. & Hill, M. J. (1971) *Br. J. Cancer*, **25**, 520–526

ratory. A total of 35 strains of various bacteria and one strain of *Candida*, isolated by Professor Vincent from human trachea, urine, blood and faeces, were examined for their ability to form *N*-nitrosomorpholine from morpholine and nitrite at neutral pH; 25 bacterial strains exhibited nitrosation activity, including 18 out of 19 *Escherichia coli* and three out of eight *Pseudomonas aeruginosa, Proteus morganii, Proteus mirabilis, Klebsiella pneumoniae* and *Neisseria* strains.

Kinetic studies were conducted with resting cells of *E. coli* A 10 (provided by Drs Suzuki and Mitsuoka[25]). The formation of *N*-nitrosomorpholine was optimal at pH 7.25 and was proportional to the incubation time and to the number of cells, and the reaction followed Michaelis-Menten kinetics. Substrate specificity for several amines is shown in Table 25. No catalytic effect was

Table 25. Substrate specificity for nitrosation of several amines catalysed by *Escherichia coli* A 10[a]

Amine	pk[a]	Yield of nitrosamine (nmol/ml per mg protein per hour)	
Pyrrolidine	11.27	1.6	(1)[b]
Piperidine	11.2	1.4	(0.9)
Dimethylamine	10.72	5.0	(3.2)
N-Methylbenzylamine	9.54	14.0	(9)
L-Proline	–	3.2	(2)
Morpholine	8.7	154.2	(100)
Aminopyrine	5.04	17.0	(11)

[a] Reactions were carried out in a medium containing 0.1 mol/L Tris-HCl buffer, pH 7.2, 25 mmol/l amine, 25 mmol/l sodium nitrite and 1 ml of intact cell suspension (10 mg as protein per ml) of *E. coli* A 10 in a total volume of 5 ml at 37°C for 1 h.
[b] % yield of the notrosamine relative to that of *N*-nitrosomorpholine

observed when boiled, acid- or alkaline-treated cells were used. These results[26] indicate that nitrosation is catalysed either by a bacterial enzyme(s) or by some unstable metabolic product *via* a non-enzymic reaction. Attempts to characterize this catalytic process in *E. coli* are in progress. In addition, bacterial strains isolated and identified in gastric juice samples from patients with chronic atrophic gastritis and in urine samples from subjects with urinary bladder infections are being tested for their ability to catalyse nitrosation.

(ii) *Identification of new* N-*nitroso compounds in human urine and their formation* (Mr H. Ohshima, Dr I. K. O'Neill, Dr M. Friesen, Mr J. C. Béréziat and Miss M. C. Bourgade)

We reported previously the occurrence in human urine of new sulfur-containing *N*-nitrosamino acids—*N*-nitrosothiazolidine 4-carboxylic acid (NTCA) and *trans*- and *cis*- isomers of

[25] Suzuki, K. & Mitsuoka, T. (1984) In: O'Neill, I. K., von Borstel, R. C., Miller, C. T., Long, J. E. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)
[26] Calmels, S. (1984) *Rapport de stage pour le D. E. A., Université Claude Bernard, Lyon et l'Ecole Nationale Vétérinaire, July 1984*

N-nitroso-2-methylthiazolidine 4-carboxylic acid (NMTCA)[27,28]. These *N*-nitrosamino acids have been detected in many human urine samples collected in the People's Republic of China, Finland, France, Italy and Japan; however, their origin is currently unknown. Because the amount of *N*-nitroso compounds formed in the human body *in vivo* or during the storage of foodstuffs may depend partly on the chemistry and kinetics of *N*-nitrosation, we studied the formation of this new type of *N*-nitrosamino acid analogue *in vitro* and in rats *in vivo*.

NTCA and NMTCA were readily formed *in vitro* following nitrosation at acidic pH of the respective precursor, thiazolidine 4-carboxylic acid (TCA) or of 2-methylthiazolidine 4-carboxylic acid (MTCA). As the latter compounds can be formed by reaction of L-cysteine with formaldehyde or acetaldehyde, respectively, NTCA and NMTCA were also formed by reacting L-cysteine with the respective aldehyde and with nitrite at optimal pH (2.5 for NTCA and 4.5 for NMTCA). Up to 95% of NTCA and NMTCA given orally to fasted rats was recovered as such in urine and faeces within two days. Administration of TCA or MTCA together with nitrite increased the urinary excretion of NTCA and NMTCA, as did co-administration of L-cysteine, nitrite and the respective aldehyde.

NTCA and NMTCA were also detected in the 24-h urine of human volunteers, and smokers tended to excrete higher levels than nonsmokers. Daily excretion levels varied, however, and a diet supplemented with ascorbic acid significantly decreased the total amount of nitrosamino acids (see Fig. 3, p. 40). NTCA and NMTCA may occur in human urine as a result of (1) intake of preformed *N*-nitroso compounds; (2) intake of thiazolidine 4-carboxylic acid or its 2-methyl derivative and subsequent nitrosation *in vivo*; or (3) endogenous two-step synthesis by the reaction of L-cysteine with the respective aldehyde and a nitrosatiang agent.

Thus, measurement of NTCA and NMTCA together with NPRO in urine may provide an index for the exposure of human subjects to nitrosamines or their precursors, i.e., nitrosating agents, certain aldehyde or aldehyde-generating compounds. Our data demonstrate unequivocally that *N*-nitroso compounds are formed in the human body, as suggested previously[29,30]. Their relevance to human cancer at specific sites is now being investigated (see Table 3, p. 34).

(iii) *Synthesis and genetic activity of* N-*nitrosated amino sugars* (Dr B. Pignatelli, Mr C. Malaveille, Dr M. Friesen and Dr H. Bartsch; in collaboration with Professor G. Descotes, Dr D. Piskorska and Miss M. Touron, Claude Bernard University and College of Industrial Chemistry, Lyon, France; and Professor B. Gross and Dr N. Moll, University of Nancy, Vandoeuvre-les-Nancy, France; partly supported by the Centre National de la Recherche Scientifique (CNRS), France)

Non-enzymatic browning (Maillard) reactions occur during the heat-processing, drying, storage and cooking of various food items and contribute to the colour, flavour and aroma of many processed and cooked foods[31,32]. They consist of reactions between amino groups of amines, amino acids, peptides or proteins with 'glycosidic' hydroxyl groups of sugars. The first stage of the Maillard reaction leads to *N*-substituted glycosylamines and their subsequent rearrangement

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[27] Ohshima, H., Friesen, M., O'Neill, I. K. & Bartsch, H. (1983) *Cancer Lett.*, **20**, 183–190

[28] Oshima, H., O'Neill, I. K., Friesen, M., Pignatelli, B. & Bartsch, H. (1984) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)

[29] Druckrey, H. & Preussmann, R. (1962) *Naturwissenschaften*, **49**, 498–499

[30] Sander, J. (1967) *Arch. Hyg. Bakteriol.*, **151**, 22–28

products, 1-amino-1-deoxy-2-ketoses (amino sugars, AS). The latter compounds, present in foodstuffs, contain secondary amino groups which are potential sites for *N*-nitrosation reactions. The *N*-nitroso derivatives of D-fructose-L-trytophan have been shown to be mutagenic[33]. Because little is known about the genetic and toxicological properties of other members of this class of *N*-nitroso compound, studies on these non-volatile compounds have been initiated. The purposes of this project are (1) to synthesize several new *N*-nitrosamino sugars (NAS); (2) to investigate their chemical and biological properties; (3) to develop analytical methods for determining the presence of NAS in foodstuffs; (4) to investigate factors affecting the formation of NAS *in vitro*; and (5) to evaluate the significance of formation of NAS *in vivo*.

So far, AS have been prepared from D-glucose and *para*-toluidine, *para*-aminobenzoic acid and several commonly occurring amino acids (phenylalanine, leucine, alanine, citrulline, tryptophan). Their *N*-nitroso derivatives are being analysed (by high-performance liquid chromatography), their structures confirmed and their mutagenic activities in *Salmonella typhimurium* strains being investigated.

(iv) *Influence of catalysts and inhibitors on the formation of* N-*nitroso compounds* in vivo *and* in vitro (Dr B. Pignatelli, Mr J. C. Béréziat and Dr H. Bartsch; in collaboration with Professor G. Descotes, Claude Bernard University and College of Industrial Chemistry, Lyon, France; and Professor R. Scriban, National College of Agricultural and Food Industries, Douai, France; partly supported by the Delegation Générale à la Recherche Scientifique et Technique (DGRST), France)

(Poly)phenolic compounds (PPC) are present in the human diet mostly in the form of flavonoids, tannins and related phenolic products. The in-vitro and in-vivo formation of *N*-nitroso compounds (NOC) was shown to be catalysed or inhibited by PPC, depending on their structure, on the pH, the nature of nitrosable amino compounds and on the relative concentrations of nitrite and PPC[34–36]. Betel-nut extracts containing large amounts of PPC were shown to stimulate or reduce *N*-nitrosation *in vitro* and *in vivo* in rats, depending on the above factors[34]. Inhibitory effects of betel-nut extracts were demonstrated in humans *in vivo*[35]. *N*-Nitrosation was also inhibited by ingredients present in malt and beer *in vitro* and in rats *in vivo*[36]. The modifying effect of beer constituents on the nitrosation of proline in man is being examined (No. 16, Table 3, p. 34).

Catalysis of nitrosation *in vivo* observed in cigarette-smoking subjects was attributable to a higher level of thiocyanate in the saliva of smokers and to higher exposure to nitrosating agents like NO_x present in cigarette smoke (No. 17, Table 3). Several studies are under way to examine the excretion of nitrosated amino acids in smokers in relation to specific types of tobacco (No. 18) or with other exposure indicators, like urinary cotinine, thioethers or excreted mutagens (Nos 18 &

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[31] Eriksson, C., ed. (1981) *Progress in Food and Nutrition Science*, Vol. 5, *Maillard Reactions in Food*, Oxford, Pergamon Press

[32] Waller, G. R. & Feather, M. S., eds (1983) *The Maillard Reaction in Foods and Nutrition (ACS Symposium Series 215)*, Washington DC, American Chemical Society

[33] Röper, H., Röper, S., Heyns, K. & Meyer, B. (1982) In: Bartsch, H., O'Neill, I. K., Castegnaro, M. & Okada, M., eds, N-*Nitroso Compounds: Occurrence and Biological Effects* (*IARC Scientific Publications* No. 41), Lyon, International Agency for Research on Cancer, pp. 87–98

[34] Stich, H. F., Dunn, B. P., Pignatelli, B., Ohshima, H. & Bartsch, H. (1983) In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, N-*Nitroso Compounds: Occurrence Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications* No. 57), Lyon, International Agency for Research on Cancer (in press)

[35] Stich, H. F., Ohshima, H., Pignatelli, B., Michelon, J. & Bartsch, H. (1983) *J. natl Cancer Inst.*, **70**, 1047–1050

[36] Pignatelli, B., Scriban, R., Descotes, G. & Bartsch, H, (1984) *J. Am. Soc. Brew. Chem.*, **42**, 18–23

19, Table 3). Although the relevance of these findings to diet- or life-style-related cancers is not known, the data reveal the great impact of modifiers on exposure to endogenously-formed NOC in man.

Taken together, these data indicate that, because of the effectiveness of nitrosation catalysts and inhibitors and other modifying factors, individual monitoring will be required, rather than measuring the intake of precursors (amine and nitrite), to associate endogenous nitroso compounds with cancer at specific sites.

(v) *Development and use of micro-encapsulated trapping agents for the detection of carcinogens in the digestive tract* (Dr I. K. O'Neill and Mr A. Povey; in collaboration with Professor J. R. Nixon, Chelsea College, University of London)

The aims of this project are to develop methods to quantitate exposure to endogenous carcinogens and their precursors, and to identify hitherto unknown DNA-damaging substances that are formed or are present in the human digestive tract. The approach is to place suitable targets within semi-permeable microcapsules, to develop recovery methods, and to utilize highly sensitive detection techniques. The semi-permeable membranes prevent the passage of macromolecules such as degrading enzymes and other macromolecules but permit small molecules such as carcinogens to enter the microcapsules. Microcapsules composed of polyhexamethylenediaminophthalamide, as first developed by Koishi *et al.*[37], have been found suitable. The microcapsules are prepared by making a stable emulsion of droplets of aqueous hexamethylenediamine in a continuous organic phase, and then adding an organic solution of terephthaloyl dichloride. Extremely rapid polymerization occurs at the droplet surfaces, yielding the membranes; inclusion of suspended ferric oxide and polyethyleneimine (PEI) within the original droplets results in a suspension of magnetic microcapsules containing PEI. Many parameters that affect microcapsule size distribution, membrane strength and permeability have been studied. As a consequence, suitable microcapsules can now be obtained.

The PEI microcapsules that have been developed can pass through the gastrointestinal tract of rodents, react with radioactive- and fluorescence-labelled compounds and be recovered from faeces by magnetic retrieval. Work has been concentrated on obtaining stable microcapsules of defined properties.

(c) *Animal model systems to study etiological factors involved in oesophageal cancer* (Dr J. R. P. Cabral, Dr H. Yamasaki and Ms D. Galendo)

Several etiological factors have been reported to be possible causes of human oesophageal cancer, e.g., opium in Iran, zinc- and riboflavin-deficiency in the People's Republic of China, phorbol esters in Curaçao. We have initiated animal model systems in which such factors can be tested experimentally.

A high incidence of oesophageal cancer in Curaçao has been suggested to be linked with the use of plants[38] in which tumour-promoting phorbol esters have been detected[39]. In order to examine

[37] Koishi, M., Fukuhara, N. & Kondo, T. (1969) *Chem. Pharm. Bull.*, **7**, 804–809
[38] Morton, J. F. (1968) *Cancer Res.*, **28**, 2268–2271
[39] Weber, J. & Hecker, E. (1978) *Experientia*, **34**, 679–682

their possible promoting effect on oesophageal cancer, BD M rats were given methylbenzylnitrosamine (1 mg/kg or 2.5 mg/kg) followed by 12-*O*-tetradecanoylphorbol 13-acetate in drinking-water (0.1 ug/ml). This study is now in progress.

Zinc deficiency has been reported to increase the incidence of oesophageal tumours in rats treated with *N*-methlybenzylnitrosamine[40]. This model may be useful for testing several suspected etiological factors for oesophageal cancers. Initial experiments to confirm earlier studies on the synergistic effect are now being carried out.

(*d*) *International network of carcinogenicity testing* (Mr J. Wilbourn, Dr H. Vainio, Dr J, R. P. Cabral, Dr R. Montesano and Dr J. Wahrendorf)

Over the past several years, the Agency, in collaboration with the International Programme on Chemical Safety (IPCS), has established a network of laboratories in which chemicals are tested for carcinogenicity. The aims of this project are to select chemicals of high priority for study and to coordinate their testing within various collaborating laboratories and, to a limited extent, within the Agency's facilities. The majority of studies involve the long-term testing of chemicals for carcinogenicity in rodents, although some deal with the development and validation of new tests *in vivo*, or concern investigations of combined effects (additive, synergistic or inhibitory) of exposures to low doses of various agents, investigations of the effects of various treatment schedules, such as fractionated doses and different lengths of exposure, and studies of transplacental carcinogenesis.

Priorities for testing have been selected with the help of expert consultants, taking into account evaluations made in *IARC Monographs*, studies already under way in various national toxicology programmes or in other laboratories reporting in the IARC *Survey of Chemicals Being Tested for Carcinogenicity*, and priorities established by IPCS.

A working group met in Lyon in January 1984 to select priorities for chemicals or complex mixtures to be evaluated in future *IARC Monographs* or to be tested for carcinogenicity (see p. 46). A report of this meeting, listing 151 chemicals and complex mixtures considered to be of higher and lower priority for testing, will be circulated to laboratories undertaking long-term carcinogenicity tests.

Carcinogenicity testing, including the design of protocols, is carried out by the collaborating laboratories in accordance with guidelines given in Supplement 2 to the *IARC Monographs*[41], to ensure the quality standardization of the testing procedures. The principal investigators and the studies underway or planned in the collaborating laboratories in the network are listed in Table 26. Collaboration with participating laboratories is implemented through ad-hoc research agreements drawn up for limited periods of time covering the specific task to be performed. The selection of laboratories is under continuous review.

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[40] Fong, L. Y. Y., Sirak, A. M. & Newberne, P. M. (1978) *J. natl Cancer Inst.*, **61**, 145–150

[41] IARC (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Suppl. 2, *Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal*, Lyon

Table 26. Principal investigators and studies underway or planned in the international network of carcinogenicity testing

Börzsönyi, M. (National Institute Of Public Health, Budapest, DEC/81/35)
Long-term study on atrazine by oral administration to rats—in progress
Long-term study in rats on simazine by oral administration to rats—planned

Cabral, R. (International Agency for Research on Cancer, Lyon, France):
Pre- and post-natal exposure of rats to styrene oxide by oral administration—completed and report in preparation (Preliminary findings of an increased incidence of neoplastic lesions of the forestomach in both sexes have been reported[a])
Long-term study on deltamethrin by oral administration to mice and rats—histology in progress
Long-term study on fenvalerate by oral administration to mice—histology in progress

Griciute, L. (Oncological Institute of the Ministry of Health of the Lithuanian SSR, Vilnius, Lithuania, USSR, DEC/81/09):
Long-term study on benzo[*a*]pyrene, ethylene oxide and styrene, alone or in various combinations, by oral administration to mice—in progress

Holmberg, B. (National Board of Occupational Safety and Health, Solna, Sweden, DEC/84/01):
Long-term study on ethanol by oral administration in isocalorific liquid diets to rats—prechronic study in progress

Kung-Võsamäe, A. (Institute of Experimental and Clinical Medicine of the Ministry of Health of Estonian SSR, Tallinn, Estonia, USSR, DEC/81/08):
Long-term study on Estonian shale oil fly ash by intratracheal administration to rats—completed
Modifying effects on benzo[*a*]pyrene carcinogenesis—in progress

Roberfroid, M. (Unit of Toxicological Biochemistry, Catholic University, Brussels, DEC/82/06):
Study of diazepam and oxazepam in the rat liver two-stage model for capacity to induce preneoplastic lesions—results being analysed

Rossi, L. (Institute of Oncology, University of Genoa, Genoa, Italy, DEC/80/13):
Long-term study on chloramphenicol by oral administration to mice—completed and report in preparation (Preliminary findings have been reported[b])
Transplacental exposure study on diazepam in mice—in progress
Long-term study on fenvalerate by oral administration to hamsters—planned

Turusov, V. (Oncological Research Centre, Moscow, DEC/81/34):
Effects of fractionated doses and varying dosage schedules on 1,2-dimethylhydrazine carcinogenicity in mice—in progress

van der Heijden, C.A. (National Institute for Public Health, Bilthoven, The Netherlands):
Long-term study on bis (tri-*n*-butyltin) oxide by oral administration to rats—histopathology in progress

[a] Ponomarkov, V. Cabral, J.R.P., Wehrendorf, J. & Galendo, D. (1983) *Toxicologist, 3,* 46
[b] Sanguineti, M., Rossi, L., Ognio, E. & Santi, L. (1983) In: *1° Riunione Nazionale di Oncologia Sperimentale e Clinica, Parma, 23-25 November 1983*

(*e*) *Immunological and biochemical techniques for detecting exposure to carcinogens* (in collaboration with the International Programme of Chemical Safety, WHO, Geneva)

(i) *Development of immunoassays for monitoring exposure to aflatoxin B_1* (Miss B. Chapot and Dr R. Montesano; in collaboration with Dr R. C. Garner, Cancer Research Unit, University of York, Heslington, York, UK, DEC/83/10; supported in part by the Ministry of Health, France)

A polyclonal rabbit antibody preparation against aflatoxin B_1 (AFB_1), produced by immunization with a bovine serum albumin-AFB_1 conjugate, has been used to develop an enzyme-linked

immunosorbent assay (ELISA)[42]. AFB_1-ovalbumin, obtained by reacting AFB_1-8,9-dichloride or -8,9-dibromide with ovalbumin, was used to coat each well of a polyvinyl 'micro-titre' dish. Rabbit antibody, diluted 1:100 000 was added to each well, left to attach for 90 min and the excess washed off with phosphate-buffered saline/Tween. Anti-rabbit IgG coupled to peroxidase was then added, left for 90 min and the excess washed away. Residual peroxidase activity was assayed using tetramethylbenzidine as substrate; the reaction was quenched at the end the 15-min incubation period with 2N sulfuric acid. Inhibitor studies to assay AFB_1 or related compounds in urine involved prior incubation of the diluted anti-AFB_1 antibody with inhibitor for 60 min at 37°C prior to being dispensed into the multi-well plates. Inhibitor studies with AFB_1 showed inhibition over a concentration range of 10^{-1} to 10^{-5} μg/ml. The minimum detectable concentration was approximately 10^{-5} μg/ml (0.032 pmol/ml). Anti-AFB_1 antibody was also inhibited by iro-AFB_1-DNA, one of the forms of AFB_1-DNA, as well as by AFB_1-guanine. Analysis of human urine samples from areas of high risk of liver cancer are in progress.

