International Agency for Research on Cancer

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INTRODUCTION

This report covers the work of the International Agency for Research on Cancer for the year ending 30 June 1978. As in previous years, this introduction presents a general review of recent developments in the Agency's programme and in those of other laboratories, which may be pertinent to that programme. The rest of the report, presented unit by unit, describes the programmes and projects of the Agency in more detail.

If certain parts of the report are repetitive with respect to those of previous years, this merely reflects the slow-moving nature of epidemiological investigations in man, since it inevitably takes several years to accumulate sufficient data before definite conclusions may be drawn.

The scientific programme

Cancer epidemiology

Work has been commenced on the fourth volume of *Cancer Incidence in Five Continents*, which will provide information on more populations than did the third volume[1]. In addition, the material now available on cancer incidence from the first three volumes in this series is being compared and analysed in depth. The objective is not only to make the data available to general oncologists in a more readily accessible form but also to provide more information on the biology of human cancer. The analysis will include temporal changes in cancer patterns and cumulated cancer risks in different environments[2]. Such material provides essential background data for investigating etiological factors in human cancer and for expressing comparative risks between different exposures and environments, as, for example, in certain occupations. The manual on *Cancer Registration and its Techniques* has been completed and is in press[3].

In collecting cancer statistics, the Agency has continued to stress that high-quality registration of defined populations of limited size may be of much greater value than poorer quality data from larger groups. While useful and satisfactory cancer statistics are now available from a number of diverse communities, including many in nonindustrialized parts of the world[4], the Agency has been specifically interested in problems of generating meaningful cancer frequency data at low cost in communities which lack the infrastructure to develop population-based registries. There is now abundant evidence that cheap and economical ratio studies supported locally within a hospital or

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[1] Waterhouse, J. A. H., Muir, C. S., Correa, P. & Powell, J., eds (1976) *Cancer Incidence in Five Continents, Volume III*, Lyon *(IARC Scientific Publications No. 15)*.

[2] Day. N. E. (1976) In: Waterhouse, J. A. H., Muir, C. S., Correa, P. & Powell, J., eds, *Cancer Incidence in Five Continents, Volume III*, Lyon *(IARC Scientific Publications No. 15), pp. 443–445*.

[3] MacLennan, R., Muir, C. S., Steinitz, R. & Winkler, A. (1978) *Cancer Registration and its Techniques*, Lyon *(IARC Scientific Publications No. 21)*.

[4] Waterhouse, J. A. H., Muir, C. S., Correa, P. & Powell, J., eds (1976) *Cancer Incidence in Five Continents, Volume III*, Lyon *(IARC Scientific Publications No.15)*.

university setting may provide useful data on cancer patterns and will also be useful for public health authorities. Such ratio studies, moreover, can often be evaluated against population-based studies in neighbouring regions. These studies have been encouraged by the Agency since its inception, because it is somewhat concerned about an increasing tendency in many countries to establish extensive population-based registries at high cost without a clear definition of the overall objectives of such registration or the benefits that might result. Cancer registration should never be regarded as an end in itself.

Similar remarks apply to the necessity for histological confirmation and standardization of classification of diseases[5, 6]. Nevertheless, for practical purposes, modest standardization may well be sufficient where an adequate laboratory and medical infrastructure exists. If, however, more exact comparisons are required, these should be the subject of specific projects with defined objectives, of the type of the Agency study on latent carcinoma of the prostate[7], where standardization was achieved under carefully controlled conditions.

International surveillance and monitoring network

There has been considerable effort during the last 18 months to establish the objectives and feasibility of a monitoring network. In general, the idea received enthusiastic support, but there is still some confusion as to the possible extent of such a network if it is to become effective. Certainly, excessive size would lead to inadequate quality control and ineffectiveness. A number of studies have now been implemented to test the feasibility of some specific aspects, and the overall possibilities should be more clearly established within the next year.

Cancer associated with sharp fibres

The feasibility studies in the man-made mineral fibre project have now been completed and the definitive study initiated. The study will probably be complemented by another on users of asbestos and man-made mineral fibres in Sweden. The major problem in such occupational studies has proved to be the confidentiality of public health records, which hinders the matching of worker exposures with the health information (including cause of death) which is essential for the success of the project. This problem continues to cause concern among oncologists attempting to study cancer in the place of work.