(ii) *Workshop on monitoring of aflatoxins in human body fluids and application to field studies* (Dr R. Montesano and Dr D. Umbenhauer)

The purpose of this workshop, held in Lyon, 26–27 April 1984, was to review critically current methodologies for detecting aflatoxin B_1 (AFB_1) and its metabolic by-products in biological materials and to identify field studies that might be set up to examine the link between ingestion of AFB_1 and hepatitis B virus infection in the etiopathogenesis of hepatocellular carcinoma. Particular attention was devoted to the development and use of immunoassays using antibodies against AFB_1 and its metabolites. In addition to Agency staff, the meeting was attended by Dr H. Autrup, Miljo OF Kraeft Laboratoriet, Copenhagen; Dr F. S. Chu, Food Research Institute and Department of Food Microbiology and Toxicology, University of Wisconsin, Madison, WI, USA; Dr C. Garner, Cancer Research Unit, York, UK; Dr C. Harris, National Institutes of Health, Bethesda, MD, USA; Dr G. E. Neal, Medical Research Council, Carshalton, UK; Dr K. Randerath, Baylor College of Medicine, Houston, TX, USA; Dr R. Ryder, Tufts University School of Medicine, Boston, MA, USA; Dr Tsung-Tang Sun, Cancer Institute, Beijing; Dr H. P. Van Egmond, National Institute of Public Health, Bilthoven, The Netherlands, Dr P. Sizaret, WHO, Geneva, Switzerland; and was chaired by Dr G. N. Wogan, Massachusetts Institute of Technology, Cambridge, MA, USA. The outcome of the workshop is summarized in a report[43].

(*f*) *Analysis of environmental carcinogens and analytical quality assurance*

(i) *International mycotoxin check sample programme* (Dr M. Friesen, Mrs L. Garren and Mrs M.-B. d'Arcy; supported in part by the Joint FAO/WHO Food Contamination Monitoring Programme and the Mycotoxins Working Group of the IUPAC Commission on Food Chemistry)

This continuing programme provides an opportunity for laboratories engaged in the analysis of mycotoxins in foodstuffs to compare their own analytical results with those of other laboratories

[42] Martin, C. N., Garner, R. C., Tursi, F., Garner, J. V., Whittle, H. C., Ryder, R. W., Sizaret, P. & Montesano, R. (1984) In: Berlin, A., Draper, M., Hemminki, K. & Vainio, H., eds, *Monitoring Human Exposure to Carcinogenic and Mutagenic Agents* (*IARC Scientific Publications* No. 59), Lyon, International Agency for Research on Cancer (in press)

[43] IARC Internal Technical Report (in preparation).

around the world. Participants analyse identical portions of a homogenous food sample for a given mycotoxin using the analytical method of their choice. Results are collected and evaluated statistically at the Agency before redistribution to the individual laboratories. At present, the programme, which is free of charge to participants, is carried out once each year. In the most recent study, samples of aflatoxin-contaminated maize (corn), peanuts and milk were distributed to 260 laboratories in 64 countries.

A subgroup of laboratories also participated as part of the Joint FAO/WHO Food Contamination Monitoring Programme, to help assure the quality of results generated by laboratories in the 22 countries collaborating in this effort. A programme of follow-up training and/or provision of necessary supplies and small equipment has been initiated for laboratories who desire support in maintaining the quality of their analytical results.

(ii) *Methods of analysis for carcinogens in environmental samples* (Dr M. Castegnaro; in collaboration with Dr C. L. Walters, British Food Manufacturers Industries Research Association, Leatherhead, UK; and Dr R. Massey, Ministry of Agriculture, Fisheries and Food, Food Science Laboratory, Norwich, UK)

A small study, involving the Agency and the two above-mentioned laboratories, to evaluate results obtained by the revised method[44] of analysis of total *N*-nitroso compounds has been organized. When satisfactory results are obtained, the study will be subjected to collaborative testing.

(iii) *Manuals of selected methods of analysis of environmental carcinogens* (Dr I. K. O'Neill, Mrs B. Dodet and Dr H. Bartsch; in collaboration with Dr L. Fishbein, National Center for Toxicological Research, Jefferson, AR, USA; supported by UNEP Contract No. FP/1017-79-02 (2070))

This series of manuals provides selected methods for the sampling and the analysis of carcinogens (known or suspected) in the environment, with the aim of improving measurements of exposure.

The Editorial Board (Table 27) met for the ninth time to consider priorities for future volumes, and a further review was held in January 1984. The Editorial Board confirmed the need to publicize this series further, for two reasons: (1) to obtain feed-back from experts while volumes are in preparation; (2) to increase the impact of the manuals. Possible subjects for future volumes were discussed, and it was confirmed that passive smoking should be the subject of volume 9, and benzene, toluene and xylene the subjects of volume 10.

Volumes 6[45] was presented at the Ninth International Meeting on *N*-Nitroso Compounds: Occurrence, Biological Effects and Relevant to Human Cancer (see p. 128). Volume 7, on certain elements and their compounds, is still in preparation. Volume 8, on halogenated alkanes and alkenes, is in preparation; the outline will be presented at the International Conference on Solvent Toxicity in Stockholm. Volumes on formaldehyde, benzene, dioxin and biological monitoring methods are anticipated. The meeting of the review board for volume 9 was held at the American Health Foundation, Valhalla, NY, USA.

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[44] IARC (1983) *Annual Report 1983*, Lyon, p. 39

[45] Preussmann, R., O'Neill, I. K., Eisenbrand, G., Spiegelhalder, B. & Bartsch, H., eds (1983) *Environmental Carcinogens — Selected Methods of Analysis*, Vol. 6, *N-Nitroso Compounds* (*IARC Scientific Publications* No. 45), Lyon, International Agency for Research on Cancer

Table 27. Members of the Ninth Meeting of the Editorial Board and of Review Boards for the Manuals of Selected Methods of Analysis of Environmental Carcinogens

9th Meeting of the Editorial Board, 13–14 October 1983

Professor E. Boyland (London School of Hygiene and Tropical Medicine, London)
Dr A. Critchlow (Health and Safety Executive, Sheffield, UK)
Professor H. Egan (Laboratory of the Government Chemist, London)
Dr L. Fishbein, Chairman (National Center for Toxicological Research, Jefferson, AR, USA)
Dr H. N. B. Gopalan (United Nations Environment Programme, Nairobi)
Dr D. Hoffmann (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)
Dr J. Järvisälo (Institute of Occupational Health, Helsinki)
Dr R. Preussmann (German Cancer Research Centre, Institute of Toxicology and Chemotherapy, Heidelberg, FRG)
Dr C. Rappe (Department of Organic Chemistry, Umeå, Sweden)
Dr P. Schuller (National Institute of Public Health, Bilthoven, The Netherlands)
Dr D. Williams (Environmental Health Centre, Ottawa)

Review Board on Passive Smoking, 8–9 December 1983

Dr J. D. Adams (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)
Dr K. D. Brunnemann (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)
Dr E. Grandjean (Institute of Hygiene and Physiology, Zurich, Switzerland)
Dr M. Jarvis (University of London)
Dr N. J. Haley (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)
Dr D. Hoffmann, Chairman (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)
Ms I. Hoffman (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)
Dr J.L. Repace (US Environmental Protection Agency, Washington DC)
Dr D. Sepkovic (Naylor Dana Institute for Disease Prevention, Valhalla, NY, USA)

The volumes and chief external collaborators foreseen are as follows:

Certain Elements and their Compounds: Dr P. L. Schuller, National Institute of Public Health, Bilthoven, The Netherlands

Halogenated Alkanes and Alkenes, Dr L. Fishbein, National Center for Toxicological Research, Jefferson, AR, USA

Passive Smoking, Dr D. Hoffmann, American Health Foundation, Valhalla, NY, USA

Mineral Fibres, Dr A. Critchlow, Health and Safety Executive, Safety in Mines Research Establishment, Sheffield, UK

Benzene, Toluene and Xylene, Dr L. Fishbein, National Center for Toxicological Research, Jefferson, AR, USA

(g) *International Meeting on* N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (Dr H. Bartsch and Dr I. K. O'Neill)

The Eighth International Meeting on *N*-Nitroso Compounds was held in Banff, Alberta, Canada, 5–9 September 1983. It was organized by the Agency and the Canadian Executive Committee (R. C. von Borstel, University of Alberta; C. T. Miller, Evironment Canada; J. E. Long, Health and Welfare Canada; M. C. Archer, Ontario Cancer Research Institute; C. Chapel, FDC Consultants Incorporation; W. Choi, University of Manitoba; P. G. Scholefield, National Cancer Institute of Canada; N. P. Sen, Health and Welfare Canada; H. F. Stich, British Columbia Cancer Research Center; and D. Williams, Health and Welfare Canada). It was co-sponsored by the

Alberta Heritage Foundation for Medical Research, the University of Alberta and the Departments of Agriculture, Consumer and Corporate Affairs, Environment, and Health and Welfare of the Canadian Federal Government.

The meeting was attended by more than 200 participants from 19 countries, who presented papers and review lectures focusing exclusively on *N*-nitroso compounds and their precursors. Major sessions included the occurrence and formation of *N*-nitroso compounds, analytical advances and identification of new nitroso compounds, DNA repair, macromolecular adducts and biological effects, metabolism and modifying factors, *N*-nitroso compounds in tobacco carcinogenesis, epidemiological studies and combined laboratory/epidemiological investigations to link *N*-nitroso compounds and their precursors with human cancers. Meeting reports have appeared[46,47], and the proceedings, containing more than 100 scientific articles, will be published in 1984 as *IARC Scientific Publications* No. 57: N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer*, I. K. O'Neill, R. C. von Borstel, C. T. Miller, J. E. Long and H. Bartsch, eds.

The next meeting in this series will be held in Vienna, Austria, 1–5 September 1986, following the 14th International Cancer Congress in Budapest (21–27 August, 1986).

(*h*) *IARC Survey of Chemicals Being Tested for Carcinogenicity* (Mrs M.-J. Ghess, Mr J. Wilbourn and Dr H. Vainio)

The IARC Survey of Chemicals Being Tested for Carcinogenicity was initiated in 1973 in collaboration with the National Cancer Institute of the USA, and 10 *Information Bulletins* have been published to date. The Survey continues to monitor long-term animal carcinogenicity tests in progress throughout the world. The major aims are to avoid unnecessary duplication of research, to increase communication between scientists and to make a census of available research facilities as well as of chemicals being tested. The survey also identifies chemicals for which future *IARC Monographs* should be prepared.

Information Bulletin No. 10, which was published in December 1982, lists 1043 chemicals under test in 103 institutes in 16 countries.

In September 1983, an eleventh survey questionnaire was sent to those laboratories that reported in *Bulletin No. 10* asking for updated data on the chemicals listed. Efforts were also made to contact other investigators who are carrying out long-term carcinogenicity testing but who do not report to the *Bulletin*. The replies are presently being collated, and *Information Bulletin No. 11* will be published in September 1984. Each entry lists the institute, the chemical being tested, the Chemical Abstracts Registry Services Number, synonyms and trade names, use, species, number of animals, route of administration and dosing schedule, stage of experiment and principal investigators. Two new data entries have been added: purity of the chemical (where available) and starting date of the experiment. A cross-index of all synonyms, trade names and CAS numbers is generated. In future *Bulletins*, it is planned to issue cumulative indices, so that previously published or discontinued studies can also be identified.

The report of a recent IARC Working Group that met in January 1984 to select priorities for chemicals or complex mixtures to be evaluated in future *IARC Monographs* or to be tested for

[46] Craddock, V. M. (1983) *Nature*, **306**, 638
[47] Bartsch, H. & O'Neill, I. K. (1984) *Cancer Res.*, **44**, 1301–1304

carcinogenicity (see p. 46) will be circulated to laboratories undertaking long-term carcinogenicity tests, with the aim of providing information relevant to the selection of future chemicals or complex mixtures to be tested.

4. SURVEY OF EXISTING COLLECTIONS OF HUMAN BIOLOGICAL MATERIAL

(Dr A. Walker, Dr G. Lenoir and Miss C. Bonnardel; in collaboration with Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik)

Analysis of preclinical disease states and metabolic conditions that may give rise to cancers poses a problem in 'retrospective' biological analysis, which is ordinarily insurmountable. One possible solution lies in the assessment of stored tissues from people who later develop cancer. In order to investigate the potential for this kind of analysis, the Agency has carried out an extensive inventory of banks of biological specimens currently available around the world, and has brought together the principals of a number of very large serum banks to share technical data and to plan collaborative projects.

A total of 1830 individuals were requested to notify the Agency of the existence of any banks of biological specimens of which they were aware. Ultimately, 312 banks were identified. The distribution of some of their characteristics is shown in Table 28. All positive responses to our inquiries have been catalogued and stored in computerized files for ready cross-referencing and identification.

Table 28. Distribution of characteristics of 312 banks of human biological material

Banks by type of specimen

Serum	*White cells*	*Red cells*	*Urine*	*Faeces*	*Saliva*	*Tissue*	*Cells*	*Other*
212	34	25	46	11	12	96	51	42

Banks by geographical origin

Europe	*America*	*Africa*	*Asia*	*Oceania*
128	97	11	60	16

Banks by starting year of collection

1960	*60–64*	*65–69*	*70–71*	*72–73*	*74–75*	*76–77*	*78–79*	*80–81*	*82–83*
13	20	28	27	32	38	25	46	43	18

A central objective of the project has been to identify substantial populations in which the relation between preclinical states and subsequent disease could be studied; therefore, a variety of questions were put to the heads of each biological collection about the potential for identifying each person represented in the collection, and the ease of identifying cancer cases. For each centre with a substantial collection, the number of person-years of follow-up (after specimen collection) was calculated. Access to moderate numbers of common cancers would require about 100 000 person-years of follow-up.

(*a*) *Interbank collaboration* (Dr A. Walker and Dr G. Lenoir; in collaboration with Dr H. Tulinius, Icelandic Cancer Registry, Reykjavik; Dr A. Aromaa, Social Insurance Institution, Helsinki; Dr R. P. Beasley, University of Washington, Seattle, WA, USA; Dr H. B. Hamilton, Radiation Effects Research Foundation, Hiroshima, Japan; Dr E. Jellum, Institute of Clinical Biochemistry, Oslo; Dr J. D. Kark, Hebrew University, Jerusalem, Israel; Dr N. Orentreich, Orentreich Foundation for the Advancement of Science, New York, USA; Dr A. Pacsa, Institute of Microbiology, Pecs, Hungary; Mr R. Peto, University of Oxford, UK; Dr E. Trell, Department of Medicine, Mälmo, Sweden; Dr P. van Noord, Rijks University of Utrecht, The Netherlands.)

On 1–2 December 1983, the Agency brought together the responsible members of all (but one) of the serum banls with at least 100 000 person-years of follow-up known to us. The group addressed the logistic and technical problems of managing serum banks, and considered a number of proposals for projects that might be undertaken collaboratively.

As a result of the group's discussions, two immediate projects were decided upon, and further proposals were made to the Agency Secretariat to enable continuation and development of coordinated work in biological banking. It was recognized that this meeting of the 'bankers' presented a unique opportunity, and that if they were to make a plausible call for support for collaborative activity they had to demonstrate a willingness to cooperate and to commit their own resources to common goals.

The first project is to be a study of dehydroepiandrosterone sulfate levels in cases of premenopausal breast cancer. Dr Orentreich has already shown, in the Kaiser-Permanente-Orentreich serum collection, that this adrenal hormone can be assayed in stored serum specimens and that its levels show a steady and steep decline throughout adult life. Participants agreed to develop a protocol for retrieval and shipment of case and control serum specimens to a common laboratory, where assays will be conducted for the entire group. The second project arose out of Dr Beasley's observations in Taiwan of strong associations between hepatitis B surface antigen (HBsAg) seropositivity and primary liver cancer. The group members agreed to submit sera from Caucasians who later developed primary hepatocellular carcinoma and from controls, in order to examine the relation in the context of the more variable age at first exposure found in Western, as opposed to Asian and African, societies.

In general, it was felt that there is an acute lack of awareness even of the existence of banks and biological specimens among scientists who might wish to avail themselves of the opportunities that they present. The members of the group agreed to provide extensive standardized tabular and narrative descriptions of their banks for assembly into a short descriptive monograph or technical report, which would be distributed to a wider audience. All principals of biological banks will be made aware of the *Directory of On-going Research in Cancer Epidemiology* (see p. 110) and be given the opportunity to list their projects therein.

(*b*) *Collaborative investigation of serum indicators of subsequent cancer risk* (Dr N. Day and Dr A. Walker; in collaboration with Dr J. D. Kark, Hebrew University, Jerusalem, Israel, DEB/84/10; Dr C. Levine, Ministry of Health, Jerusalem, Israel; and Dr U. Goldbourt, Heart Institute, Tel Hashomer, Israel)

The Israel Ischaemic Heart Disease Study (IIHDS) examined an ethnically stratified random sample of 10 000 male civil servants in 1963 with follow-up examinations in 1965 and 1968. This study has produced numerous reports in the realm of cardiovascular epidemiology and, more

recently, on the prediction of total mortality and specific causes of death, including cancer. The cohort was linked to the National Population Registry (NPR) by personal identification number. By 1978 (after 15 years' follow-up), 1664 of the study population had died, 366 from cancer as recorded in death certificates. Approximately 500 deaths are estimated to have occurred by the end of 1983, and over 800 incident cases of cancer. Serum samples were stored from the 1965 and 1968 examinations and have been maintained at –18–20°C in the Department of Immunohaematology of the Israel Ministry of Health by Dr Cyril Levine.

The stored sera, which have not been used for the past 15–18 years, are disorganized and, as a result, difficult to locate and utilize for prospective case-control studies of cancer occurrence in the study population. These studies also require re-linkage with the NPR to ascertain new deaths that have occurred to date, with the National Cancer Registry to find cases that had occurred by the end of 1981, and with the Central Bureau of Statistics to define underlying causes of deaths that occurred after the Cancer Registry was updated (between 1982 and 1984).

Under a collaborative research agreement with IARC, Israeli investigator are reboxing and relabelling the stored sera, placing them in new freezer facilities, and linking serum data to the National Cancer Registry. As a first substantive project, all cases of primary hepatocellular carcinoma in the serum bank are to be identified, along with a series of controls, and assayed for hepatitis B viral markers, in conjunction with the second cooperative project described above.

5. DESTRUCTION OF CARCINOGENIC WASTES FROM LABORATORIES (Supported by NCI Contract NOI-DS-2-2130)

The following steps are involved in the development of this programme:

(1) collection of literature related to degradation techniques and chemistry of the carcinogens and classes of carcinogens considered;
(2) evaluation of the available bibliography and preparation of an intermediate document;
(3) laboratory testing of the efficiency of the proposed methods and, when necessary, development of new methods;
(4) descriptions of method in an ISO style in an intermediate document and initiation of collaborative studies to ascertain their efficiency; and
(5) critical review of the final document by a meeting of experts drawn from the participants in the collaborative study and publication as an *IARC Scientific Publication.*

(*a*) *Collection of literature* (Dr M. Castegnaro)

Updating of the literature on nitrosamides, hydrazines, chloroethers and aromatic amines was performed using available on-line facilities. Bibliographic searches on 18 antineoplastic agents and on some mycotoxins has also been performed.

(*b*) *Evaluation of bibliography and preparation of monographs* (Dr M. Castegnaro)

A document on the degradation of wastes contamined with aromatic amines has been revised, and a document on 18 antineoplastic agents is being prepared.

(c) *Assays and development of methods*

(i) *Chemical degradation of hydrazines and mutagenicity testing of residues* (Dr M. Castegnaro, Mrs I. Brouet, Miss J. Michelon and Mr C. Malaveille; in collaboration with Dr E. B. Sansone, NCI-Frederick Cancer Research Facility, Frederick, MD, USA)

Four methods of degradation were considered for the degradation of this class of compounds[48]: (1) reduction with nickel aluminium alloy under alkaline conditions; (2) oxidation by potassium iodate under acidic conditions; (3) oxidation by potassium permanganate/sulfuric acid; and (4) oxidation by hypochlorites (sodium or calcium). Method 4 was found to yield residues with mutagenic effects. When the reaction conditions were changed (i.e., using four times the amount of oxidant and allowing 12 h reaction time, instead of 0.5 h), no mutagenic effect was detected with the residues of hydrazine, but significant mutagenicity was seen with the residues of 1,1-dimethylhydrazine. Moreover, traces of nitrosamines were found in the residues of degradation of 1,1-dimethylhydrazine and monomethylhydrazine. Nitrosamines were also found in residues of these two compounds after degradation by method 2. When using method 3, only 1,1-dimethylhydrazine produced *N*-nitrosodimethylamine, at up to 50% yield. Only with method 1 was no mutagenic activity found in *Salmonella typhimurium* strains TA1530, TA1535, TA100 and TA98 in degradation products of the hydrazines tested.

(ii) *Chemical degradation of nitrosamides and mutagenicity testing of residues* (Dr M. Castegnaro, Miss J. Michelon, Mrs I. Brouet and Mr C. Malaveille; in collaboration with Dr E. B. Sansone, NCI-Frederick Cancer Research Facility, Frederick, MD, USA)

The four following methods have been investigated[49]: (1) denitrosation in 3 mol/l hydrochloric acid in the presence of sulfamic acid; (2) denitrosation in 3 mol/l hydrochloric acid in the presence of iron filings; (3) denitrosation with a 3% solution of hydrobromic acid in glacial acetic acid; and (4) oxidation by potassium permanganate under acidic conditions; on *N*-nitrosomethylurea (MNU), *N*-nitrosoethylurea (ENU), *N*-nitrosomethylurethane (MNUT), *N*-nitrosoethylurethane (ENUT), *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine (ENNG).

Residues of treatment of ENUT by method 1 and residues of treatment of ENUT, MNNG and ENNG by method 2 were mutagenic to *S. typhimurium* strains TA1530 and TA1535. Use of method 2 in the presence of acetone also produced mutagenic residues of all the nitrosamides tested. After treatment with potassium permanganate in sulfuric acid within 8 h (method 3), better than 99.5% degradation and non-mutagenic residues were found. Method 4 was found to produce mutagenic residues after degradation of MNU.

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[48] IARC (1983) *Annual Report 1983*, Lyon, pp. 124–125
[49] IARC (1983) *Annual Report 1983*, Lyon, p. 125

(iii) Chemical degradation of chloromethylmethylether (CMME) and bis-chloromethylether (BCME) and mutagenicity testing of residues (Dr M. Castegnaro, Mrs I. Brouet and Mr C. Malaveille; in collaboration with Dr M. Alvarez, FMC Corporation, Princeton, NJ, USA; and Dr G. Telling, Unilever Research Laboratory, Sharnbrook, UK)

First attempts to analyse these compounds after degradation involved direct injection of a solution onto a gas chromatograph with electron capture (GC-ECD) or mass-spectrometric detection (GC-MS). However, it was found that this method could produce over-estimation of the levels of degradation due to further reaction in the injection port of the gas chromatograph and that a headspace GC-ECD or GS-MS technique would be preferable.

The following three degradation methods were investigated: (1) addition of an ammonia solution; (2) addition of a methanolic solution of sodium phenate; and (3) addition of a methanolic solution of sodium methoxide. None of the residues produced by these methods was mutagenic to *S. typhimurium* strains TA1530, TA1535 or TA100 with or without metabolic activation.

(iv) Chemical degradation of aromatic amines and mutagenicity testing of residues (Dr M. Castegnaro, Miss J. Michelon, Mrs I. Brouet and Mr C. Malaveille; in collaboration with Dr J. Barek, Charles University, Prague; Dr M. Lafontaine, INRS, Vandoeuvre, France; and Dr A. M. Klibanov, Massachusetts Institute of Technology, Cambridge, MA, USA)

The efficiency of the following methods has been investigated: (1) oxidation by potassium permangante in the presence of sulfuric acid[50]; (2) oxidation by hydrogen peroxide in the presence of horse-radish peroxidase; (3) deamination using diazotization in the presence of hypophosphorous acid; and (4) diazotization on 4-aminobiphenyl (4-ABP), benzidine (benz), 3,3'-dichlorobenzidine (DClB), 3,3'-dimethylbenzidine (DMB), 3,3'-dimethoxybenzidine (DMoB), 4,4'-methylene bis-(2-chloroaniline) (MOCA), 1-naphthylamine (1-NAP), 2-naphthylamine (2-NAP) and 2,4-diaminotoluene (TOL). The residues were tested for mutagenicity in *S. typhimurium* strains TA97, TA98 and TA100 with and without metabolic activation.

All residues produced by method 1 were non-mutagenic[51]. The solutions produced by method 2 were all found to be non-mutagenic; however, solid residues from Bz, DClB, DMoB and 2-NAP were mutagenic. It is therefore recommended that this method be used only for the removal of aromatic amines from large volumes (> 1 litre) of wastes and not to degrade aromatic amines.

Up to 60 times the number of spontaneous revertants were detected both in the residues and supernatants of TOL, 1-NAP and 2-NAP degradation mixtures degraded by method 3. The method must not, therefore, be used to degrade these compounds. Slight mutagenicity was detected when degradation mixtures of DClB, DMB and DMoB were tested, which increased when the reaction was carried out in the presence of dimethylformamide or dimethyl sulfoxide and decreased or disappeared when it was carried out in the presence of methanol or ethanol. Method 3 is therefore being reconsidered for these compounds. No mutagenicity was detected in the residues of treatment of the other aromatic amines.

A strong mutagenic effect was seen in degradation mixtures of TOL, 1-NAP, DCIB and DMoB after treatment by method 4. The method must not, therefore, be used to degrade these compounds. Degradation mixtures for the other compounds showed no mutagenic effect.

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[50] Castegnaro, M., Malaveille, C., Brouet, I., Michelon, J. & Barek, J. (1983) *Am. ind. Hyg. Assoc. J.* (in press)

(v) Chemical degradation of 4-nitrobiphenyl and mutagenicity testing of the residues (Dr M. Castegnaro, Mrs I. Brouet and Mr C. Malaveille; in collaboration with Dr J. Barek, Charles University, Prague)

No direct method could be found to degrade this compound. Two methods have been proposed, both involving reduction to 4-aminobiphenyl: (1) The compound in dimethyl sulfoxide is completely reduced by the action of nickel-aluminium alloy in the presence of sodium hydroxide. The resulting 4-aminobiphenyl is degraded using method 3 above (see section iv). (2) The compound in glacial acetic acid is completely reduced by zinc powder in the presence of sulfuric acid. The resulting 4-aminobiphenyl is degraded using method 1 above (see section iv). Both methods gave residues that showed no mutagenic activity in *S. typhimurium* strains TA97, TA98 or TA100, with or without metabolic activation. However, although quantitative disappearance of 4-nitrobiphenyl was observed when using method 1, only 16–20% 4-aminobiphenyl was recovered. Therefore, the group that took part in revision of the document withdrew this method.

(d) Initation of collaborative studies (Dr M. Castegnaro)

At the request of the group that participated in revision of the documents on hydrazines and nitrosamides, samples were circulated to some of the participants to determine whether the low efficiency of the degradation methods observed was real or was due to analytical problems. The latter was found generally to be the reason, except in the case of reduction of procarbazine, where the low reduction levels were confirmed. A collaborative study to test the methods of degradation of CMME and BCME has been organized, involving six laboratories in Canada, France, Roumania, the UK and the USA. A complementary study to test a second method of degradation of 4-nitrobiphenyl was organized with the same participants.

(e) Organization of meeting to finalize documents, and publication (Dr M. Castegnaro, Mrs Z. Schneider and Mrs E. Heseltine)

After the results of the complementary study on hydrazines and nitrosamides had been obtained, the documents were finalized and published at the end of 1983 and early 1984[51,52].

A meeting to finalize the document on aromatic amines and 4-nitrobiphenyl was held in Lyon on 9–11 January 1984. All the methods for aromatic amine degradation were maintained, but the method for degradation of 4-nitrobiphenyl was withdrawn because of the non-quantitative formation of 4-aminobiphenyl by reduction with Ni-Al alloy. Another method was proposed for subsequent collaborative study (see *(d)* above).

A meeting to finalize the document on BCME and CMME was held in Lyon on 12–13 January 1984. All three methods were maintained.

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[51] Castegnaro, M., Ellen, G., Lafontaine, M., Van der Plas, H. C., Sansone, E. B. & Tucker, S. P., eds (1983) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Hydrazines* (*IARC Scientific Publications* No. 54), Lyon, International Agency for Research on Cancer

[52] Castegnaro, M., Bernard, M., Van Broekhoven, L. W., Fine, D., Massey, R., Sansone, E. B., Smith, P. L. R., Speigelhalder, B., Stacchini, A., Telling, G. & Vallon, J. J., eds (1983) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some N-Nitrosamides* (*IARC Scientific Publications* No. 55), Lyon, International Agency for Research on Cancer

IV. TECHNICAL SUPPORT

1. COMPUTING AND BIOSTATISTICAL SUPPORT (Dr J. Estève, Mr M. Smans, Dr J. Wahrendorf, Mr X. Nguyen-Dinh, Dr J. Kaldor, Miss B. Charnay, Mr P. Damiecki, Mrs A. Arslan, Mr M. Jaboulin and Mrs B. Kajo)

The Biostatistics Unit gives regular consultation in statistics and computing. It also takes charge of the data management of several epidemiological studies. This work is now done by generalizing the use of a data base management system for scientific data (SIR), and several analysts developed expertise in this field last year. A specialized seminar was organized in the Agency to provide training.

The graphic software developed by M. Smans has had more and more success inside and outside the Agency and proved to be a good tool for research. It has been decided to make it more widely available, with the help of Mr D. Williams, who has been engaged on a short-term basis to develop an interactive graphical package, using the routines written previously.

A project for a computerized documentation system has occupied some members of the Unit, in identifying computer software and methods for the best implementation of this project on the Agency's VAX computer. Because of this increasing activity, an upgrading of the VAX configuration is envisaged.

Statistical consultation for day-to-day problems is still an important part of this programme, and the addition of a statistician to the existing staff as well as the presence in the Unit of visiting scientists has increased efficiency in this respect.

2. BIBLIOGRAPHIC SUPPORT

(*a*) *Library services*

The library provides active support to all scientific programmes, including field studies.

The number of journal and serial subscriptions currently received is 245; the present stock of bound journals is approximately 7500. The total number of books is 7300, many of which were purchased with funds provided by voluntary donors.

The *Library Bulletin* continues to provide news and notes about library acquisitions and a list of papers published by members of the Agency staff.

The Librarian participates in the preparation of the *Directory of On-going Research in Cancer Epidemiology.*

(*b*) *Computerized bibliographic services* (Mrs M. Coudert)

This year, the Agency's terminal made the BRS databases (Bibliographic Retrieval Services) available, in addition to the three sources already in use (NLM, Dialog, Telesystem). This new source of information should help the retrieval of more chemical references.

During the past year, a total of 172 hours were spent to make 350 on-line searches and 40 off-line searches for staff members and attached scientists. A total of 24 monthly up-datings were provided to staff members.

3. COMMON LABORATORY SERVICES (Dr J. R. P. Cabral and Dr H. Yamasaki)

These include animal breeding, maintenance of the animal house, disposal of animal bedding and wastes, the histology laboratory and the glass-washing service. The Agency's scientists use animals bred in-house for the majority of their work, since they now have considerable detailed knowledge of the spontaneous tumour rates in the strains used—BDIV and BDVI rats and C57B1/6 mice.

The histology laboratory processes all the histological material from experimental animals in the Agency as well as biopsy material sent by Agency researchers doing field work abroad.

The glass-washing unit is a unified service for the experimental work carried out in chemistry, biochemistry and virology.

V. EDUCATION AND TRAINING

1. RESEARCH TRAINING FELLOWSHIPS (Dr R. Montesano, Mrs M. Davis and Miss E. Welton)

(*a*) *The Fellowships Selection Committee*

The Fellowships Selection Committee met in Lyon, 17–19 April 1984, to review applications; the members of the Committee were:

Dr N. N. Blinov	N. N. Petrov Research Institute of Oncology, Leningrad, USSR
Dr D. Bootsma	Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands
Dr T. M. Mack	Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA
Dr B. Mansourian	Office of Research Promotion and Development, WHO, Geneva, Switzerland
Dr E. F. Pastorelo	National Campaign for the Fight Against Cancer, Rio de Janeiro, Brazil
Dr T. J. Slaga	University of Texas System Cancer Center, Smithsville, TX, USA
Dr M. Terada	Serology Division, National Cancer Center Research Institute, Tokyo

The Agency representatives were Dr R. Montesano (Chairman), Dr R. Saracci and Dr G. Lenoir.

Table 29. Distribution of Research Training Fellowships by discipline, 1984

Scientific discipline	No. of fellowships
Epidemiology and Biostatistics	2
Chemical Carcinogenesis	2
Viral Carcinogenesis	3
Cell Biology, Cell Differentiation and Cell Genetics	4
Biochemistry and Molecular Biology	1

Table 30. Fellowships awarded in 1984

Name	Institute of origin	Host institution
D'Andrea, E.	Cattedra di Oncologia c/o Osp. Busonera Padova, Italy	Laboratory of Viral Oncology Memorial Sloan-Kettering Cancer Center New York, NY, USA
Frixen, U. H.	Institüt für Zellbiologie Universitätsklinikum, Essen, FRG	IARC Lyon, France
Lobanenkov, V. V.	All-Union Cancer Research Center, AMS, Moscow, USSR	Institute of Cancer Research: Royal Cancer Hospital Chester Beatty Laboratories London
Nandakumar, A.	Kidwai Memorial Institute of Oncology, Bangalore, India	NH & MRC Research Unit in Epidemiology and Preventive Medicine, University Department of Medicine Queen Elizabeth II Medical Centre Nedlands, WA, Australia
Pirsel, M.	Department of Molecular Genetics Cancer Research Institute Slovak Academy of Sciences Bratislava, Czechoslovakia	Laboratory of Biology Division of Cancer Cause and Prevention, National Cancer Institute Bethesda, MD, USA
Preat, V. M. F.	Laboratory of Biochemical Toxicology and Cancerology Catholic University of Louvain Brussels	Department of Pathology University of Toronto Banting Institute Toronto, Ontario, Canada
Rajagopalan, M. S.	Department of Virology ICMR Centre of Virology Christian Medical College Hospital Vellore, India	Department of Laboratory Medicine University of California School of Medicine San Francisco, CA, USA
Record, M.	INSERM U. 101 Biochimie des Lipides Hôpital Purpan Toulouse, France	Medical and Health Sciences Division, Oak Ridge Associated Universi- ties, Oak Ridge, TN, USA
Rooney, C. M.	Department of Cancer Studies The Medical School Birmingham, UK	Department of Paediatrics Yale University School of Medicine New Haven, CT, USA
Stanley, I. J.	The Walter & Eliza Hall Institute of Medical Research and Ludwig Institute for Cancer Research Melbourne, Vic., Australia	European Molecular Biology Laboratory, Heidelberg, FRG
Tomasson, H.	Statistiska Institutionen Göteborg, Sweden	IARC Lyon, France
Wild, C. P.	Paterson Laboratories Christie Hospital and Holt Radium Institute Manchester, UK	IARC Lyon, France

(b) Fellowships awarded

Out of 76 applications received, 15 were considered ineligible since their proposals fell outside the scope of the programme, and five withdrew their applications. The Committee recommended

the award of fellowships to 12 of the 56 applications it reviewed; of these, three were for fellowships tenable at the Agency. The distribution by discipline of the fellowships awarded is given in Table 29, and the list of Fellows in Table 30. The Fellowships Selection Committee also discussed the progress made with regard to the review of the programme by Professor Sohier.

2. TRAINING COURSES (Dr W. Davis and Mrs C. Déchaux)

(a) *Course on cancer epidemiology (in French), Yaoundé, United Republic of Cameroon, 14–27 November 1983*

In collaboration with the WHO Regional Office for Africa and the University Centre for Health Sciences (CUSS) (Director: Professor J. Ngu), the Agency organized the first course destined for the Francophone countries of Africa. It was attended by 33 participants from 19 countries. The Chancellor of the University, Professor Owona, officially opened the course. The programme was prepared and coordinated by Dr A. J. Tuyns, of the Unit of Analytical Epidemiology. The other members of the teaching faculty were Mr K. E. Adikpeto (WHO Regional Office for Africa, Brazzaville), Dr E. Benhamou (Gustave Roussy Institute, Villejuif, France), Dr W. Davis (IARC), Dr D. Hemon (INSERM Research Unit 170, Villejuif, France), Dr G. E. Martin (Institute for Medical Research and Study on Medicinal Plants, Yaoundé), Mr R. Mfoulou (Institute for Demographic Training and Research, Yaoundé), Professor C. Quenum (Faculty of Medicine, Amiens, France), Dr B. Yvonnet (Institute of Virology, Tours, France) and Professor Zung Kanyi (Ministry of Health of the United Republic of Cameroon, Yaoundé).

(b) *Course on cancer epidemiology (in Spanish), Lima, Peru, 27 February–9 March 1984*

In collaboration with the Universidad Peruana Cayetano Heredia (Rector: Dr Homero Silva), the Agency organized the third course of this kind for the Region. There were 42 participants, from Brazil, Colombia, Ecuador, Paraguay and Peru. The programme for the course was prepared and coordinated by Dr Nubia Muñoz of the Unit of Biostatistics and Field Studies; the local organization was in the hands of Dr Rodolfo Gonzales, of the Universidad Peruana Cayetano Heredia, Lima. The other members of the faculty were Dr V. Barbosa (University of São Paulo, Brazil), Dr F. X. Bosch (District Hospital, Gerona,Spain), Professor N. Breslow (University of Washington, Seattle, WA, USA), Professor P. Correa (Louisiana State University, New Orleans, LA, USA), Dr R. Guerrero and Dr G. Llanos (Universidad del Valle, Cali, Colombia) and Dr Laura Olivares (National Institute for Neoplastic Diseases, Lima).

(c) *Course on cancer epidemiology, Rome, 19–30 March 1984*

In collaboration with the Istituto Regina Elena (Director: Professor A. Caputo) and with the help of Professor Massimo Crespi, the Agency organized a course on cancer epidemiology at the Istituto Superiore di Sanitá (Director: Professor F. Pocchiari). There were 46 participants from 19 countries. The programme for the course was prepared by Dr R. Saracci and Dr A. Walker of the Unit of Analytical Epidemiology. The other members of the faculty were Professor M. Crespi (Istituto Regina Elena, Rome), Dr W. Davis (IARC), Dr M. Gardner (University of Southampton,

UK), Professor D. Trichopoulos (University of Athens) and Dr N. Weiss (University of Washington, Seattle, WA, USA).

(*d*) *Future courses*

The following courses and seminars are planned for 1984–1985:

— Advanced course in cancer epidemiology, Sydney (6–17 August 1984)
— Cancer epidemiology, Bangkok (29 October–16 November 1984)
— The commonest forms of cancer in Africa (in French), Bangui (1985)
— Epidemiological aspects of occupational cancer (in Spanish), Buenos Aires (18–30 March 1985)
— Occupational cancer—epidemiology and prevention, Luxembourg (6–10 May 1985) (course organized by the European School of Oncology, Milan, in collaboration with IARC and the Health and Safety Directorate of the Commission of the European Communities)
— Statistical methods in cancer epidemiology, IARC, Lyon, France (8–12 July 1985)
— Cancer epidemiology, Eastern Mediterranean Region (1985)

3. MEETINGS AND SYMPOSIA

The Agency is organizing a workshop on 'Evaluation of Methods for Assessing Human Health Hazards from Drinking-Water' which will take place at the Agency, 11–14 December 1984. This meeting is organized in collaboration with the WHO Regional Office for Europe, the International Programme on Chemical Safety, the Directorate-General for Research, Science and Education, Commission of the European Communities and the Mission for Study and Research of the French Ministry of the Environment.

The aim of the workshop is to review available methods for evaluating possible health hazards—particularly cancer—associated with drinking-water and to evaluate methods of monitoring exposure and of measuring effects of exposure on human populations. The meeting will be limited to about 50 participants.

4. PUBLICATIONS (Mrs E. Heseltine, Mrs M. Coudert, Mrs J. Thevenoux, Miss E. Welton and Mrs M.-M. Courcier)

The Agency's Editorial and Publications Service is responsible for the production of the *IARC Scientific Publications* series and of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. It also provides an in-house editorial service for scientists submitting papers to scientific journals, book chapters and conference proceedings. In 1983, a photocomposer was purchased by the Agency, which should eventually reduce both the time and the cost of producing certain Agency publications.

As of 31 July 1984, the *IARC Scientific Publications* are to be distributed by Oxford University Press, which has branches in Oxford, London, New York, Toronto, Delhi, Bombay, Calcutta, Madras, Karachi, Kuala Lumpur, Singapore, Hong Kong, Tokyo, Nairobi, Dar-es-Salaam, Cape

Town, Melbourne, Auckland, and associated companies in Beirut, Berlin, Ibadan, Mexico City and Nicosia. This should make it possible for the publications to be ordered through any bookshop. The *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* will continue to be distributed through WHO, Geneva.