A most interesting report of Dr Y. Baris (Hacettepe University, Ankara) indicated that mesothelioma occurs in villagers in Central Anatolia perhaps as a result of exposure to a volcanic rock excavated to provide housing and shelter. This indicates that the risk of sharp fibres may not be confined to industrialized zones. With the collaboration of the MRC Pneumoconiosis Unit in Cardiff (UK), the Agency is cooperating with Dr Baris and his colleagues in the hope that this study may also throw light on the role of other sharp fibres in human carcinogenesis.

It is proposed to review the overall problem of sharp fibre carcinogenesis at a symposium to be held in Lyon in September 1979.

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[5] World Health Organization (1967-1978) *International Histological Classification of Tumours*, Nos 1-20, Geneva.

[6] World Health Organization (1976) *ICD-O, International Classification of Diseases for Oncology*, 1st ed., Geneva.

[7] Breslow, N., Chan, C.W., Dhom, G., Drury, R.A.B., Franks, L.M., Gellei, B., Lee, Y.S., Lundberg, S., Sparke, B., Sternby, N.H. & Tulinius, H. (1977) *Int. J. Cancer*, 20, 680–688

Clearing-house for on-going research in cancer epidemiology

The Directory prepared by the clearing-house[8] presents very useful data regarding on-going research, particularly in the occupational field, and also indicates many areas where further work is clearly necessary. Its success is dependent on voluntary collaboration and the willingness of research workers and institutes to provide information on their activities, and the level of response has been gratifying.

Cancer and alcoholic beverages

The series of studies on the association between consumption of alcoholic beverages and a number of cancers is continuing satisfactorily, as indicated in previous annual reports[9]. The possibility has emerged in a number of studies that different alcoholic beverages may vary in their carcinogenic potential and in the cancers with which they are associated, but the nature of alcohol-associated cancer remains to be established.

Comparisons of brewery workers in Ireland and Denmark have shown an apparent increase of rectal cancer in Ireland but not in Denmark, where, however, there were significantly increased risks of cancer of the œsophagus and larynx and of other diseases associated with alcohol consumption.

The study in southern Europe of the possible synergistic role of alcoholic beverages with cigarette smoking in the production of laryngeal cancer has now begun.

Chemical carcinogenesis

An important development has taken place in the monograph series on the evaluation of the carcinogenic risk of chemicals to humans. Two workshops were held during the past year in which attempts were made to revise and update the criteria used to assess carcinogenic risks to humans on the basis of animal experiments in the light of the most recent biological data.

The lack of an adequate biological base for extrapolating from animal experiments to man is well-recognized, and high priority should be given to expanding basic research aimed at achieving a better understanding of fundamental mechanisms in chemical carcinogenesis. Since, however, opinions must be expressed even in the absence of definitive data, it was decided that for each compound reviewed in the monographs the available animal data should be assessed as to whether it could be regarded as 'sufficient' from the viewpoint of animal experimentation. In the first 17 monographs, 380 chemicals have been reviewed. Of these 26 chemicals or industrial processes have been found to be associated causally (or strongly suspected of being etiologically associated) with the production of cancer in man. For those chemicals reported to produce tumours in experimental animals (230), reports can be classified into those in which the evidence is regarded as 'sufficient' (111 chemicals) and those in which the evidence is regarded as 'limited'[10]. The terms 'sufficient' and 'limited' indicate the quality of the experimental evidence available and do not indicate the level of carcinogenic potential of the particular chemical to man or other animal species. Nevertheless, the newly-adopted formulation should be of more assistance to decision-making bodies.

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[8] Muir, C. S. & Wagner, G., eds (1977) *Directory of On-Going Research in Cancer Epidemiology, 1977*, Lyon *(IARC Scientific Publications No. 17)*.

[9] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, pp. 33–40.

[10] International Agency for Research on Cancer (1977) *IARC intern. tech. Rep.* No. 77/002, Lyon.

Rapid-screening techniques

Although it is now generally agreed that mutagenesis and carcinogenesis are not synonymous, the use of mutagenic tests has proved valuable for screening substances to distinguish those for which long-term testing would be desirable. The technique has also been used to elucidate metabolic mechanisms in man and animals and is now being developed as a possible method of identifying environmental carcinogens in tissue fluids and excreta.