(*a*) *New titles*

Since the last *Annual Report*[1], the following publications have appeared:

Cancer Incidence in the USSR. Second Revised Edition (*IARC Scientific Publications No. 48*)

Directory of On-going Research in Cancer Epidemiology 1983 (*IARC Scientific Publications No. 50*)

Modulators of Experimental Carcinogenesis (*IARC Scientific Publications No. 51*)

Second Cancer In Relation to Radiation Treatment for Cervical Cancer: Results of a Cancer Registry Collaboration (*IARC Scientific Publications No. 52*)

Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Hydrazines (*IARC Scientific Publications No. 54*)

Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some N-*Nitrosamides* (*IARC Scientific Publications No. 55*)

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 32, *Polynuclear Aromatic Compounds, Part 1, Chemical, Environmental and Experimental Data*

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 33, *Polynuclear Aromatic Compounds, Part 2, Carbon Blacks, Mineral Oils and Some Nitroarenes*

A full list of IARC publications is given on the inside covers of this Report.

(*b*) *Publications in preparation*

The following titles are being prepared for publication:

Nickel in the Human Environment (*IARC Scientific Publications No. 53*)

Models, Mechanisms and Etiology of Tumour Promotion (*IARC Scientific Publications No. 56*)

N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer* (*IARC Scientific Publications No. 57*)

Age-related Factors in Carcinogenesis (*IARC Scientific Publications No. 58*)

Monitoring Human Exposure to Carcinogenic and Mutagenic Agents (*IARC Scientific Publications No. 59*)

Burkitt's Lymphoma: A Human Cancer Model (*IARC Scientific Publications No. 60*)

Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Haloethers (*IARC Scientific Publications No. 61*)

Directory of On-Going Research in Cancer Epidemiology 1984 (*IARC Scientific Publications No. 62*)

Virus-associated Cancers in Africa (*IARC Scientific Publications No. 63*)

Environmental Carcinogens. Selected Methods of Analysis, Vol. 7, *Halogenated Alkanes/Alkenes*

Environmental Carcinogens. Selected Methods of Analysis, Vol. 8, *Some Elements*

Transformation Assay of Established Cell Lines: Mechanisms and Application

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[1] IARC (1983) *Annual Report 1983*, Lyon, p. 135

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 34, *Polynuclear Aromatic Compounds, Part 3, Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding*

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 35, *Polynuclear Aromatic Compounds, Part 4, Bitumens, Coal-tar and Some Coal-tar-derived Products, Shale Oils and Soots*

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 36, *Some Alkyl Compounds, Aldehydes, Epoxides and Peroxides*

Table 31. Distribution and sales of IARC publications up to 30 June 1984

	Official distribution	Sales
Scientific Publications		
No. 1	772	994
2	860	1494
3	1024	1090
4	993	1007
5	1131	1753
6	979	1417
7	1128	891
8	1114	1116
9	1062	960
10	1089	1131
11—part 1	1158	786
11—part 2	1158	801
12	1339	1253
13	1037	935
14	1036	914
15	1079	1123
16	1154	915
17	1058	542
18	1075	776
19	1199	685
20	984	553
21	1374	1053
22	1025	555
23	1112	1042
24—part 1	923	546
546 24—part 2	924	593
25	1173	712
26	1202	511
27	1138	782
28	1017	451
29	1003	671
30—part 1	1212	676
30—part 2	1212	676
31	1109	740
32	1898	2724
33	1389	1561
34	951	718
35	652	493
36	942	461
37	1778	601
38	929	552
39	1218	581
40	1411	573
41	1222	597

	Official distribution	Sales
42	1284	701
43	1530	590
44	1060	586
45	955	558
46	957	388
47	904	425
48	927	601
49	1480	545
50	859	526
51	760	515
54	1241	521
55	1266	520
Non-serial publications		
Alcool et Cancer	683	185
Cancer Morbidity and Causes of Death among Danish Brewery Workers	747	468
Information Bulletin No. 8	363	344
Information Bulletin No. 9	232	353
Information Bulletin No. 10	341	248
Monographs Series		
No. 1	2638	2099
2	2065	2414
3	2115	2362
4	1930	2297
5	1855	2010
6	1982	1980
7	2261	1835
8	2179	1754
9	2161	1597
10	2245	1832
11	2341	1478
12	2227	1621
13	2176	1450
14	2410	2132
15	2263	1640
16	2206	1542
17	2370	1428
18	2272	1452
19	2239	1427
20	2273	1322
21	2225	1096
22	2214	1235
23	2364	1212
24	2392	1175
25	2212	1023
26	2288	924
27	2287	962
28	2323	946
29	2262	941
30	2214	772
31	2160	744
32	2176	753
33	1960	483
Suppl. 1	2470	1440
Suppl. 2	2527	1665
Suppl. 3	2120	790
Suppl. 4	2747	1227

(*c*) *Distribution and sales*

Up to 30 June 1984, the numbers of copies of *IARC Scientific Publications* and of *IARC Monographs* that had been distributed free of charge and those that had been sold were as outlined in Table 31.

(*d*) *Scientific illustrations* (Mr J. Déchaux and Mr G. Mollon)

Illustrations for IARC publications and for journal articles, lectures and poster presentations of the scientific staff, as well as for other purposes are prepared by a draughtsman and a photographer. Photographic work is also carried out in connection with various laboratory activities.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE TWENTY-FIFTH SESSION OF THE IARC GOVERNING COUNCIL 3–4 May 1984

Australia

Dr B. P. KEAN *(Chairman)*
Assistant Director General
International Health and Tuberculosis Branch
Australian Department of Health
Woden, A.C.T.

Mr L. J. WILLETT
Director-General
Department of Health
Woden, A.C.T.

Belgium

Professor A. R. M. LAFONTAINE
Honorary Director
Institute of Hygiene and Epidemiology
Brussels

Canada

Dr R. SIMARD
Scientific Director
Montreal Cancer Institute
Montreal, P.Q.

Dr E. SOMERS *(Vice-Chairman)*
Director-General
Environmental Health Directorate
Department of National Health and Welfare
Ottawa

France

Dr A. LELLOUCH
Technical Adviser to the Ministry of Social Affairs and National Solidarity
Directorate-General for Health
Sub-Directorate for Programmes and Medical Treatments
Paris

Professor P. LOUISOT
South-Lyon Faculty of Medicine
Laboratory of General and Medical Biochemistry
INSERM Research Group U.189
Oullins

Mr L. SORIANO
Officer-in-charge
Life Sciences and Health Department
Ministry of Research and Industry
Paris

Federal Republic of Germany

Mr H. VOIGTLANDER
Director
International Health Relations Section
Federal Ministry for Youth, Family Affairs and Health
Bonn

Italy

Professor L. SANTI *(unable to attend)*
Director, Institute of Oncology
University of Genoa
Genoa

Japan

Dr N. KOINUMA
Deputy Director
Division of International Affairs
Ministry of Health and Welfare
Tokyo

Dr E. NAKAMURA
Director General
Statistics and Information Department
Ministry of Health and Welfare
Tokyo

The Netherlands

Dr A. P. M. BERSEE
Staff Bureau of International Health Affairs
Ministry of Welfare, Public Health and Cultural Affairs
Leidschendam

Dr J. SPAANDER
Past Director-General of the National Institute of Public Health and Environmental Hygiene
Bilthoven

Sweden

Professor B. BORGSTRÖM
Swedish Medical Research Council
Department of Medical and Physiological Chemistry
Lund

Union of Soviet Socialist Republics

Professor N. N. BLOKHIN
President, Academy of Medical Sciences of the USSR
Director, Cancer Research Center
Moscow

Dr (Mrs) T. A. SHAMARO
Senior Medical Officer
External Relations Board
Ministry of Health of the USSR
Moscow

United Kingdom

Sir James LEARMONTH GOWANS
Medical Research Council
London

Professor R. COLE *(Rapporteur)*
Deputy Chief Scientist
Department of Health and Social Security
London

United States of America

Dr (Mrs) J. HENNEY
Deputy-Director
National Cancer Institute
Washington DC

Mr N. A. BOYER
Director, Health and Narcotics Programs
Bureau of International Organization Affairs
US Department of State
Washington DC

World Health Organization

Dr LU RUSHAN
Assitant Director-General

Mr A. GROENENDIJK
Director, Division of Budget and Finance

Dr J. STJERNSWARD
Chief, Cancer Unit

Dr C. H. VIGNES
Legal Counsel

Observers

Dr A. ENGLUND
Executive Director
International Union Against Cancer
Geneva

Dr N. E. GRAY
Outgoing Chairman, Scientific Council

Mr W. E. HARLE
Deputy-Director
Exchequer and Audit Department
Audit House
London

Professor A. B. MILLER
Incoming Chairman, Scientific Council

Mr R. T. O'CONNOR
External Audit
World Health Organization
Geneva

Annex 2

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS TWENTIETH SESSION, 31 JANUARY–2 FEBRUARY 1984

Dr N. GRAY *(Chairman)*
Director
Anticancer Council of Victoria
Keogh House
East Melbourne, Victoria
Australia

Professor R. FLAMANT *(Vice-Chairman)*
Head, Department of Medical Statistics
Gustave Roussy Institute
Villejuif
France

Professor A. B. MILLER *(Rapporteur)*
Director, Epidemiology Unit
National Cancer Institute of Canada
University of Toronto
Toronto, Ontario
Canada

Professor H. J. EVANS
Director, Medical Research Council
Clinical and Population Cytogenetics Unit
Edinburgh
UK

Professor D. HENSCHLER
Director
Pharmacology and Toxicology Institute
Department of Medicine
Bayerische Julius-Maximilians-Universität
Würzburg
FRG

Dr T. HIRAYAMA
Chief, Epidemiology Division
National Cancer Center Research Institute
Tokyo

Dr R. KROES
Director
National Institute of Public Health and Environment
Bilthoven
The Netherlands

Professor A. R. M. LAFONTAINE
Honorary Director
Institute of Hygiene and Epidemiology
Brussels

Professor J. PONTÉN
Department of Pathology
University of Uppsala
Sweden

Dr B. TERRACINI
Institute of Morbid Anatomy
University of Turin
Italy

Professor N. N. TRAPEZNIKOV
Deputy Director-General
Cancer Research Centre
Academy of Medical Sciences of the USSR
Moscow

World Health Organization:

Dr J. HAMON
Assistant Director-General

Dr L. KAPRIO
Director, WHO Regional Office for Europe

Dr J. E. MAYNARD
Director, WHO Collaboration Center for Reference and Research on Viral Hepatitis
Atlanta, GA, USA

Dr M. S. TSECHKOVSKI
Medical Officer, Cancer Unit

Observer

Dr A. ENGLUND
Executive Director
International Union Against Cancer
Geneva, Switzerland

Annex 3

STAFF AT IARC[1]

Office of the Director

Director	Dr L. TOMATIS
Senior Scientist	Dr G. O'CONOR
Administrative Assistant	Mrs E. RIVIÈRE
Secretary	Mrs W. FEVRE-HLAHOLUK

Unit of Research Training and Liaison

Administrative Assistant	Mrs M. DAVIS
Chairman, Fellowships Selection Committee	Dr R. MONTESANO
Head, Editorial and Publications Services	Mrs E. HESELTINE
Librarian	Mrs A. NAGY-TIBORCZ
Library Assistant	Mrs L. OSSETIAN
Consultant	Dr W. DAVIS
Technical Clerk/Search Analyst	Mrs M. COUDERT
Secretary	Mrs C. DÉCHAUX
Secretary	Miss E. WELTON
Clerk	Mrs J. THEVENOUX
Clerk	Mrs M. COURCIER
Photographic Assistant	Mr G. MOLLON
Draughtsman	Mr J. DÉCHAUX

Division of Epidemiology and Biostatistics

Administrative Assistant	Mrs A. GESER
Secretary	Miss A. SHANNON

Unit of Analytical Epidemiology

Chief	Dr R. SARACCI
Scientists	Dr G. ENGHOLM
	Dr N. MUÑOZ (until September 1983)
	Dr F. G. PEERS (until September 1983)
	Dr E. RIBOLI (from September 1983)
	Dr L. SIMONATO
	Dr A. WALKER
	Dr D. ZARIDZE

[1] At 30 June 1984

Consultants	Dr A. J. TUYNS (September 1983–January 1984) Dr J. P. VELEMA (from December 1983)
Programmer/Statistician	Miss M. BLETTNER
Technical Clerk	Miss R. WINKLEMANN (from February 1984)
Secretaries	Mrs S. DARTOY Mrs K. ESSOULAMI (until December 1983) Mrs J. LAVALLÉE-HAWKEN Mrs S. STALLARD Mrs A. ZITOUNI (from February 1984)

Unit of Biostatistics and Field Studies

Chief	Dr N. E. DAY
Scientists	Dr J. ESTÈVE Dr J. KALDOR (from January 1984) Dr N. MUÑOZ (from October 1983) Dr J. WAHRENDORF Mr P. DAMIECKI
Programme Analysts	Miss B. CHARNAY Mr X. NGUYEN-DINH
Consultants	Dr F. X. BOSCH (from December 1983) Mr P. DAMIECKI (from February 1984) Dr J. KALDOR (August–December 1983)
Statistical Assistants	Mrs A. ARSLAN Miss D. MAGNIN
Secretaries	Mrs K. ESSOULAMI (from January 1984) Miss J. HAWKINS Mrs A. RIVOIRE
Statistical Clerks	Mr M. JABOULIN Mrs B. KAJO

Unit of Descriptive Epidemiology

Chief	Dr C. S. MUIR
Scientists	Dr D. M. PARKIN Mr M. SMANS
Consultant	Mr P. DELFOSSE (January–February 1984)
Technical Assistants	Mrs E. DEMARET Mrs J. NECTOUX Miss S. WHELAN
Secretaries	Miss O. BOUVY Miss A. M. CORRE Mrs A. ROMANOFF

Division of Environmental Carcinogenesis

Administrative Assistant	Mr C. AUGROS

Unit of Environmental Carcinogens and Host Factors

Chief	Dr H. BARTSCH
Scientists	Dr M. CASTEGNARO
	Dr M. FRIESEN
	Dr E. HIETANEN
	Dr C. MALAVEILLE
	Dr I. O'NEILL
	Mr H. OHSHIMA
Technicians	Mr A. BARBIN
	Mr J. C. BÉRÉZIAT
	Miss M. C. BOURGADE
	Mrs I. BROUET
	Mrs G. BRUN
	Miss A. M. CAMUS
	Mrs L. GARREN
	Mrs A. HAUTEFEUILLE
	Miss J. MICHELON
	Dr B. PIGNATELLI
Secretaries	Mrs M. B. D'ARCY (from December 1983)
	Miss Y. GRANJARD
	Mrs D. MARCOU (until November 1983)
	Mrs Z. SCHNEIDER
	Mrs M. WRISEZ

Unit of Mechanisms of Carcinogenesis

Chief	Dr R. MONTESANO
Scientists	Dr J. R. P. CABRAL
	Miss C. DREVON
	Dr V. GURTSEVITCH
	Dr M. HOLLSTEIN (from January 1984)
	Dr G. LENOIR
	Dr A. LIKHACHEV
	Dr H. YAMASAKI
Consultants	Dr J. M. BECHET
	Professor R. SOHIER
Technical Assistant	Miss C. BONNARDEL
Technicians	Mrs A. M. AGUELON-PEGOURIES
	Miss H. BRÉSIL
	Miss B. CHAPOT
	Miss M. COLLARD (until February 1984)
	Miss O. DEBLOCK
	Miss M. P. DESVAUX (from May 1984)
	Mrs D. GALENDO
	Miss M. LAVAL
	Mrs M.-F. LAVOUÉ
	Mrs N. LYANDRAT
	Mrs G. MARTEL-PLANCHE
	Miss N. MARTEL
	Mrs S. PAULY
	Mrs C. PICCOLI
	Mrs M. VUILLAUME

Secretaries	Mrs P. COLLARD-BIANCHI Mrs C. FUCHEZ
Laboratory Aides	Mr J. CARDIA-LIMA Mr R. DRAY Mrs M. ESSERTEL Mr F. FARIA Mrs J. FARINA (until May 1984) Mr J. GARCIA Miss M. MARANHAO Mrs S. VEYRE

Unit of Carcinogen Identification and Evaluation

Chief	Dr H. VAINIO
Scientists	Miss L. HAROUN Mr J. D. WILBOURN
Bibliographic Researchers	Mrs C. PARTENSKY Mrs I. PETERSCHMITT
Technical Assistants	Mrs M.-J. GHESS Mrs J. CAZEAUX
Bibliographic Assistant	Mrs D. MIETTON
Secretaries	Mrs M. LEZERE Miss S. REYNAUD

Division of Administration and Finance

Director	Mr K. SAITA
Budget & Finance Officer	Mr R. M. SCOTT (until 11 May 1984)
Finance Officer	Mr G. W. DALSTON
Translator	Mr Y. POLLET
Administrative Services Officer	Mr B. BORGSTRØM
Administrative Assistant (Personnel)	Mrs A. ESCOFFIER
Administrative Assistant (Supplies)	Mrs J. POPOFF
Administrative Assistants (Finance)	Mrs F. CAFFO Miss M. ROMATIER
Administrative Assistant (Documents)	Mrs J. NIELSEN-KOLDING
Administrative Assistant (Building)	Mr E. CATHY
Administrative Assistant (Registry)	Mrs M.-H. CHARRIER
Administrative Assistant (ASO)	Mrs R. SEXTIER
Secretaries	Mrs J. BAILLY Mrs D. MARCOU Mrs J. MARTINEZ
Clerks (Finance)	Mrs F. FLORENTIN (half-time) Mrs D. LOMBARDO (half-time) Mr D. HORNEZ
Clerks (Registry)	Mrs M. GREENLAND (half-time) Mrs E. PEREZ (half-time)

Clerks (Supplies)	Mrs A. TROCHARD
Maintenance Technicians	Mr P. BARBIEUX Mr J. P. BONNEFOND Mr G. THOLLY
Equipment Operators (Printing)	Mr D. GRAIZELY Mr J. M. AMALFITANO (until 30 April 1984) Mr K. AMIR (from April 1984)
Clerk Stenographers (Pool)	Mrs E. BRUSSIEUX (until November 1983) Miss S. COTTERELL Miss M. GEESINK Mrs J. VALLES (from May 1984)
Other Services	Mr M. BAZIN Mrs R. KIBRISLIYAN Mr C. MAGNIARD Mr M. PRAT

Annex 4

VISITING SCIENTISTS, FELLOWS AND TRAINEES AT IARC 1 July 1983–30 June 1984

Visiting Scientists

Dr A. Al-Fouadi, Unit of Descriptive Epidemiology (December 1983–February 1984)

Dr B. Balkau, Unit of Biostatistics and Field Studies (July–August 1983)

Dr N. Breslow, Unit of Biostatistics and Field Studies (July–August 1983)

Dr R. Brookmeyer, Unit of Biostatistics and Field Studies (September–November 1983)

Mr P. Brooks, Unit of Mechanisms of Carcinogenesis

Dr D. G. Clayton, Unit of Biostatistics and Field Studies (from April 1984)

Mrs Y. Enomoto, Unit of Mechanisms of Carcinogenesis

Mrs E. Mark-Vendel, Unit of Mechanisms of Carcinogenesis

Dr D. Piskorska, Unit of Environmental Carcinogens and Host Factors (from February 1984)

Dr S. Preston-Martin, Unit of Analytical Epidemiology (from April 1984)

Dr A. Sasco, Unit of Biostatistics and Field Studies (from July 1983)

Miss M. Toubon, Unit of Environmental Carcinogens and Host Factors (from December 1983)

Mr D. P. Williams, Unit of Biostatistics and Field Studies (April–May 1984)

Fellows

Dr K. Athanasiou, Unit of Mechanisms of Carcinogenesis, fellowship from European Science Foundation (until August 1983)

Dr R. Becker, Unit of Mechanisms of Carcinogenesis, fellowship from US National Cancer Institute

Dr T. Enomoto, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellow

Dr K. Fujie, Unit of Mechanisms of Carcinogenesis, fellowship from Osaka Prefecture, Japan (until March 1984)

Dr R. Gurevicius, Unit of Descriptive Epidemiology, IARC Research Training Fellow (from February 1984)

Dr J. Hall, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellow (until December 1983)

Dr V. Kobljakov, Unit of Environmental Carcinogens and Host Factors, IARC Research Training Fellow (until April 1984)

Dr J. Nair, Unit of Environmental Carcinogens and Host Factors, IARC Research Training Fellow (from November 1983)

Dr A. Tzonou, Unit of Biostatistics and Field Studies, IARC Research Training Fellow (until September 1983)

Dr D. Umbenhauer, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellow (until June 1984)

Dr S. West, Unit of Biostatistics and Field Studies, ICRETT Fellow (from January 1984)

Trainees

Miss V. Bussachini, Unit of Environmental Carcinogens and Host Factors (from December 1983)

Miss S. Calmels, Unit of Environmental Carcinogens and Host Factors (from September 1983)

Miss R. Cartier, Unit of Environmental Carcinogens and Host Factors (until September 1983)

Mr M. César, Unit of Biostatistics and Field Studies (until July 1983)

Mr P. Delfosse, Unit of Descriptive Epidemiology (October–December 1983)

Mr M. Fontvieille, Unit of Mechanisms of Carcinogenesis (until July 1983)

Mr P. Giacomini, Unit of Biostatistics and Field Studies (from May 1984)

Miss L. Giroldi, Unit of Mechanisms of Carcinogenesis (February–June 1984)

Miss E. Hamel, Unit of Mechanisms of Carcinogenesis

Miss A. Lowenfels, Unit of Analytical Epidemiology (February–May 1984)

Mrs O. Maritaz, Unit of Mechanisms of Carcinogenesis (until September 1983)

Miss S. Moss, Unit of Descriptive Epidemiology (from January 1984)

Miss D. Niehoff, Unit of Biostatistics and Field Studies (from March 1984)

Mr A. Povey, Unit of Environmental Carcinogens and Host Factors

Miss S. Seuchter, Unit of Biostatistics and Field Studies (June–July 1983)

Miss A. M. Sørensen, Unit of Descriptive Epidemiology (from May 1984)

Miss R. Winkelmann, Unit of Biostatistics and Field Studies (June–July 1983)

Annex 5

RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS 1 July 1983–30 June 1984

Collaborating centres

DEB/74/03	Institute for Documentation, Information and Statistics, German Cancer Research Centre, Heidelberg, Federal Republic of Germany (Clearing-house for on-going research in cancer epidemiology)
DEB/81/19	Regina Elena Institute for the Study and Therapy of Tumours, Rome (Reference centre for the epidemiology of precancerous lesions and environmental carcinogens)
DEB/83/28	University Hospital of Vaud, Lausanne, Switzerland (Multinational study on the epidemiology of lymphoid neoplasia)

Cancer registries/Incidence studies

DEB/73/16	International Association of Cancer Registries (Provision of a secretariat and other supporting services)
DEB/81/23	Ministry of Health, Suva (Establishment of a population-based cancer registry in the Fiji Islands)
DEB/81/27	London School of Hygiene and Tropical Medicine, London (Case-control study of cervical cancer patients registered in selected cancer registries and clinics in the United Kingdom, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)
DEB/81/28	Danish Cancer Registry, Copenhagen (Case-control study of cervical cancer patients in Denmark, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)
DEB/81/29	Finnish Cancer Registry, Helsinki (Case-control study of cervical cancer patients in Finland, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)
DEB/81/30	Department of Gynaecology, Norwegian Radium Hospital, Oslo (Case-control study of cervical cancer patients in Norway, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/81/31 Department of Gynaecology, Karolinska Hospital, Stockholm
(Case-control study of cervical cancer patients in Sweden, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/81/36 Slovenian Cancer Registry, Institute of Oncology, Ljubljana, Yugoslavia
(Case-control study of cervical cancer patients in Slovenia, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/82/03 Unit of Epidemiology, National Cancer Institute of Cancer, Toronto, Canada
(Case-control study of cervical cancer patients registered in selected cancer registries of Canada, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/82/04 Department of Epidemiology, National Institute for the Study and Therapy of Tumours, Milan, Italy
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/82/05 Department of Gynaecology, University Women's Clinic, Gottingen, Federal Republic of Germany
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/82/07 Institute of Radiotherapy, Oncological Centre, Prague
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/82/08 Women's Clinic, University of Heidelberg, Heidelberg, Federal Republic of Germany
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/82/09 Department of Radiation, University Women's Clinic, Munich, Federal Republic of Germany
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/82/11 Ontario Cancer Treatment and Research Foundation, Toronto, Canada
(Case-control study of cervical cancer patients registered by the Ontario Cancer Treatment and Research Foundation, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/82/12 Department of Radiology, Clinic of Gynaecology, University of Vienna, Vienna
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/82/13 Unit of Epidemiology and Biostatistics, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Canada
(Case-control study of cervical cancer patients registered in Manitoba, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/82/17 Department of Gynaecology, Gustave Roussy Institute, Villejuif, France
(Follow-up of cervical cancer patients to ascertain the risk of developing second primary tumours following radiotherapy)

DEB/83/03 Icelandic Cancer Registry, Reykjavik
(Case-control study of cervical cancer patients registered in Iceland, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/83/04 National Cancer Society of Norway, Oslo
(Case-control study of cervical cancer patients registered in Norway, to assess the risk of developing second primary tumours, other than leukaemia, in patients exposed to radiation)

DEB/83/08 Cancer Institute of Montreal, Montreal, Canada
(Long-term carcinogenic hazards of chemotherapy treatment for cancer)

DEB/83/09 Cancer Registry, Central Institute for Cancer Research, Berlin-Buch
(Long-term carcinogenic hazards of chemotherapy treatment for cancer)

DEB/83/07 Ministry of Health, Mbabane, Swaziland
(Cancer registry of Swaziland)

DEB/83/17 Cancer Registry, Central Institute for Cancer Research, Berlin-Buch
(Preparation of cancer incidence atlas of the German Democratic Republic)

DEB/83/19 Israel Cancer Registry, Israel Centre for Registration of Cancer and Allied Diseases, Jerusalem, Israel
(Monograph on cancer incidence in Jewish migrants to Israel)

DEB/83/24 London School of Hygiene and Tropical Medicine, London
(Multiple tumours in England and Wales)

DEB/84/09 Ontario Cancer Treatment and Research Foundation, Toronto, Canada
(Second cancer among individuals diagnosed with a cancer of the ovary or testis, or with Hodgkin's disease)

Studies on cancers linked with herpesviruses

DEB/71/07 Shirati Mission Hospital, Tarime District, Tanzania
(Study on the epidemiology of Burkitt's lymphoma in the North Mara District, Tanzania)

DEC/82/15 Department of Pediatric Surgery, Mustapha University Hospital, Alger, Algeria
(Characterization of Burkitt's lymphoma in Algeria)

DEC/83/09 Laboratoire de Cytogénétique, Centre de transfusion sanguine, 42023 Saint-Etienne Cedex, France
(Caractérisation des anomalies cytogénétiques observées dans les cellules de lymphome de type Burkitt)

Liver cancer studies

DEB/79/21 Department of Social Medicine and Public Health, University of Singapore, Singapore
(Cohort study on hepatitis B carriers and liver cancer)

DEB/81/11 Immunology Section, University of Philippines, Manila
(Case-control study of parents of patients with liver-cell cancer and of control patients)

DEB/83/02 University Department of Medicine, Singapore General Hospital, Singapore
(Monitoring of liver cancer trends before and after the introduction of hepatitis B vaccine)

Studies on nutrition and on cancer of the gastrointestinal tract

DEB/78/14 School of Public Health, Free University of Brussels, Laboratory of Epidemiology and Social Medicine, Brussels
(Study of digestive-tract cancer in Belgium)

DEC/81/04 Leatherhead Food Research Association, Leatherhead, UK
(Determination of total *N*-nitroso compounds in the gastric juice of patients with precancerous lesions)

DEB/81/38 Medical Research Council, London
(IARC coordinated international study of diet and faecal characteristics in relation to colo-rectal and other cancers)

DEB/81/40 Regina Elena Institute for the Study and Therapy of Tumours, Rome
(Case-control study of adenomatous polyps of large bowel)

DEB/81/41 Public Health Laboratory Service, Centre for Applied Microbiology and Research, Salisbury, UK
(Analysis of faeces and urine samples from the case-control study of adenomatous polyps of the large bowel in Rome)

DEB/82/10 Edouard Herriot Hospital, Lyon, France
(Nitroso-compounds in gastric juice)

DEB/83/06 Cancer Institute, Beijing and Provincial Cancer Institute, Henan, People's Republic of China
(Double-blind intervention study on precancerous lesions of the oesophagus and selected vitamins)

DEC/83/06 Department of Hygiene, Aikita University School of Medicine, Aikita, Japan
(Study on the endogenous formation of *N*-nitroso compounds and nutritional status of subjects in high- and low-incidence areas for stomach cancer in Japan)

DEB/83/14 Clinical Investigation Unit, Dudley Road Hospital, Birmingham, UK
(Biochemical analyses of blood samples collected during a screening survey of precancerous lesions of oral cavity and oesophagus in Samarkand region, USSR)

DEB/83/16 All-Union Cancer Research Centre of the USSR, Academy of Medical Sciences, Moscow
(Chemopreventive trial of precancerous lesions of the mouth and oesophagus in Uzbek SSR (USSR))

DEB/83/21 Icelandic Cancer Registry, Reykjavik
(Nutrition and breast cancer in Iceland)

DEB/83/22 Clinical Investigation Unit, Dudley Road Hospital, Birmingham, UK
(Biochemical analyses of blood samples collected during an intervention study on precancerous lesions of the oesophagus in the People's Republic of China)

DEB/83/23 Medical Center, University of Colorado, Denver, USA
(Zinc analyses of blood and hair samples collected during an intervention study on precancerous lesions of the oesophagus in the People's Republic of China)

DEB/84/01 Singapore Cancer Registry, Department of Pathology, University of Singapore, Singapore
(Development of methodology for the conduct of diet-directed case-control studies in Singapore)

DEC/84/02 Cancer Institute, Chinese Academy of Medical Sciences, Beijing
(Studies on the endogenous formation of *N*-nitroso compounds in high- and low-incidence areas for oesophageal cancer in the People's Republic of China)

Studies on occupational cancer

DEB/83/20 Regional Centre of Environmenal Carcinogenesis, University of Padua, Padua, Italy
(Historical follow-up mortality study of workers compensated for silicosis)

DEB/83/25 Institute of Anatomy, University of Turin, Turin, Italy
(Historical follow-up mortality study of anthracite miners in La Thuile and Cogne (Aosta))

DEB/83/26 Danish Cancer Registry, Copenhagen
(Analysis of routinely collected statistical data to investigate a possible association between silica dust exposure and increased lung cancer mortality)

DEB/83/27 Medical Research Council Environmental Epidemiology Unit, University of Southampton, Southampton, UK
(Historical follow-up mortality study of a cohort of pottery workers)

DEB/84/03 Danish Cancer Registry, Copenhagen
(Man-made mineral fibres (MMMF) historical prospective investigation in the producer industry)

DEB/84/04 Medical Research Council Environmental Epidemiology Unit, University of Southampton, Southampton, UK
(Man-made mineral fibres (MMMF) historical prospective investigation in the producer industry)

DEB/84/05 Institute for Documentation, Information and Statistics, German Cancer Research Centre, Heidelberg, Federal Republic of Germany
(Man-made mineral fibres (MMMF) historical prospective investigation in the producer industry)

DEB/84/06 Clinic 'Luigi Devoto', University of Milan, Milan, Italy
(Man-made mineral fibres (MMMF) historical prospective investigation in the producer industry)

DEB/84/07 Swedish Labour Organization, Stockholm
(Man-made mineral fibres (MMMF) historical prospective investigation in the producer industry)

DEB/84/11 Department of Epidemiology, National Institute for the Study and Therapy of Tumours, Milan, Italy
(Study on the possible role of environmental factors in the origin of human cancer, with special emphasis on occupational exposures)

Studies on various other cancer forms

DEC/78/13 Department of Clinical Genetics, University Hospital of Lund, Lund, Sweden
(Study on the possibility of correlating the karyotypes of cancer cells to specific etiological factors)

DEB/81/17 Danish Cancer Registry, Copenhagen
(Evaluation of screening programmes for the detection of cervical cancer)

DEB/82/19 Icelandic Cancer Registry, Reykjavik
(Evaluation of familial factors by determining risk for cancers of the breast and other sites)

DEB/83/05 Unit of Epidemiology and Biostatistics, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Canada
(International study of malignant melanoma)

DEB/83/10 Department of Pathology, Princess Alexandra Hospital, Brisbane, Australia
(International study on change in diagnostic criteria for pigmented skin lesions)

DEB/83/11 Department of Pathology, University of Otago, Dunedin, Australia
(International study on change in diagnostic criteria for pigmented skin lesions)

DEB/83/12 Division of Dermatopathology and Oral Pathology, Johns Hopkins University, Baltimore, MD, USA
(International study on change in diagnostic criteria for pigmented skin lesions)

DEB/83/13 Department of Pathology, The North Brisbane Hospital, Brisbane, Australia
(International study on change in diagnostic criteria for pigmented skin lesions)

DEB/83/15 National Council of Scientific and Technical Investigations, Buenos Aires, Argentina
(Feasibility study on long-term effects of pesticides on human health in Argentina)

Studies on chemical carcinogenesis

DEC/78/02 School of Pharmacy, Catholic University of Louvain, Brussels
(Creation of an IARC Reference Centre for the in-vivo monitoring of drug metabolizing enzymes)

DEC/79/06 Institute of Medical Sciences, University of Tokyo, Tokyo
(Mutagenesis and neoplastic transformation *in vitro* of cultured cells by environmental chemicals)

DEC/79/10 Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow
(Investigation on the development of cellular and biochemical markers of in-vitro transformation of epithelial cells in culture)

DEC/80/01	Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan (Investigation of mutagenicity testing in bacteria and yeast by environmental chemicals within an international network of carcinogenicity testing)
DEC/80/13	Institute of Oncology, University of Genoa, Genoa, Italy (Long-term carcinogenicity testing of environmental chemicals)
DEC/80/18	Curie Institute, Biology Section, Faculty of Sciences, Orsay, France (Synthesis of unlabelled and radio-labelled chemicals to be used in experimental studies)
DEC/81/02	Cancer Institute, Chinese Academy of Medical Sciences, Beijing (Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines)
DEC/81/03	Institute for Cell Biology, University of Essen, Essen, Federal Republic of Germany (Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines)
DEC/81/08	Institute of Experimental and Clinical Medicine, Tallin, Estonia, USSR (Studies on the mutagenic and carcinogenic activities of fly ashes originating from the combustion of shale oil)
DEC/81/09	Oncological Institute of the Ministry of Health, Ministry of Health of Lithuanian SSR, Vilnius, Lithuanian SSR, USSR (Long-term carcinogenicity testing of environmental chemicals)
DEC/81/24	Institute of Oncology, Medical Academy, Sofia (Investigation on the possible relationship between endemic nephropathy, cancer of the urinary tract and ochratoxin contamination of food)
DEC/81/25	Clinical Pharmacology Laboratory, Karolinska Institute, Huddinge, Sweden (Investigation of the comparative capacity of tissues and cells of human and rodent origin to repair DNA modifications induced by environmental chemicals)
DEC/81/32	Laboratory of Mutagenicity, Institute of Occupational Health, Helsinki (Study on sister chromatid exchange rates as an indicator of cancer risk in chemical carcinogenesis)
DEC/81/33	N. N. Petrov Research Institute of Oncology, Leningrad, USSR (Study of role of promoting factors in possible carcinogenic effect of 5-bromodeoxyuridine)
DEC/81/34	Oncological Research Center, Academy of Medical Sciences, Moscow (Long-term carcinogenicity testing of environmental chemicals)
DEC/81/35	National Institute of Hygiene, Budapest (Long-term carcinogenicity testing of environmental chemicals)
DEC/82/01	Life Science Laboratory, Teeside Polytechnic, Cleveland, UK (Study on carcinogenic effects in the offspring of male Swiss mice treated with MNU or ENU before mating)
DEC/82/06	School of Pharmacy, Catholic University of Louvain, Brussels (Study on the promoting activity of diazepam and related compounds)

DEC/82/16 Laboratory of Biophysics and Radiobiology, Free University of Brussels, Rhode-Saint-Genese, Belgium
(Investigation of an in-vitro assay for measuring genetic changes in mammalian cells)

DEC/82/21 Centre for Medical Research, University of Sussex, Brighton, UK
(Studies on an in-vitro assay for measuring genetic changes in human cells)

DEC/82/22 Joint Mass Spectrometry Centre, Claude Bernard University, Lyon, France
(Study on the development of methods of analysis of carcinogens by combined high-performance liquid chromatography-mass spectrometry)

DEC/83/01 Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK
(Preparation and characterization of antibodies against DNA modifications induced by nitrosamines to be used for the determination of human exposure to that group of carcinogens)

DEC/83/02 Institute of Oncology, Ljubljana, Yugoslavia
(Study on the role of carcinogenic agents in determining the metastatic potential of induced tumours)

DEC/83/03 Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, UK
(Studies on analgesic-associated renal pelvic and ureteral/urothelial hyperplasia and carcinoma)

DEC/83/04 University of Kuopio, Kuopio, Finland
(Purification of cytochrome P-450-DMN demethylase and preparation of its antibody)

DEC/83/05 N. N. Petrov Institute of Oncology, Leningrad, USSR
(Study on the activation of chemical carcinogens by embryonal tissues at various stages of development)

DEC/83/07 Laboratoire de Recherche Appliquée aux Cancérogènes Chimiques, Institut de Recherches Scientifiques sur le Cancer, Villejuif, France
(Investigation of quantitative initiation-promotion carcinogenesis on mouse skin)

DEC/83/10 Cancer Research Unit, University of York, York, UK
(Detection of aflatoxin B_1 and metabolites by immunoassay in human biological materials)

DEC/83/11 Institute of Oncology, Medical Academy, Sofia
(Mycotoxins and individual oxidative susceptibility in relation to endemic nephropathies and tumours of the urinary system)

DEC/83/12 Laboratoire des Hépatites, INSERM U 45, Lyon, France
(Interactions entre l'infection chronique par le virus de l'hépatite B du canard et la consommation d'aflatoxine dans le déterminisme de l'hépatocarcinome)

DEC/84/01 Research Department, National Board of Occupational Safety and Health, Solna, Sweden
(Long-term carcinogenicity testing of environmental chemicals)

DEC/84/03 Cancer Research Institute, Tata Memorial Centre, Bombay, India
(Monitoring of carcinogen exposure in tobacco/betel quid chewers and smokers)

DEC/84/04	I Institute of Pathology, Semmelweis Medical University, Budapest (Study of the capacity of UV light to induce DNA repair processes in human cells)

Support of meetings

DEB/83/18	Osaka Cancer Registry, Department of Field Research, Centre for Adult Diseases, Osaka, Japan (Annual meeting of the International Association of Cancer Registries (IACR), Fukuoka, Japan, 27–29 September 1984)

Annex 6

MEETINGS AND WORKSHOPS ORGANIZED BY IARC
July 1983–June 1984

Meeting of the International Association of Cancer Registries	Heidelberg, FRG 1–3 September 1983
8th International Symposium on *N*-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer	Banff, Canada 4–9 September 1983
IARC Scientific Council Sub-Committee and Peer Review of Tumour Promotion Programme	Lyon, 6–7 October 1983
Working Group on Laryngeal Cancer Study	Lyon, 13–14 October 1983
Working Group on the Establishment and Maintenance of an International Register of Persons Exposed to Phenoxy Acid Herbicides and Contaminants	Lyon, 13–14 October 1983
9th Meeting of the Editorial Board for the Manuals on Environmental Carcinogens—Selected Methods of Analysis	Lyon, 13–14 October 1983
Working Group on Confidentiality in Cancer Registries	Lyon, 18–19 October 1983
IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding	Lyon, 18–25 October 1983
Working Group on the Evaluation of Cervical Cancer Screening Programmes	Copenhagen, 26–28 October 1983
Working Group on 'Statistical Methods in Descriptive Epidemiology'	Lyon, 4–5 November 1983
Working Group on the Pancreatic Study	Lyon, 10–11 November 1983
Course on Cancer Epidemiology (in French)	Yaoundé, Cameroon, 14–27 November 1983
Joint IARC/JEMRB Meeting on the Man-made Mineral Fibre Study	Lyon, 23–24 November 1983
International Symposium on Burkitt's Lymphoma—A Human Cancer Model	Lyon, 6–9 December 1983
Meeting on Age-related Factors in Carcinogenesis	Leningrad, 7–9 December 1983