Foodstuffs and beverages, for example, are being checked for mutagenic activity prior to using more sophisticated analytical chemical techniques. Bruce[11] has reported the presence of a mutagenic fraction in faeces of normal human subjects. Wong *et al.*[12] have found the presence of aflatoxicol, a carcinogenic metabolite of aflatoxin, in the plasma of rats to whom aflatoxin had been administered. The metabolite was not found in mice or monkeys, species which are more resistant to aflatoxin carcinogenesis. Theoretically it may be possible to use the test of aflatoxicol formation *in vivo* or *in vitro* to predict individual human susceptibility to aflatoxin. The Agency is attempting to develop tests such as these for application in its field programmes, particularly in relation to the projects on large-bowel and œsophageal cancers.

Environmental carcinogenesis

The refinement and standardization of analytical chemical techniques for environmental carcinogens play an important role in the development of modern epidemiological research. The publication of the first manual of selected analytical methods, dealing with volatile nitrosamines in food, is therefore timely[13]. More recently, techniques have been developed to determine nitrosamine precursors in human saliva, and their application in the field in Iran may yield interesting data.

Nevertheless, it must be said that the role of nitrosamines in human cancer remains obscure, especially in view of reports of the presence of nitrosamines in body fluids under apparently normal conditions.

Viruses and cancer

Studies of the etiology of Burkitt's lymphoma are continuing in two directions—the detection of Burkitt's lymphoma cases amongst the cohort of children in the West Nile district, Uganda who were bled between 1972–1974 and the development of a malaria intervention trial in North Mara, Tanzania. In both aspects of the study there are certain difficulties in evaluating the results, because of the apparent fall in the number of new Burkitt's lymphoma cases each year in both study areas.

In Uganda, the sera of 14 children who subsequently contracted Burkitt's lymphoma have been compared for Epstein-Barr virus antiviral capsid antigen antibody titres, with matched

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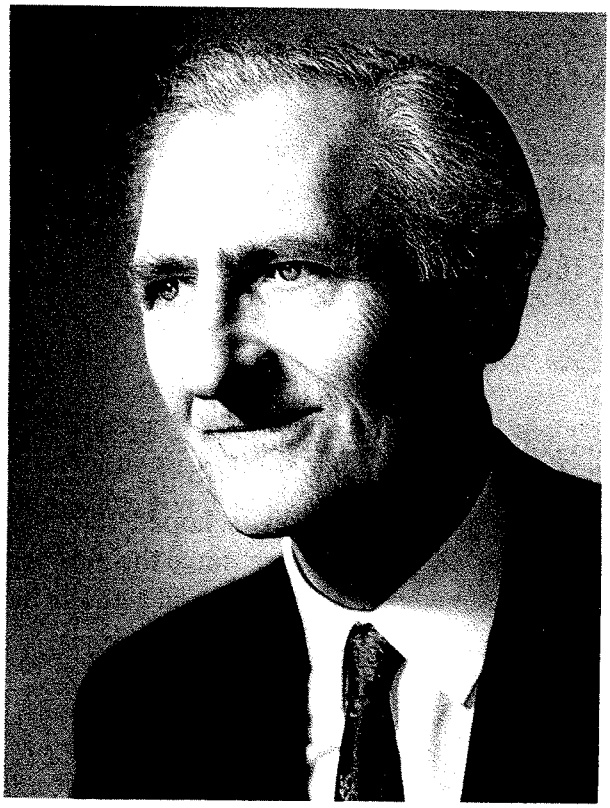
[11] Bruce, W. R., Varghese, A. J., Furrer, R. & Land, P. C. (1977) In: Hiatt, H. H., Watson, J. D. & Winsten, J. A., eds, *Origins of Human Cancer*, Vol. 4, Cold Spring Harbor, Cold Spring Harbor Laboratory, pp. 1641–1646.

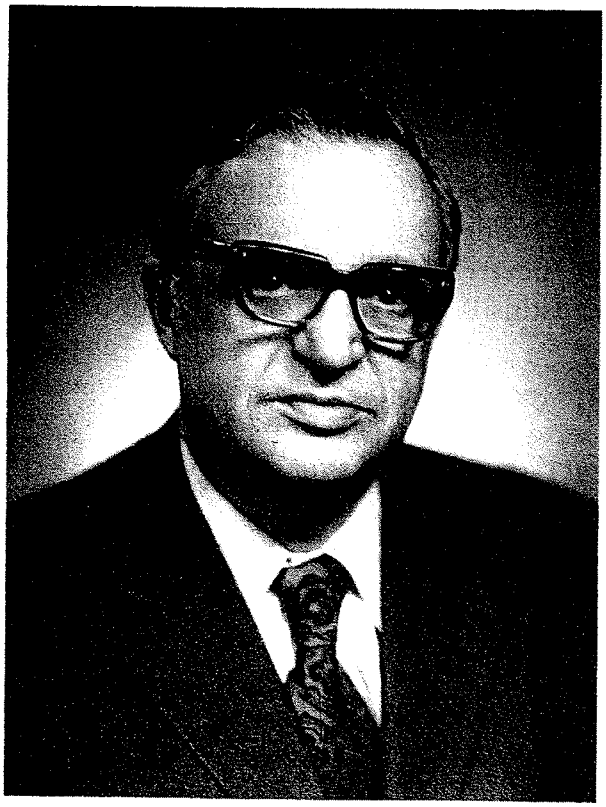
[12] Wong, Z. A. & Hsieh, D. P. (1978) *Science*, **200**, 325–327.

[13] Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds (1978) *Volume 1: Analysis of Volatile Nitrosamines in Food.* In: Egan, H., ed., *Environmental Carcinogens - Selected Methods of Analysis*, Lyon (*IARC Scientific Publications No. 18*).

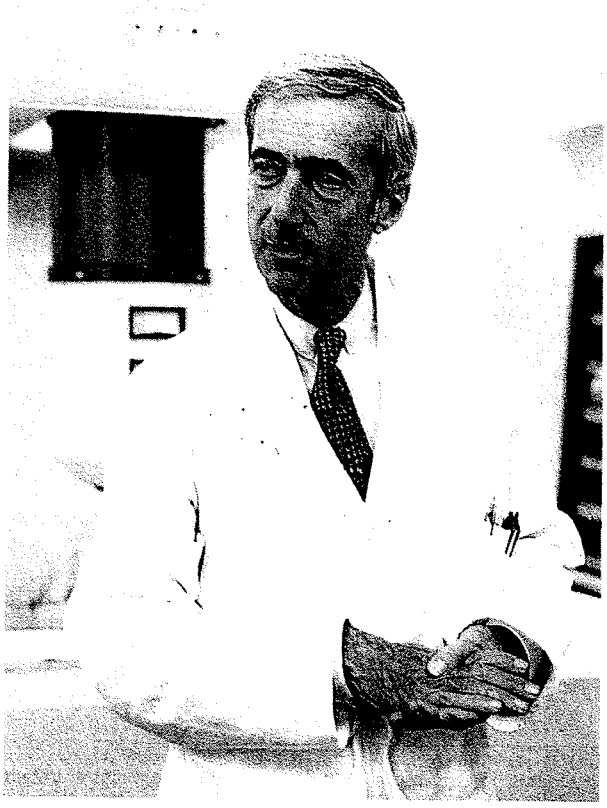
Fig. 1 New members of the Scientific Council



Professor Sir Richard Doll



Professor P. Bogovski



Professor M. Tubiana

controls, and found to have significantly higher titres. The case detection will continue to the end of 1979.

In Tanzania, the malaria suppression programme in North Mara has been going well since September 1977, but it is as yet too early to expect an impact on the incidence of Burkitt's lymphoma in that area.

After a long period of neglect, the role of hepatitis B virus in human liver cancer is actively being studied in several laboratories. There is an increasing body of evidence to show that there is a cocarcinogenic association between active hepatitis B virus infection and primary liver cancer; but the interrelationship between aflatoxin ingestion in the causation of primary liver cancer and hepatitis B virus infection has yet to be understood.

Manpower training

Through an active programme of fellowships and courses, the Agency continues to make its contribution to raising the level of scientific manpower, particularly in the fields of the Agency's own research interest—epidemiology and environmental carcinogenesis. It is hoped that the temporary limitation of funds for the Fellowships programme will be overcome, since the number of first-class candidates continues to exceed by far the number to whom fellowships can actually be awarded.