Review Board Meeting for the Manual on Environmental Carcinogens—Selected Methods of Analysis: Passive Smoking	Valhalla, NY, USA, 8–9 December 1983
Joint IARC/IPCS/IOH/CEC International Seminar on Methods of Monitoring Human Exposure to Carcinogenic and Mutagenic Agents	Espoo, Finland, 12–15 December 1983
Meeting on the Collaborative Study Manual on Destruction and Disposal of Laboratory Wastes: Aromatic Amines	Lyon, 9–11 January 1984
Meeting on the Collaborative Study Manual on Destruction and Disposal of Laboratory Wastes: Haloethers	Lyon, 12–13 January 1984
IARC Working Group on Priorities for Chemicals or Mixed Exposures to be Evaluated in *IARC Monographs* or Tested for Carcinogenicity	Lyon, 17–20 January 1984
Meeting on Case-control Studies of Large-bowel Cancer in Majorca	Lyon, 23–24 January 1984
IARC Scientific Council	Lyon, 31 January–2 February 1984
Working Group on the Evaluation of Bladder Cancer Studies	Lyon, 6–8 February 1984
Workshop on Case-control Assessment of Occupational Hazards	Lyon, 9–10 February 1984
Workshop on the Use of *in vitro* Transformation of Established Cell Lines for the Prediction of Carcinogenic Chemicals	Lyon, 15–17 February 1984
IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Bitumens, Coal-tar and some Coal-tar-derived Products, Shale Oils and Soots	Lyon, 21–28 February 1984
Course on Cancer Epidemiology (in Spanish)	Lima, 27 February–9 March 1984
Working Group on the International Radiation Study to Evaluate the Risks of Radiation Exposure in Cervical Cancer Patients	Lyon, 13–14 March 1984
Meeting on Second Malignancies Following Chemotherapy for Cancer: Collaborative Study	Lyon, 15 March 1984
Working Group on Laryngeal Cancer Study	Lyon, 15–16 March 1984
Course on Cancer Epidemiology	Rome, 19–31 March 1984
Meeting on Breast Cancer	Reykjavik, 12–13 April 1984
Working Group on Passive Smoking Risks	Lyon, 12–13 April 1984
IARC Fellowships Selection Committee	Lyon, 17–19 April 1984
Working Group on Monitoring of Aflatoxins in Human Body Fluids and Application to Field Studies	Lyon, 26–27 April 1984
Planning Meeting for the Design and Analysis of Long-term Animal Experiments	Bethesda, MD, USA, 26–27 April 1984

IARC Governing Council	Lyon, 3–4 May 1984
Meeting on the Hepatitis B Vaccination Trial in The Gambia	Lyon, 21–22 May 1984
Working Group on Cerebral Tumours Protocol	Lyon, 5–7 June 1984
Workshop on Practice of Confidentiality in the Cancer Registry	Lyon, 5–7 June 1984
IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Allyl Compounds, Aldehydes, Epoxides and Peroxides	Lyon, 19–26 June 1984
Programme Committee Meeting for the Workshop on Evaluation of Methods for Assessing Human Health Hazards from Drinking-Water (to be held at the Agency, 11–14 December 1984)	Lyon, 28 June 1984

Annex 7

VISITORS TO IARC, JULY 1983–JUNE 1984

Dr M. ABDELMOUMENE
Chief, Office of Research Promotion and Development, World Health Organization, Geneva, Switzerland

Dr A. ADROVER*
Colorectal Cancer Study Group, Palma de Mallorca, Spain

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Central Laboratory for Medical Research, Alwyiah, Baghdad

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Department of Preventive and Social Medicine, State University of Campinas, Campinas, Brazil

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Chemical Research and Development Center, FMC Corporation, Princeton, NJ, USA

Dr P. F. AMBIDGE*
British Cast Iron Association and British Foundry Association, Birmingham, UK

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Chief, Data Processing, Cancer Registry of Norway, Institute for Epidemiological Research, c/o Norwegian Radium Hospital, Oslo 3

Dr G. ARESINI*
Commission of the European Communities, Health & Safety Directorate, Luxembourg

A. AROMAA*
Social Insurance Institution, Helsinki

Dr D. ARSENE*
Calvados District Cancer Registry, Caen, France

Dr F. A. ASSAAD
Division of Communicable Diseases, World Health Organization, Geneva, Switzerland

Dr F. ATTENA
Institute of Hygiene and Preventive Medicine, Naples, Italy

Dr H. AUTRUP*
Miljo OG Kraeft Laboratory, Copenhagen

Professor O. AXELSON*
Department of Occupational Medicine and Industrial Ergonomics, University Hospital, Linköping, Sweden

Professor H. AZUMA
Institute of Immunological Sciences, Hokkaido University, Sapporo, Japan

Dr K. BAGHURST
Commonwealth Scientific and Industrial Research Organization, Division of Human Nutrition, Adelaide, Australia

Dr. R. BALLESTER*
Colorectal Cancer Study Group, Palma de Mallorca, Spain

Professor P. BANNASCH*
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* *Member of working group*
** *Consultant or temporary adviser*

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Department of Analytical Chemistry, Charles University, Prague

Professor D. BARKER
Acting Director, MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK

Mr W. C. BARTLEY
International Health Attaché
United States Mission to the United Nations Office and other International Organizations at Geneva, Chambésy, Switzerland

Sir Derek BARTON
Director, Institute of Chemistry of Natural Substances, Gif-sur-Yvette, France

Dr R. BASS*
Pharmacological Institute, Ministry of Health of Federal Republic of Germany, Berlin (West)

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Annex 8

VISITING LECTURERS TO IARC
July 1983–June 1984

Dr M. Ahotupa	'Response of biotransformation enzymes to polchlorinated biphenyls and modification of the response by body fat'
Dr F. Berrino	'Increased androgenic activity and breast cancer risk'
Dr R. Brookmeyer	'The effect of additional follow-up and accrual on survival time data'
Dr Cadet	'Modifications to dinucleotides and DNA components—determination of structures by recent techniques of FTNMR and mass spectroscopy'
Dr D. Coggon	'The young cancer study'
Professor J. Craighead	'Study of Kaposi's sarcoma in Africa'
Dr G. Giraldo	'Kaposi's sarcoma in AIDS: a tumour of local importance and of international significance'
Dr A. N. Gjorgov	'Barrier contraception and breast cancer: prospects for prevention'
Dr P. Greenwald	'Cancer prevention'
Dr A. W. Hsie	'A multiphasic approach of mammalian cell genetic toxicology'
Dr E. Huberman	'The control fo cell differentiation by chemicals which enhance malignant cell transformation'
Dr A.S. Ibrahim	'Bladder cancer'
Dr H. Ishiwata	'Behaviour of the precursors of *N*-nitrosodimethylamine in humans and experimental animals'
Dr A. Kalache	'Betacarotene and cancer in Salvador, Brazil'
Professor S. Kamiyama	'Mutagenic effects in the diet of inhabitants living in a high and low risk area for stomach cancer in Japan'
Dr T. Lindhal	'Mechanisms of repair of alkylated DNA'
Dr R. K. Mitchum	'Mass spectrometry in environmental chemistry and cancer research'
Professor N. P. Napalkov	'Cancer control'

Dr H. Norppa	'Erythrocyte-mediated activation of styrene and other chemicals'
Dr R. Palmer Beasley	'Studies on hepatitis and liver cancer'
Dr M. Parvinen	'Toxic and mutagenic influences on spermatogenesis'
Professor O. Pelkonen	'Genetic and environmental regulation of aryl hydrocarbon hydroxylase in man'
Professor S. Plesnicar	'The heterogeneity of metastatic cell populations: clinical evidence'
Dr J. D. Potter	'Case-control study of colo-rectal cancer in Adelaide'
Professor M. Roberfroid	'A new model to study the biological mechanism of hepatocarcinogenesis'
Professor D. Schmähl	'Experimental and practical approaches to cytostatistics-induced carcinogenesis'
Professor T. Sugimura	'Recent topics from the National Cancer Center Research Institute, Tokyo'
Dr E. Trell	'Population studies of mixed function oxidase enzymes'
Dr Tsung-Tang Sun	'Epidemiological and experimental studies in the etiology of liver cancer in China'
Dr J. C. M. van der Hoeven	'Natural mutagens occurring in food plants'
Professor S. Vesselinovitch	'Kinetics of hepatocarcinogenesis'
Professor G. N. Vyas	'Hepatitis B virus dissemination in non-hepatocellular oncogenesis'
Dr J. L. Young	'Cancer survival in the United States by ethnic group'

Annex 9

INTERNAL TECHNICAL REPORTS, 1983–1984

IARC Internal Technical Report No.	
83/002	Multiple Tumours Working Group Report, IARC, Lyon (1983)

Annex 10

PAPERS PUBLISHED OR SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS

Anisimov, V. N., Bespalov, V. G., Ovsyannikov, A. I. & Likhachev, A. J. (1984) *Effect of ageing on carcinogenesis and DNA synthesis in the liver of rats exposed to 1,2-dimethylhydrazine after partial hepatectomy.* In: van Bezooijen, C.F.A., ed., *Proceedings of the meeting EURAGE, Rijswijk. Pharmacological, Morphological and Physiological Aspects of Liver Ageing,* pp. 217–222

Barbin, A., Laib, R. L. & Bartsch, H. (1983) Analysis of chloroethylene oxide-treated poly(dG-dC) and evidence that vinyl chloride alters the processivity and fidelity of replication through various primary and secondary DNA-lesions (submitted for publication)

Bartsch, H. & O'Neill, I. K. (1984) Meeting Report: Eighth International Meeting on *N*-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer. *Cancer Res.,* **44,** 1301–1304

Bartsch, H., Aitio, A., Camus, A. M., Malaveille, C., Roberfroid, M., Vo Thi, K. O. & Sabadie, B. (1983) *Carcinogen-metabolizing enzymes and susceptibility to chemical carcinogens.* In: Turusov, V. & Montesano, R., eds, *Modulators of Experimental Carcinogenesis (IARC Scientific Publication No. 51),* Lyon, International Agency for Research on Cancer, pp. 147–156

Bartsch, H., Malaveille, C., Camus, A. M., Brun, G. & Hautefeuille, A. (1983) *Validation and comparative mutagenicity studies in* S. typhimurium *on 180 chemicals.* In: Kolber, A. R., Wong, T. K., Grant, L. D., DeWoskin, R. S. & Hughes, T. J., eds, *In vitro Toxicity Testing of Environmental Agents: Current and Future Possibilities—Part B,* New York and London, Plenum Press, pp. 251–279

Bartsch, H., Ohshima, H., Muñoz, N., Crespi, M. & Lu, S. H. (1983) *Measurements of endogenous nitrosation in humans: potential applications of a new method and initial results.* In: Harris, C. C. & Autrup, H. N., eds, *Human Carcinogenesis,* New York, Academic Press, pp. 833–856

Bartsch, H., Ohshima, H., Muñoz, N., Pignatelli, B., Friesen, M., O'Neill, I., Crespi, M. & Lu, S. H. (1983) *Assessment of endogenous nitrosation in humans in relation to the risk of cancer of the digestive tract.* In: Hayes, A. W., Schnell, R. C. & Miya, T. S., eds, *Developments in the Science and Practice of Toxicology,* Amsterdam, Elsevier Science Publishers, pp. 299–309

Bartsch, H., Ohshima, H., Muñoz, N., Crespi, M., Cassale, V., Ramazotti, V., Lambert, R., Minaire, Y., Forichon, J. & Walters, C. L. (1984) In-vivo *nitrosation, precancerous lesions and cancers of the gastrointestinal tract: on-going studies and preliminary results.* In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Battey, J., Moulding, C., Taub, R., Murphy, W., Stewart, T., Potter, H., Lenoir, G. & Leder, P. (1983) The human c-myc oncogene: Structural consequences of translation into the IgH locus in Burkitt lymphoma. *Cell,* **34,** 779–787

Béchet, J. M., Bornkamm, G., Freese, U. K. & Lenoir, G. M. (1984) The c-sis oncogene is not activated in Ewing's sarcoma. *New Engl. J. Med.*, **310**, 393

Begg, C. B., Walker, A. M., Wessen, B. & Zelen, M. (1983) Alcohol consumption and breast cancer (letter). *Lancet*, **i**, 293-294

Beldjord, C., Lapoumeroulie, C., Baird, M. L., Girot, R., Adjrad, L., Lenoir, G., Benabadji, M. & Labie, D. (1983) Four haplotypes observed in Algerian beta-thalassemia patients. *Human Genet.*, **65**, 204–206

Bernheim, A., Berger, R. & Lenoir, G. (1983) Cytogenetic studies on Burkitt's lymphoma cell lines. *Cancer Genet. Cytogenet.*, **8**, 223–229

Blettner, M. & Wahrendorf, J. (1984) What does an observed relative risk convey about possible misclassification? *Meth. Inform. Med.*, **23**, 37–40

Börzsönyi, M., Day, N. E., Lapis, K. & Yamasaki, H., eds (1984) *Models, Mechanisms and Etiology of Tumour Promotion (IARC Scientific Publications No. 56)*, Lyon, International Agency for Research on Cancer (in press)

Boyle, P. & Zaridze, D. G. (1984) Colorectal cancer as a disease of the environment. *Ecol. Dis.* (in press)

Boyle, P., Day, N. E. & Magnus, K. (1983) Mathematical modelling of malignant melanoma trends in Norway. *Am. J. Epidemiol.*, **118**, 887–896

Brookmeyer, R., Day, N. E. & Pompe-Kirn, V. (1984) Assessing the impact of additional follow up in cohort studies (submitted for publication)

Cabral, J. R. P. & Neal, G. E. (1984) Hepatocarcinogenesis in Fischer rats following limited exposures to *N*-2-fluorenylacetamide (FAA). *Toxicologist*, **5** *(in press)*

Camus, A. M., Aitio, A., Sabadie, B., Wahrendorf, J. & Bartsch, H. (1984) Metabolism and urinary excretion of mutagenic metabolites of benzo[*a*]pyrene in C57 and DBA mice strains. *Carcinogenesis*, **5**, 35–39

Castegnaro, M., Benard, M., van Broekhoven, L. W., Fine, D., Massey, R., Sansone, E. B., Smith, P. L. R., Spiegelhalder, B., Stacchini, A., Telling, G. & Vallon, J.J., eds (1983) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some* N*-Nitrosamides (IARC Scientific Publications No. 55)*, Lyon, International Agency for Research on Cancer

Castegnaro, M., Brouet, I. & Michelon, J. (1983) *Destruction of hydrazines in laboratory wastes using hypochlorites.* In: Castegnaro, M., Ellen, G., Lafontaine, M., Van der Plas, H. C., Sansone, E. B. & Tucker, S. P., eds, *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Hydrazines (IARC Scientific Publications No. 54)*, Lyon, International Agency for Research on Cancer, pp. 49–57

Castegnaro, M., Brouet, I. & Michelon, J. (1983) *Destruction of hydrazines in laboratory wastes using potassium permangante in sulfuric acid.* In: Castegnaro, M., Ellen, G., Lafontaine, M., Van der Plas, H. C., Sansone, E. B. & Tucker, S. P., eds, *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Hydrazines (IARC Scientific Publications No. 54)*, Lyon, International Agency for Research on Cancer, pp. 31–39

Castegnaro, M., Ellen, G., Lafontaine, M., Van der Plas, H. C., Sansone, E. B. & Tucker, S. P., eds (1983) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Hydrazines (IARC Scientific Publications No. 54)*, Lyon, International Agency for Research on Cancer

Castegnaro, M., Malaveille, C., Michelon, J. & Brouet, I. (1983) *Destruction of nitrosamides in laboratory wastes using hydrobromic acid.* In: Castegnaro, M., Benard, M., van Broekhoven, L. W., Fine, D., Massey, R., Sansone, E. B., Smith, P. L. R., Spiegelhalder, B., Stacchini, A., Telling, G. & Vallon, J. J., eds, *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some* N-*Nitrosamides (IARC Scientific Publications No. 55),* Lyon, International Agency for Research on Cancer, pp. 37–45

Castegnaro, M., Malaveille, C., Michelon, J. & Brouet, I. (1983) *Destruction of nitrosamides in laboratory wastes using potassium permanganate in sulfuric acid.* In: Castegnaro, M., Benard, M., van Broekhaven, L. W., Fine, D., Massey, R., Sansone, E. B., Smith, P. L. R., Spiegelhalder, B., Stacchini, A., Telling, G. & Vallon, J. J., eds, *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some* N-*Nitrosamides (IARC Scientific Publications No. 55),* Lyon, International Agency for Research on Cancer, pp. 29–35

Castegnaro, M., Malaveille, C., Brouet, I., Michelon, J. & Barek, J. (1984) Destruction of aromatic amines in laboratory wastes through oxidation with potassium permanganate/sulfuric acid into non-mutagenic derivatives. *J. Am. Ind. Hyg. Assoc.* (in press)

Cohen, J. H. M., Bouic, P., Schmitt, D., Lenoir, G. & Revillard, J. P. (1983) Endocytosis of class II histocompatibility antigens and formation of intracytoplasmic granules at the final differentiation stage of human B lymphocytes. *Immunol. Lett.,* **7,** 123–127

Collette, H. J. A., Rombach, J. J., Day, N. E. & de Waard, F. (1984) Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case-control study. *Lancet,* **i,** 1224–1226

Crespi, M., Grassi, A., Muñoz, N., Guo-Quing, W. & Guanrei, Y. (1984) Endoscopic features of suspected precancerous lesions in high-risk areas for eosophageal cancer. *Endoscopy,* **3,** 85–91

Crespi, M., Muñoz, N., Grassi, A., Shen Qiong, Wang Kuo Jing & Lin Jing Jien (1984) Precursor lesions of oesophageal cancer in high- and low-risk populations in China (submitted for publication)

Croce, C. M., Thierfelder, W., Erikson, J., Nishikura, K., Finan, J., Lenoir, G. M. & Nowell, P. C. (1983) Transcriptional activation of an unrearranged and untranslocated c-myc oncogene by translocation of a C locus in Burkitt lymphoma cells. *Proc. natl Acad. Sci. USA,* **80,** 6922–6926

Croisy, A., Ohshima, H. & Bartsch, H. (1984) *Nitrosating properties of bismethylthio diiron tetranitrosyl (Roussin's Red methyl ester), a nitroso compound isolated from pickled vegetables consumed in Northern China.* In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Day, N. E. (1983) Time as a determinant of risk in cancer epidemiology: the role of multi-stage models. *Cancer Surveys,* **2,** 577-593

Day, N. E. (1983) *The assessment of negative epidemiological evidence: some statistical considerations.* In: Wald, N. & Doll, R., eds, *Proceedings of the Symposium on Practical Value of Negative Epidemiological Evidence, Oxford, 4–6 July 1983* (in press)

Day, N. E. (1984) The effect of cervical cancer screening in Scandinavia. *Obstet. Gynecol.,* **63,** 714–718

Day, N. E. (1984) The geographic pathology of cancer of the oesophagus. *Br. med. Bull.* (in press)

Day, N. E. (1984) *Epidemiological methods for the assessment of human cancer risk.* In: Clayson, D. B., Krewski, D. & Munro, I. C., eds, *Toxicological Risk Assessment,* New York, CRC Press (in press)

Day, N. E. & Boice, J. D., Jr, eds (1983) *Second Cancer in Relation to Radiation Treatment for Cervical Cancer. A Cancer Registry Collaboration (IARC Scientific Publications No. 52),* Lyon, International Agency for Research on Cancer

Day, N. E. & Walter, S. D. (1983) Simplified models for screening: estimation procedures from mass screening programmes. *Biometrics,* **40,** 1–13

Day, N. E., Walter, S. D. & Collette, B. (1984) *Statistical models of disease natural history: their use in the evaluation of screening programmes.* In: *Venice Conference on Evaluation of Screening Programs for Cancer (UICC tech. Rep. Ser.), 14–16 November 1983* (in press)

Day, N. E., Smith, P. G. & Lachet, B. (1984) *The latent period of Burkitt's lymphona: the evidence from epidemiological clustering.* In: Lenoir, G., O'Conor, G. & Olweny, C., eds, *Burkitt's Lymphoma: A Human Cancer Model (IARC Scientific Publications No. 60),* Lyon, International Agency for Research on Cancer (in press)

Day, N. E., Malaveille, C., Friesen, M. & Bartsch, H. (1983) *The possible role of opium and tobacco pyrolysates in esophageal cancer.* In: Stich H., ed., *Carcinogens and Mutagens in the Environment,* Vol. III, *Naturally Occurring Compounds,* Boca Raton, FL, CRC Press, pp. 59–72

Dellagi, K., Brouet, J. C., Portier, M. M. & Lenoir, G. M. (1984) Abnormal expression of vimentin intermediate filaments in human lymphoid cell lines with deletion or translocation of the distal end of chromosome 8. *J. natl Cancer Inst.,* **73,** 95–99

Dreyfus, J. C., Belon, J. P., Gautron, S., Lenoir, G. & Poenaru, L. (1984) High-frequency of beta-hexosaminidase deficiency in lymphoblastoid cell lines. *Biochem. biophys. Res. Commun.,* **119,** 841–849

EIAS (1984) Une étude épidemiologique sur les cancers du tube digestif en Belgique. *Ann. Arch. Belges med. Soc.* (in press)