Table 1. Income and expenditure for 1978[a]

	Amount (US$)	Percentage of total
Income		
Statutory budget	4 810 000	68.90
Extrabudgetary	2 171 000	31.10
Total	6 981 000	100.—
Expenditure		
Intramural		
Headquarters scientific staff	1 982 000	28.39
Administrative staff and office services	947 000	13.57
Building management	466 000	6.68
Laboratory research (supplies and staff salaries)	656 000	9.40
Publications and information programme	424 000	6.07
Building renovations	186 000	2.66
Other (data processing, library, organizational and scientific meetings)	239 000	3.42
Total	4 900 000	70.19
Extramural		
Contractual and collaborative research	1 697 000	24.31
Fellowships	285 000	4.08
Duty travel	99 000	1.42
Total	2 081 000	29.81
Grand total	6 981 000	100.—

[a] All figures are estimates. Statutory budget income and expenditure details are extracted from the approved budget, whereas the extrabudgetary figures are those contained in the estimates of income and expenditure for 1977.

The Agency's specialized courses both in Lyon and in the Regions have provided participants with an insight into the most recent advances, especially in cancer epidemiology and environmental carcinogenesis. Close collaboration with the Regional Office for the Eastern Mediterranean, WHO, resulted in a successful epidemiology course in Karachi.

Personnel

In June 1978, the Agency's staff of 152 was made up of 32 scientists, 56 technicians and 64 administrative and secretarial staff. Seventeen visiting scientists, consultants and fellows contributed to the research programmes of the Agency during the year.

Funding

During 1978, the income of the Agency totalled US$6 981 000. Of this, US$4 810 000 came from the contributions of the Participating States and US$2 171 000 from grants and contracts. The details are given in Table 1.

Some comments on the environment

As indicated by the Director in his introduction to the *Annual Report, 1977,* considerable confusion exists both among the public and scientists regarding the nature of environmental factors in human cancer, and especially the role of indirect environmental factors. In his opinion, it is often forgotten that the term 'environment' covers not only direct exposures, such as occur in the workplace or are derived from cultural habits, but also the complex interplay of all stimuli which modify the individual's reaction to his environment. Such stimuli include initiators, promoters or inhibitors and should even include physical exercise, which modifies calorie intake and its utilization. Today, definite proposals, based on sound scientific observations, could be advanced which, if practised, could prevent up to 40–50 % of cancers in males in Western industrialized societies and a much smaller percentage in females. This level of prevention cannot be achieved, however, for a variety of scientific and nonscientific reasons. Experience has shown that individuals are very resistant to changes in cultural habits like smoking, even in the face of the threat of cancer, since for those whose life is hard, frustrating or boring the satisfaction gained from such habits outweighs the theoretical risk of cancer to a much greater extent than for the more fortunate members of society. Too often in public health circles, excessive emphasis is given to the voluntary nature of cultural habits, and the addictive effects of smoking and alcohol are ignored. In contrast, there has been little difficulty in getting the public to accept that iatrogenic or industrial exposures should be controlled, in which the individual is not involved personally. However, the overall impact of such controls on the reduction of cancer rates will be limited.

There are a number of factors that inhibit an advance towards primary prevention of cancer in both the public and scientific sectors. These include:

(1) unwillingness to accept that cigarette smoking is the major causal factor so far identified in human cancer;

(2) erroneous belief in a predominant role in cancer causation of industrial pollution, whether point source or ambient, to the detriment of studies of other environmental factors. This is supported by the assumption that industrial exposures are controllable;

(3) inability to understand the complex biology of cancer in man and the technical difficulties of analysing and defining the role of 'lifestyle' in its widest sense. No distinction is made between direct carcinogens and carcinogenic risk factors;
(4) failure to distinguish between the identification and control of existing hazards and the identification and control of future hazards—and the relative weight to be given to evaluating the implications of experimental studies in each case. This is compounded by insufficient appreciation of the limitations of present technological and biological means for rational quantitative extrapolation from the results of animal experiments to man;
(5) ignorance of the fact that the establishment of exposure standards protects only against future and not against past exposures;
(6) insufficient understanding of the different types of statistical risks—the difference between relative and absolute risk—so that 'real' and 'potential' hazards are not separated. This may result in failure to appreciate the different options involved in controlling a hazard;
(7) inability to understand that 'safety' is a statistical concept and not a biological absolute;
(8) lack of acceptance that regulatory decisions are based on many considerations and not only on scientific data;
(9) tendency to 'over-kill', leading to a widespread public opinion that 'everything is dangerous'—this in turn has led to the neglect of obvious, controllable hazards;
(10) excessive hope in the development of a 'miracle' cure or preventive vaccine in the immediate future. This has diminished support for prevention.