El-Bolkainy, N., Dahba, N., O'Conor, G., Gad-El-Mawia, N. & Morad, N. (1984) *Primary extranodal lymphomas in Egypt.* In: *Program and Abstracts, Second International Conference on Malignant Lymphoma, June 13–16, 1984, Lugano, Switzerland*

Enomoto, T., Martel, N., Kanno, Y. & Yamasaki, H. (1984) Inhibition of cell-cell communication between BALB/c 3T3 cells by tumor promoters and protection by cAMP. *J. Cell Phys.* (in press)

Erikson, J., Nishikura, K., Ar-Rushdi, A., Finan, J., Emanuel, B., Lenoir, G., Nowell, P. C. & Croce, C. M. (1983) Translocation of an immunoglobulin k locus to a region 3' of an unrearranged c-myc oncogene enhances c-myc transcription. *Proc. natl Acad. Sci. USA,* **80,** 7581–7585

Estève, J., Tuyns, A., Raymond, L. & Vineis, P. (1984) *Tobacco and the risk of cancer: Importance of kinds of tobacco.* In: O,Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Favrot, M. C., Philip, I., Philip, T., Dore, J. F. & Lenoir, G. M. (1984) Possible duality in Burkitt lymphoma origin. *Lancet,* **i,** 745–746

Ghadirian, P., Stein, G., Gorodetsky, C., Roberfroid, M. B., Mahon, G. A. T., Bartsch, H. & Day, N. E. (1984) Oesophageal cancer studies in the Caspian littoral of Iran: some residual results, including opium use as risk factor (submitted for publication)

Griciute, L., Castegnaro, M. & Béréziat, J. C. (1984) *Influence of ethyl alcohol on carcinogenesis induced with N-nitrosodiethylamine.* In: Börzsönyi, M., Lapis, K., Day, N. E. & Yamasaki, H., eds, *Models, Mechanisms and Etiology of Tumour Promotion (IARC Scientific Publications No. 56),* Lyon, International Agency for Research on Cancer (in press)

Habs, H., Kunstler, K., Schmähl, D. & Tomatis, L. (1983) Combined effects of fast-neutron irradiation and subcutaneously applied carbon tetrachloride or chloroform in C57B16 mice. *Cancer Lett.,* **20,** 13–20

Hall, J., Brésil, H. & Montesano, R. (1984) O^6-Alkylguanine DNA transferase activity in human, monkey and rat liver (submitted for publication)

Hamel, E., Martel, N., Tayot, J. L. & Yamasaki, H. (1984) Characterization of a human placental factor which inhibits specific binding of phorbol esters to cultured cells. *Carcinogenesis,* **5,** 15–21

Hamel, E., Tayot, J. L. & Yamasaki, H. (1984) *A phorbol ester binding inhibitory factor from human placenta—partial purification, characterization and biological effects.* In: Börzsönyi, M., Day, N. E., Lapis, K. & Yamasaki, H., eds, *Models, Mechanisms and Etiology of Tumor Promotion (IARC Scientific Publications No. 56),* Lyon, International Agency for Research on Cancer (in press)

Hemminki, K. & Vainio, H. (1984) *Human exposure to potentially carcinogenic compounds.* In: Berlin, A., Draper, M., Hemminki, K. & Vainio, H., eds, *Monitoring of Human Exposure to Carcinogenic and Mutagenic Agents (IARC Scientific Publications No. 59),* Lyon, International Agency for Research on Cancer (in press)

Hollis, G. F., Mitchell, K. F., Battey, J., Potter, H., Taub, R., Lenoir, G. M. & Leder, P. (1984) A variant translocation places the immunoglobulin genes 3' to the c-myc oncogene in Burkitt's lymphoma. *Nature,* **307,** 752–755

Hsieh, C. C., Walker, A. M. & Hoar, S. K. (1983) Grouping occupations according to carcinogenic potential: Occupation clusters from an exposure linkage system. *Am. J. Epidemiol.,* **117,** 575–589

Hsieh, C. C., Crosson, A. W., Walker, A. M., Trapido, E. J. & MacMahon, B. (1984) Oral-contraceptive use and fibrocystic breast disease of different histologic classifications. *J. natl Cancer Inst.,* **72,** 285–290

Hsieh, C. C., Walker, A. M., Trapido, E. J., Crosson, A. W. & MacMahon, B. (1984) Age at first birth and breast atypia. *Int. J. Cancer,* **33,** 309–312

Huerre, C., Depoisse, S., Gilgenkrantz, S., Lenoir, G. M. & Junien, C. (1983) c-Ha-ras 1 is not deleted in aniridia-Wilms' tumour association. *Nature,* **305,** 638–641

Jensen, O. M., Wahrendorf, J., Rosenqvist, A. & Geser, A. (1984) The reliability of questionnaire-derived historic dietary information and temporal stability of food habits in individuals. *Am. J. Epidemiol.* (in press)

Jick, H. & Walker, A. M. (1983) Cigarette smoking and ulcerative colitis. *New Engl. J. Med.,* **308,** 261–263

Junien, C., Turleau, C., Lenoir, G. M., Philip, T., Said, R., Despoisse, S., Laurent, C., Rethoré, M. O., Kaplan, J. C. & de Grouchy, J. (1983) Catalase determination in various etiologic forms of Wilms' tumor and gonadoblastoma. *Cancer Genet. Cytogenet.,* **10,** 51–75

Kaldor, J. M. (1984) Model-based statistical procedures for the analysis of *in vitro* mutagenesis assays (submitted for publication)

Kaldor, J. M. & Clayton, D. (1984) Comment on 'The logistic analysis of epidemiologic prospective studies; investigation by simulation' (submitted for publication)

Kaldor, J. M. & Day, N. E. (1984) *The use of epidemiological data for the assessment of human cancer risk.* In: *Risk Quantitation and Regulatory Policy (Banbury Report),* Cold Spring Harbor, NY, Cold Spring Harbor Laboratory (in press)

Kaldor, J. M., Peto, J., Day, N. E., Doll, R., Herman, C. & Morgan, L. (1984) Models for respiratory cancer in nickel workers (submitted for publication)

Kaldor, J. M., Harris, J., Glazer, E., Glaser, S., Neutra, R., Mayburry, R., Nelson, V., Robinson, L. & Reed, D. (1984) The statistical association between cancer incidence and major cause mortality, and estimated residential exposure to air emissions from petroleum and chemical plants. *Environ. Health Perspectives,* **54,** 319–332

Kanno, Y., Enomoto, T., Shiba, Y. & Yamasaki, H. (1984) Protective effect of cyclic AMP on tumor promoter-mediated inhibition of cell-cell communication (electrical coupling). *Exp. Cell Res.,* **152,** 31–37

Klein, E., Torsteinsdottir, S., Masucci, M. G., Lenoir, G. & Klein, G. (1983) *NK sensitivity of human B cell lines with various characteristics.* In: *Proceedings of the International Symposium on Natural Killer Activity and its Regulation, Kyoto, Japan, August 20–21*

Ladjadj, Y., Philip, T., Lenoir, G. M., Tazerout, F. Z., Bendisari, K., Boukheloua, R., Biron, P., Brunat-Mentigny, M. & Aboulola, M. (1984) Abdominal Burkitt-type lymphomas in Algeria. *Br. J. Cancer,* **49,** 503–512

Lamelin, J. P. & Lenoir, G. M. (1983) *Immunodeficiency secondary to viral infection.* In: Chandra, R. K., ed., *Primary and Secondary Immunodeficiency Disorders,* Edinburgh, Churchill Livingstone, pp. 204–218

Leder, P., Battey, J., Lenoir, G., Moulding, C., Murphy, W., Potter, H., Stewart, T. & Taub, R. (1983) Translocations among antibody genes in human cancer. *Science,* **222,** 765–771

Lenoir, G. M. & Philip, T. (1983) Marqueurs cytogénétiques et lymphomes malins de type Burkitt. *J. Genet. hum.,* **31,** 53–55

Lenoir, G. M., Philip, T. & Sohier, R. (1984) *Burkitt-type lymphoma→EBV association and cytogenetic markers in cases from various geographic locations.* In: Magrath, I. T., O'Conor, G. T. & Ramot, B., eds, *Pathogenesis of Leukemias and Lymphomas: Environmental Influences,* New York, Raven Press, pp. 283–295

Likhachev, A. J. (1984) *Some factors determinint transplacental effects of carcinogens.* In: Reznik-Schuller, H. M., ed., *Comparative Perinatal Carcinogenesis,* Boca Raton, FL, CRC Press (in press)

Likhachev, A. J., Tomatis, L. & Margison, G. P. (1983) Incorporation and persistence of 5–bromodeoxyuridine in newborn rat tissue DNA. *Chem. –biol. Interactions,* **46,** 31–38

Likhachev, A. J., Ohshima, H., Anisimov, V. N., Ovsyannikov, A. I., Revskoy, S. Y., Keefer, L. K. & Reist, E. J. (1983) Carcinogenesis and ageing. II. Modifying effect of ageing on metabolism of methyl(acetoxymethyl)nitrosamine and its interaction with DNA of various tissues in rats. *Carcinogenesis,* **4,** 967–973

Lu, S. H., Ohshima, H. & Bartsch, H. (1984) *Recent studies on nitrosamine and oesaphageal cancer.* In: O'Neill, I. K., von Borstel, R. C., Miller, C. T., Long J. E. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Lunn, G., Sansone, E. B., Andrews, A. W., Castegnaro, M., Malaveille, C., Michelon, J., Brouet, I. & Keefer, L. K. (1984) *Destruction of carcinogenic and mutagenic N-nitrosamides in laboratory wastes* In: O'Neill, I. K., von Borstel, R. C., Miller, C. T., Long, J. E. & Bartsch, H., eds, *N-Nitroso compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Malaveille, C. & Bartsch, H. (1984) *Metabolic activation systems in short-term in vitro tests.* In: Kilbey, B. J., Legator, M., Nichols, W. & Ramel, C., eds, *Handbook of Mutagenicity Test Procedures,* 2nd ed., Amsterdam, Elsevier Science Publishers, pp. 615–641

Malaveille, C., Croisy, A., Brun, G. & Bartsch, H. (1983) Hydroxylation and nitroreduction are required to activate dimethylnitramine into alkylating and mutagenic agents. *Carcinogenesis,* **5,** 1477–1481

Malaveille, C., Hautefeuille, A., Perin-Roussel, O., Saguem, S., Croisy-Delsey, M., Zajdela, F. & Bartsch, H. (1984) Studies on the activation of dibenzo[*a,e*]fluoranthene into bacterial mutagens: possible involvement of a vicinal, non-bay region, 12,13–dihydrodiol-epoxide (submitted for publication)

Manousos, O., Day, N. E., Tzonou, A., Papadimitriou, C., Kapetanakis, A., Polychronopoulou-Trichopoulou, A. & Trichopoulos, D. (1984) Diet and other factors in the aetiology of diverticulosis: an epidemiological study in Greece (submitted for publication)

Margison, G. P., Cooper, D. P., Smith, R. A., Montesano, R., Brésil, H., Planche-Martel, G. & O'Connor, P. J. (1984) Enhanced repair of O^6-alkylguanine in mammalian tissues. *Folio biol. (Praha)* Special Publication

Mark-Vendel, E., Philip, T., Ladjaj, Y., Aboulola, M. & Lenoir, G. M. (1983) Chromosomal translocations in Algerian Burkitt's lymphoma. *Lancet,* **i,** 8353

Martin, C. N., Garner, R. C., Tursi, F., Garner, J. V., Whittle, H. C., Ryder, R. W., Sizasret, P. & Montesano, R. (1984) *An ELISA procedure for assaying aflatoxin B_1.* In: Berlin, A., Draper, M., Hemminki, K. & Vainio, H., eds, *Monitoring Human Exposure to Carcinogenic and Mutagenic Agents (IARC Scientific Publications No. 59),* Lyon, International Agency for Research on Cancer (in press)

Mazzorana, M., Garrone, R., Martel, N. & Yamasaki, H. (1984) Specific binding and biological effects of tumor promoting phorbol esters on sponges. *J. Biol. Cell* (in press)

McCann, J., Horn, L. & Kaldor, J. M. (1984) An evaluation of *Salmonella* (Ames) test data in published literature: Application of statistical procedures and analysis of mutagenic potency. *Mutat. Res.,* **134,** 1-47

McMichael, A. M., Jensen, O. M., Parkin, D. M. & Zaridze, D. (1984) Dietary and endogenous cholesterol and human cancer: A review of the evidence. *Epidemiol. Rev.,* **6** (in press)

Merletti, F., Heseltine, E., Saracci, R., Vainio, H. & Wilbourn, J. (1984) Target organs for carcinogenicity of chemicals and industrial exposures in humans: A review of results in the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Cancer Res.,* **44,** 2244–2250

Metivier, H., Wahrendorf, J. & Massé, R. (1984) Multiplicative effect of inhaled plutonium oxide and benzo(a)pyrene on lung carcinogenesis in rats (submitted for publication)

Montagnac, R., Baatard, R., Lesavre, Ph., Lenoir, G. & Schillinger, F. (1983) Syndrome de Kawasaki et virus d'Epstein-Barr. Réflexion à partir d'une observation. *Med. Mal. infect.,* **13,** 460–464

Montesano, R. & Hall, J. (1983) *Nitrosamine metabolism and carcinogenesis.* In: Chu, E. H. Y., Generoso, W. M. & Tan, C. C., eds, *Proceedings of the International Workshop on the Principles of Environmental Mutagenesis, Carcinogenesis and Teratogenesis,* New York, Plenum (in press)

Montesano, R. & Hall, J. (1983) *Species and organ specificity in nitrosamine carcinogenesis.* In: Turusov, V. & Montesano, R., eds, *Modulators in Experimental Carcinogenesis (IARC Scientific Publications No. 51),* Lyon, International Agency for Research on Cancer, pp. 173–181

Montesano, R. & Slaga, T. (1983) Initiation and promotion in carcinogenesis: an appraisal. *Cancer Surveys,* **2,** 613–621

Montesano, R., Brésil, H., Planche-Martel, G., Margison, G. P., & Pegg, A. E. (1983) Stability and capacity of dimethylnitrosamine-induced O^6-methylguanine repair system in rat liver. *Cancer Res.,* **43,** 5808–5814

Muir, C. S. (1983) *Cancer epidemiology: Past, present and future.* In: Mirand, E. A., Hutchinson, W. B. & Mihich, E., eds, *Current Perspectives in Cancer,* New York, Alan R. Liss, pp. 71–105

Muir, C. S. (1983) *Role of epidemiology in cancer research.* In: *Proceedings of the 6th Asia Pacific Cancer Conference,* 17–32

Muir, C. S. (1983) Nasopharyngeal carcinoma—A historical vignette. *Cancer,* **33,** 180–185

Muir, C. S & Parkin, D. M. (1983) *The prevention of cancer.* In: Bourke, G. D., ed., *The Epidemiology of Cancer,* London, Croom Helm Ltd, pp. 343–364

Muir, C. S., Boyle, P. & Smans, M. *The plans for a European cancer atlas.* In: *Proceedings of the Symposium 'Maps and Cancer', Southampton,* 5–9

Muñoz, N. (1983) *Profil epidemiologique de l'association entre les composes nitroses et le cancer humain.* In: *L'Eau, la Recherche, l'Environnement, Lille, France, 25–27 October 1983,* pp. 47–57

Muñoz, N. (1984) *Epidemiological evidence of transplacental carcinogenesis.* In: *11th Conference of the European Teratology Society, Paris, 29–31 August 1983* (in press)

Muñoz, N. (1984) *Estudio sobre los posibles efectos teratogenicos de los plaguicidas en Colombia.* In: *1st International Conference on Potentially Toxic Chemicals and 2nd Symposium on Pesticides and Health, Madrid, May 1983* (in press)

Muñoz, N. (1984) *Hepatocellular carcinoma and hepatitis B virus.* In: *Third Annual Meeting of the Spanish Society of Epidemiology, Murcia, Spain: 17–18 November 1983* (in press)

Muñoz, N. & Crespi M. (1984) *Studies on the aetiology of oesophageal carcinoma.* In: Watson, A. & Celestin, L. R., eds, *Disorders of the Oesophagus, Advances and Controversies,* London, Pitman, pp. 147–154

O'Conor, G. T. (1984) *Geography of lymphoid neoplasia: An overview.* In: Magrath, I. T., O'Conor, G. T. & Ramot, R., eds, *Pathogenesis of Leukemias and Lymphomas: Environmental Influences,* New York, Raven Press, pp. 1–8

O'Conor, G. T. (1984) *Geographical variations in the occurrence of leukemias and lymphomas: Summary and comments.* In: Magrath, I. T., O'Conor, G. T. & Ramot, R., eds, *Pathogenesis of Leukemias and Lymphomas: Environmental Influences,* New York, Raven Press, pp. 123–127

O'Conor, G. T. (1984) *Opportunities for study of lymphoid neoplasia in Africa.* In: Wiliams, A. O., O'Conor, G. T., de-Thé, G. B. & Johnson, C. T., eds, *Virus-Associated Cancers in Africa (IARC Scientific Publications No. 63),* Lyon, International Agency for Research on Cancer (in press)

Ohshima, H. & Bartsch, H. (1983) *A new approach to quantitate endogenous nitrosation in humans.* In: Stich, H., ed., *Carcinogens and Mutagens in the Environment,* Vol. II, *Naturally Occurring Compounds,* Boca Raton, FL, CRC Press, pp. 3–15

Ohshima, H. & Bartsch, H. (1984) *Monitoring endogenous nitrosamine formation in man.* In: Berlin, A., Draper, E., Hemminki, K. & Vainio, H., eds, *Monitoring of Human Exposure to Carcinogenic and Mutagenic Agents (IARC Scientific Publications No. 59),* Lyon, International Agency for Research on Cancer (in press)

Ohshima, H., Mahon, G. A. T., Wahrendorf, J. & Bartsch, H. (1983) A dose-response study of *N*-nitrosoproline formation in rats and a deduced kinetic model for predicting carcinogenic effects caused by endogenous nitrosation. *Cancer Res.,* **40,** 5072–5076

Ohshima, H., O'Neill, I. K., Friesen, M., Béréziat, J. C. & Bartsch, H. (1984) Occurrence in human urine of new sulphur-containing *N*-nitrosamino acids, *N*-nitrosothiazolidine 4-carboxylic acid and its 2-methyl derivative and their formation. *J. Cancer Res. clin. Oncol.* (in press)

Ohshima, H., O'Neill, I. K., Friesen, M., Pignatelli, B. & Bartsch, H. (1984) *Presence in human urine of new sulphur-containing* N-*nitrosamino acids;* N-*nitrosothiazolidine 4-carboxylic acid and* N-*nitroso 2-methylthiazolidine 4-carboxylic acid.* In: O'Neill, I. K., von Borstel, R. C., Miller, C. T., Long J. E. & Bartsch, H., eds, N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Papadimitriou, C., Day, N. E., Tzonou, A., Gerovassilis, F., Manousos, O. & Trichopoulos, D. (1984) Bio-social correlates of colorectal cancer in Greece. *Int. J. Epidemiol.,* **13,** 155–159

Parkin, D. M. & Al-Fouadi, A. (1984) Cancer in Iraq: seven years' data from the Baghdad tumour registry. *Int. J. Cancer,* **34** (in press)

Parkin, D. M. & Muir, C. S. (1984) *Malignant disease in warm climates.* In: Robinson, D., ed., *Epidemiology and the Community Control of Disease in Warm Climate Countries* (in press)

Parkin, D. M. & Muir, C. S. (1984) *Cancer data from developing countries.* In: Guinee, V. F., ed., *Current Problems in Cancer* (in press)

Parkin, D. M., Sohier, R. & O'Conor, G. T. (1984) *Geographic distribution of Burkitt's lymphoma.* In: Lenoir, G., O'Conor, G. & Olweny, C., eds, *Burkitt's Lymphoma: A Human Cancer Model (IARC Scientific Publications No. 60),* Lyon, International Agency for Research on Cancer (in press)

Parkin, D. M., Stjernsward, J. & Muir, C. S. (1984) Estimates of the worldwide frequency of twelve major cancers. *Bull. WHO,* **62,** 163–182

Parkin, D. M., Day, N. E. & Nguyen-Dinh, X. (1984) The impact of screening on the incidence of cervix cancer in England and Wales. *Br. J. Obstet. Gynaecol.* (in press)

Philip, I., Philip, T., Chamard, D., Vuillaume, M. & Lenoir, G. M. (1984) Establishment of lymphomatous cell lines from bone-marrow samples from patients with Burkitt's lymphoma. *J. natl Cancer Inst.* (in press)

Philip, T. & Lenoir, G. M. (1983) Le lymphome de type Burkitt — un modèle d'étude où s'associent recherche clinique et recherche fondamentale. *Cahiers med.,* **9,** 167–172

Pignatelli, B., Scriban, R., Descotes, G. & Bartsch, H. (1984) Modifying effects of polyphenols and other constituents of beer on the formation of *N*-nitroso compounds. *Am. Soc. Brewing Chem. J.,* **42,** 18–23

Pluijmen, M., Drevon, C., Montesano, R., Malaveille, C., Hautefeuille, A. & Bartsch, H. (1984) Lack of mutagenicity of synthetic pyrethroids in *Salmonella typhimurium* strains and in V79 Chinese hamster cells. *Mutat. Res.* (in press)

Ponomarkov, V., Cabral, J. R. P., Wahrendorf, J. & Galendo, D. (1984) A carcinogenicity study of styrene oxide in rats (submitted for publication)

Porter, J. B., Walker, A. M. & Jick, H. (1984) Cancer of the breast, colon, ovary and testis, in the United States: rates 1970–1978 from a reporting system. *Am. J. publ. Health,* **74,** 585–588

Roberfroid, M. B., Malaveille, C., Hautefeuille, A., Brun, G. & Bartsch, H. (1983) Interrelationships in mice of antipyrine half-life, hepatic monooxygenase activities and liver S9-mediated mutagenicity of aflatoxin B_1, benzo[*a*]pyrene, 7,8-dihydrodiol, 2-acetylaminofluorene and *N*-nitrosomorpholine. *Chem.-biol. Interactions,* 175–194

Rossi, L., Barbieri, O., Sanguineti, M., Cabral, J. R. P., Bruzzi, P. & Santi, L. (1983) Carcinogenicity study with technical-grade dichlorodiphenyltrichloroethane and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene in hamsters. *Cancer Res.,* **43,** 776–781

Saracci, R. (1983) *Hazard control in the occupational and general environments.* In: Holland, W. W., ed., *Evaluation of Health Care,* Oxford, Oxford University Press, pp. 129–143

Saracci, R. (1983) *Valutazione delle techniche di screening.* In: *Il Carcinoma del Pulmone, Epidemiologia e Prevenzione. Atti del Congresso, 161–169, Padova, Centro Regionale Cancerogenesi Ambientale*

Saracci, R. (1984) *Beryllium.* In: Wald, N. & Doll, R., eds, *Proceedings of the Symposium on Practical Value of Negative Epidemiological Evidence, Oxford, 4–6 July 1983* (in press)

Saracci, R. (1984) *The epidemiology of ischaemic heart diseases revisited (short synopsis).* In: Donato, L. & L'Abbate, A., eds, *Frontiers of Cardiology for the Eighties,* London, Academic Press, pp. 107–109

Saracci, R. (1984) *Carcinogenesis, mutagenesis and teratogenesis.* In: Suess, R., ed., *Ambient Air Pollutants from Industrial Sources,* Copenhagen, WHO Regional Office for Europe (in press)

Saracci, R. (1984) *Neoplasms.* In: Holland, W. W., ed., *Textbook of Public Health,* Oxford, Oxford University Press (in press)

Saracci, R. (1984) *Assessing exposure of individuals in the identification of disease determinants.* In: Berlin, A., Draper, M., Hemminki, K. & Vainio, H., eds, *Monitoring Human Exposure to Carcinogenic and Mutagenic Agents (IARC Scientific Publications No. 59),* Lyon, International Agency for Research on Cancer (in press)

Saracci, R. & Repetto, F. (1984) *Confidentiality prescriptions and epidemiological research in Italy.* In: *EEC Report on Confidentiality in Member Countries* (in press)

Saracci, R. & Simonato, L. (1983) Man-made vitreous fibers and workers' health: An overview of the epidemiologic evidence. *Scand. J. Work environ. Health,* **9,** 515–519

Saracci, R., Simonato, L., Acheson, E. D., Andersen, A., Claude, J., Charnay, N., Estève, J., Frentzel-Beyme, R. R., Gardner, M. J., Jensen, O. M., Maasing, R., Olsen, J. H., Teppo, L., Westerholm, P. & Zocchetti, C. (1984) Mortality and cancer incidence of workers in the man-made vitreous fribres producing industry: an international investigation at thirteen European plants. *Br. J. ind. Med.* (in press)

Saracci, R., Simonato, L., Acheson, E. D., Andersen, A., Bertazzi, P. A., Claude, J., Charnay, N., Estève, J., Frentzel-Beyme, R. R., Gardner, M. J., Jensen, O. M., Maasing, R., Olsen, J. H., Teppo, L., Westerholm, P. & Zocchetti, C. (1984) *The International Agency for Research on Cancer (IARC) mortality and cancer incidence study of man-made mineral (vitreous) fibers (MMM(V)F) production workers in seven European countries.* In: *Proceedings of the Conference on Biological Effects of Man-Made Mineral Fibres — Occupational Health, April 20–22, 1982, Copenhagen,* Copenhagen, WHO Regional Office for Europe (in press)

Saracci, R., Giuntini, C., Paoletti, P., Fornai, E., Di Pede, F., Fazzi, P., DaPorto, R., Cipriani, M., Pistelli, G., Giuliano, G. & Dalle Luche, A. (1984) *A comparison of the ability of different lung function tests to discriminate asymptomatic smokers and non-smokers.* In: Cummings, G., ed., *The Effects of Cigarette Smoking on the Lung (Series in Life Sciences),* New York, Plenum Press (in press)

Sasco, A. J., Day, N. E. & Walter, S. D. (1984) Case-control studies for the evaluation of screening (submitted for publication)

Simonato, L. & Lavallée-Hawken, J. (1983) *Evidenza epidemiologica di rischio cancerogeno a carico del polmone connesso con l'ambiente lavorativo.* In: *International Congress Proceedings: Il Carcinoma del Polmone: Epidemiologia e Prevenzione, Padova 6–8 October 1983,* Universita di Padova, Centro Regionale Specializzato in Cancerogenesi Ambientale, pp. 87–97

Simonato, L. & Saracci, R. (1984) Epidemiological research and silica dust exposure: the role of IARC (in press)

Simonato, L. Saracci, R., Estève, J. & Charnay, B. (1983) Man-made mineral fiber industry: some aspects of the International Agency for Research on Cancer's European epidemiologic investigation. *Scand. J. Work environ. Health,* **9,** 71

Smith, P. G. & Day, N. E. (1984) The design of case-control studies: the influence of confounding and interaction effects. *Int. J. Epidemiol.* (in press)

Sohier, R. & Tuyns, A. J. (1983) Epidémiologie en France—Essai critique, rétrospectif et suggestions. *Méd. Armées,* **11,** 277–279

Stich, H. F., Dunn, B. P., Pignatelli, B., Ohshima, H. & Bartsch, H. (1984) *Dietary phenolics and betel nut extracts as modifiers on* N-*nitrosation in rat and man.* In: O'Neill, I. K., von Borstel, R. C., Long, J. E., Miller, C. T. & Bartsch, H., eds, N-*Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57),* Lyon, International Agency for Research on Cancer (in press)

Taub, R., Moulding, C., Battey, J., Murphy, W., Vasicek, T., Lenoir, G. M. & Leder, P. (1984) Activation and somatic mutation of the translocated c-myc gene in Burkitt lymphoma cells. Cell, **36,** 339–348

Taub, R., Kelly, K., Battey, J., Latt, S., Lenoir, G. M., Tantravahi, U., Tu, Z. & Leder, P. (1984) A novel alteration in the structure of an activated c-myc gene in a variant t (2;8) Burkitt lymphoma. *Cell,* **37,** 511–520

Tomatis, L. (1983) Trends in cancer epidemiology. *J. exp. clin. Cancer Res.,* **3,** 257–260

Tomatis, L. (1984) *Presentazione.* In: *Monografie IARC per la valutazione del rischio cancerogeno da sostanze chimiche per l'uomo. Sostanze chimiche, processi industriali e lavorazioni associati a tumore nell'uomo. Monografie IARC, dal 1 al 29 volume, Supplemento 4,* Florence, Agenzia Internazionale per la Ricerca sul Cancro, Lega Italiana per la Lotta i Tumori

Tomatis, L. (1984) *Influenze ambientali sulla genesi e lo sviluppo delle malattie cancerose.* In: *Proceedings of Ecologia dalla ricerca al progetto, Roma 15–17 marzo, 1984,* Rome, Istituto Gramsci (in press)

Tomatis, L. (1984) Exposures associated with cancer in humans. *J. Cancer Res. clin. Oncol.,* **107** (in press)

Tomatis, L. (1984) *Prospects for cancer prevention.* In: *Proceedings of the Eighth International Symposium on Polynuclear Aromatic Hydrocarbons,* Columbus, OH, Battelle Columbus Laboratories (in press)

Trichopoulos, D., Tzonou, A., Polychronopoulou-Trichopoulou, A. & Day, N. E. (1983) *A case-control investigation of a possible association between coffee consumption and ovarian cancer in Greece (Banbury Conference),* Cold Spring Harbor, NY, Cold Spring Harbor Laboratory (in press)

Truhaut, R., Nguyen Phu Lich, Castegnaro, M., Bourgade, M. C. & Martin, G. (1984) Volatile nitrosamines in the main stream smoke of black tobacco. *J. Cancer Res. clin. Oncol.* (in press)

Turc-Carel, C., Philip, I., Berger, M. P., Philip, T. & Lenoir, G. (1983) Chromosomal translocation in Ewing's sarcoma. *New Engl. J. Med.*, **309**, 496–498

Turc-Carel, C., Philip, I., Berger, M. P., Philip, T. & Lenoir, G. M. (1984) Chromosome study of Ewing's sarcoma (ES) cell lines. Consistency of a reciprocal translocation t(11;22) (q24;q12). *Cancer Genet. Cytogenet.*, **12**, 1–19

Turusov, V. & Montesano, R., eds (1982) *Modulators of Experimental Carcinogenesis (IARC Scientific Publications No. 51)*, Lyon, International Agency for Research on Cancer

Tuyns, A. J. (1983) Gesophageal cancer in non-smoking drinkers and in non-drinking smokers. *Int. J. Cancer*, **34**, 443–444

Tuyns, A. J. (1983) Facteurs alimentaires, alcool et tabac dans le cancer de l'œsophage. *Information diét.*, **3**, 39-41

Tuyns, A. J. (1983) Facteurs d'environnement dans les cancers digestifs. *Rev. méd.*, **42**, 2031–2034

Tuyns, A. J. (1983) Sodium chloride, alcohol and cancer of the digestive tract. *Nutr. Cancer*, **5**, 92–95

Tuyns, A. J. (1983) Protective effect of citrus fruit on esophageal cancer in Calvados (France). *Nutr. Cancer*, **5**, 195–200

Tuyns, A. J. & Estève, J. (1983) Present and past alcohol consumption in Calvados (France). *Rev. Epidémiol. Santé publ.*, **31**, 487–488

Tuyns, A. J., Péquignot, G. & Hu, M.X. (1983) Alcohol consumption patterns in the department of Calvados (France). *Rev. Epidémiol. Santé publ.*, **31**, 179–197

Tuyns, A. J., Estève J. & Péquignot, G. (1984) Ethanol is cirrhogenic, whatever the beverage. *Br. J. Addict.* (in press)

Tuyns, A. J., Péquignot, G. & Estève, J. (1984) Greater risk of ascitic cirrhosis in females in relation to alcohol consumption. *Int. J. Epidemiol.*, **13**, 53–57

Tzonou, A., Day, N. E., Walker, A., Saliaraki, M., Papapostolou, M. & Polychronopoulou-Trichopoulou, A. (1984) The epidemiology of ovarian cancer in Greece: a case-control study. *Eur. J. Cancer* (in press)

Vainio, E., Lenoir, G. M. & Franklin, R. M. (1983) Autoantibodies in three populations of Burkitt's lymphoma patients. *Clin. exp. Immunol.*, **54**, 387–396

Vainio, H. & Hietanen, E. (1983) Tobacco smoke as an environmental hazard. *Duodecim*, **99**, 1638–1645 (in Finnish)

Vainio, H. & Sorsa, M. (1984) *Application of short-term tests in monitoring occupational exposure to complex mixtures.* In: Waters, M. D., Sandhers, S. S., Lewtas, J., Claxton, L. & Nesnow, S., eds, *Short-term Biossays in the Analysis of Complex Environmental Mixtures, IV* (in press)

Vainio, H., Sorsa, M. & Falck, K. (1984) *Bacterial urinary assay in monitoring exposure to mutagens and carcinogens.* In: Berlin, A., Draper, E., Hemminki, K. & Vainio, H., eds, *Monitoring of Human Exposure to Carcinogenic and Mutagenic Agents (IARC Scientific Publications No. 59)*, Lyon, International Agency for Research on Cancer (in press)

Venkitaraman, A. R., John, T. J., Rangad, F., Singh, A. D., Date, A. & Lenoir, G. (1983) Epstein-Barr virus-associated Burkitt's lymphoma in India. *Trop. geogr. Med.*, **35**, 273–277

Verbeek, A. C. M., Holland, R., Strauss, F., Hendriks, J. H. L. L., Mravunac, M. & Day, N. E. (1984) Reduction of breast cancer mortality through mass screening with modern mammography: first results of the Nijmegen project 1975–81. *Lancet*, **i**, 1222–1224

Vilmer, E., Lenoir, G. M., Virelizier, J. L. & Griscelli, C. (1984) Epstein-Barr serology in immunodeficiencies: an attempt to correlate with immune abnormalities in Wiskott-Aldrich and Chediak-Higashi syndromes and ataxia telangiectasia. *Clin. exp. Immunol.*, **55**, 249–256

Wahrendorf, J. (1984) Discussion of D. R. Cox's paper on 'interaction'. *Int. stat. Rev.*, **52**, 29–30

Wahrendorf, J. & Walker, A. M. (1984) Integrated clinical and epidemiological research: diagnostic refinement and questions of etiology (submitted for publication)

Wahrendorf, J., Mahon, G. A. T. & Schumacher, M. (1984) Non-parametric approach to the statistical analysis of mutagenicity data (submitted for publication)

Walker, A. M. (1984) Declining relative risks for lung cancer after cessation of asbestos exposure. *J. occup. Med.*, **26**, 422–426

Walker, A. M. & Suit H. D. (1983) Assessment of local tumor control using censored tumor response data. *Int. J. Rad. Oncol. Biol. Phys.*, **9**, 383–386

Walker, A. M., Loughlin, J. E., Friedlander, E. R., Rothman, K. J. & Dreyer, N. A. (1983) Projections of asbestos-related disease 1980–2009. *J. occup. Med.*, **25**, 409–425

Walker, A. M., Cody, R. J., Jr, Greenblatt, D. J. & Jick, H. (1983) Drug toxicity in patients receiving dioxin and quinidine. *Am. Heart J.*, **105**, 1025–1028

Walker, A. M., Jick, H., Hunter, J. R. & McEvoy, J. (1983) Vasectomy and nonfatal myocardial infarction: Continued observation indicates no elevation of risk. *J. Urol.*, **130**, 936–937

Walker, A. M., Arrigg, C. A., Hertzmark, E. & Epstein, D. L. (1984) Carbonic anhydrase inhibitors induce elevations in human whole blood zinc. *Arch. Ophthalmol.* (in press)

Walter, S. D. & Day, N. E (1983) Estimation of the duration of a preclinical disease state using screening data. *Am. J. Epidemiol.*, **118**, 865–886

Wilbourn, J. D., Haroun, L., Vainio, H. & Montesano, R. (1984) Identification of chemicals carcinogenic to man. *Toxicol. Pathol.*, **12** (in press)

Yamasaki, H. (1983) Evaluation of environmental chemicals for carcinogenic risk to humans. *Toxicol. Forum*, **6**, 170–183 (in Japanese)

Yamasaki, H. (1984) *Modulation of cell differentiation by tumor promoters.* In: Slaga, T. J., ed., *Mechanisms in Tumor Promotion*, Vol IV, Boca Raton, FL, CRC Press pp. 1–26

Yamasaki, H. (1984) In-vitro approaches to identify tumor promoting agents; cell transformation and intercellular communication. *Food Add. Contam.* (in press)

Yamasaki, H. (1984) Tumor promotion—Mechanisms and implication to risk estimation. *Acta pharmacol. toxicol.* (in press)

Yamasaki, H. & Weinstein, I. B. (1984) *Cellular and molecular mechanisms of tumor promotion and their implications with respect to risk assessment.* In: Vouk, V. B., Batler, G. C., Hall, O. G. & Peakall, D. B., eds, *Mehtods for Estimating Risks of Chemical Injury: Human and Non-human Biota and Ecosystems,* New York, John Wiley (in press)

Yamasaki, H., Enomoto, T., Martel, N., Shiba, Y. & Kanno, Y. (1983) Tumor promoter-mediated reversible inhibition of cell-cell communication (electrical coupling): Relationship with phorbol ester binding and *de novo* macromolecule synthesis. *Exp. Cell Res.,* **146,** 297–308

Yamasaki, H., Martel, N., Fusco, A. & Ostertag, W. (1984) Continous suppression of globin gene expression and differentiation of Friend erythroleukaemia cells by phorbol 12-myristate 13-acetate (PMA) despite the loss of PMA binding sites by down regulation. *Proc. natl Acad. Sci. USA,* **81,** 2075–2079

Yamasaki, H., Enomoto, T., Hamel, E. & Kanno, Y. (1984) *Membrane interaction and modulation of gene expression by tumor promoters.* In: *Proceedings of the 14th Princess Takamatsu Symposium,* Tokyo, University Park Press (in press)

Yamasaki, H., Enomoto, T. & Martel, N. (1984) *Intercellular communication, cell differentiation and tumor promotion.* In: Börzsonyi, M., Day, N. E., Lapis, K. & Yamasaki, H., eds, *Models, Mechanisms and Etiology of Tumor Promotion (IARC Scientific Publications No. 56),* Lyon, International Agency for Research on Cancer (in press)

Zambon, P., Simonato, L., Mastrangelo, G., Winkelman, R., Saia, B. & Crepet, M. (1984) *A mortality study of workers compensated for silicosis during the period 1959–1963 in the Veneto region of Italy.* In: *Proceedings of the Chapel Hill Conference, 3–5 April 1984, NC, USA* (in press)

Zaridze, D. G. (1984) Role of nutrition in cancer prevention. *Vest AMNSSSR,* **5** (in press)

Zaridze, D. G. & Boyle, P. (1984) Epidemiology of prostatic cancer. Proceedings of the 3rd Congress of the European Society of Urological Oncology and Endicronology (Rome, 24–26 november 1983). *Acta med. Rome* (in press)

Zaridze, D. G., Boyle, P. & Smans, M. (1984) International trends in prostatic cancer. *Int. J. Cancer,* **33,** 223–230

Zaridze, D. G., Kuvshinov, J. P., Matiakin, E., Boyle, P. & Bletter, M. (1984) *Chemoprevention of precancerous lesions of the mouth and esophagus.* In: *Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin (Natl Cancer Inst. Monogr.)* (in press)

IARC Fellows:

Douer, D., Fabian, I. & Cline, M. J. (1983) Circulating pluripotent haemopoietic cells in patients with myeloproliferative disorders. *Br. J. Haematol.,* **54,** 373–381

Sawicki, J. F. & Dipple, A. (1983) Effects of butylated hydroxyanisole and butylated hydroxytoluene on 7,12-dimethylbenz[*a*]anthracene-DNA adduct formation in mouse embryo cell cultures. *Cancer Lett.,* **20,** 165–171

Bigger, C. A. H., **Sawicki J. F.,** Blake, D. M., Raymond, L. G. & Dipple, A. (1983) Products of binding of 7,12-dimethylbenz[*a*]anthracene to DNA in mouse skin. *Cancer Res.,* **43,** 5647–5651

Dipple, A., **Sawicki, J. F.,** Moschel, R. C. & Bigger, C. A. H. (1983) *7,12-Dimethylbenz*[a]*anthracene-DNA interactions in mouse embryo cell cultures and mouse skin.* In: Rydström, J., Montelius, J. & Bengtsson, M., eds, *Extrahepatic Drug Metabolism and Chemical Carcinogenesis,* Amsterdam, Elsevier Science Publishers, pp. 439–448

Sawicki, J. F., Moschel, R. C. & Dipple, A. (1983) Involvement of both *syn-* and *anti*-dihydrodiol-epoxides in the binding of 7,12-dimethylbenz[*a*]anthracene to DNA in mouse embryo cell cultures. *Cancer Res.,* **43,** 3212–3218

Manousos, O., Day, N. E., Trichopoulos, D., Gerovassilis, F. & **Tzonou, A.** (1983) Diet and colorectal cancer: a case-control study in Greece. *Int. J. Cancer,* **32,** 1–5

Zatonski, W., Didkowska, J. & Gadomska, H. (1983) Cancer of the larynx in Warsaw and in selected rural areas. *Neoplasma,* **30,** 379–384

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