It has also unfortunately become true that, in many societies, decision-making in the face of a potential carcinogenic hazard has become a matter of confrontation rather than of rational evaluation and discussion; and the conflict between different interests has become increasingly bitter, leading to difficulties for both scientists and regulators. Many of these problems were reviewed at an Agency symposium, organized jointly with the French National Institute of Health and Medical Research (INSERM), in December 1977. The symposium brought together scientists and epidemiologists involved in chemical carcinogenesis studies with lawyers, trade unionists, public health administrators and industrial managers. Although the symposium helped each group better to understand the other's problems, the inability of scientists, at the present time, to provide unequivocal answers to some of the decision-makers' questions clearly remains a major shortcoming that only increased research effort can remove.

Conclusions

The Director feels that the role of the regulator and of scientists in decision-making has never been better expressed than by Ashby[14], who wrote:

> For many political decisions (not only decisions about the environment), there has to be an ingredient of hard data: scientific, technological, economic, statistical. But before the decision can be made, another ingredient has to be added. I called it 'hunch' but a more respectable name for it is 'political judgement'. This can be shallow, as it is mere vote-catching; but it can be profound, and sometimes it tips the balance even against the weight of cognitive evidence.

The objectives of the Agency are to continue to provide and evaluate that ingredient of 'hard data'.

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[14] Ashby (1976) *Proc. roy. Soc. Med.*, **69**, 721–730.

1. UNIT OF EPIDEMIOLOGY AND BIOSTATISTICS

Dr C. S. MUIR (Chief)

1. INTRODUCTION

The Agency continues to play a coordinating role in the field of descriptive epidemiology. Following the publication of the third volume of the monograph *Cancer Incidence in Five Continents*, a commentary is being prepared, describing in non-technical terms the content of the first three volumes. The Clearing-House for On-Going Research in Cancer Epidemiology has produced its third annual directory. Planning for a joint WHO/IARC Expert Committee on Cancer Statistics has continued. Collaboration with the International Association of Cancer Registries has resulted in the production of a monograph on cancer registration.

The search for etiological factors in œsophageal cancer continues, particularly in the Caspian littoral of Iran and in Normandy. The Unit also coordinates an extensive series of international studies to explore the role of alcoholic beverages in neoplasia, which are currently being extended to Switzerland and Belgium. In view of the relatively high and increasing mortality from laryngeal cancer in parts of western and southern Europe, an international case-control study into the roles of tobacco, alcohol and occupation has been undertaken. The reasons for the high lung cancer mortality in Cuban women are being examined, also by a case-control study, and studies of lung cancer in Cantonese women continue.

Different constituents of diet may increase or decrease the risks of cancer. This finding and related metabolic aspects are being studied in urban and rural populations of Denmark and Finland in relation to variations in incidence of colon cancer. However, there are no valid methods for assessing diet in relation to carcinogenesis in populations. Collaborative work to develop such methods is being initiated.

The programme for the study of occupational carcinogenesis has been expanded. Investigation in Europe of the health effects of man-made mineral fibres, with particular reference to cancer, continues; and the possibility of extending the study to users of these products is being explored. The Agency is also collaborating in an epidemiological assessment of the significance of an epidemic in Central Turkey of mesothelioma, which is apparently not due to asbestos exposure.

Initial feasibility studies have been designed for the proposed international epidemiological cancer network.

The biostatistical section continues to contribute to many of the research programmes of the Agency. It is now developing a series of studies that have a major statistical component: e.g., an evaluation of the efficacy of screening campaigns for the early detection of cervical cancer in relation to mortality and optimum screening intervals. A monograph on modern techniques in the analysis of case-control studies nears completion.

2. DESCRIPTIVE EPIDEMIOLOGY

The aim of the programme of descriptive epidemiology is to map the occurrence of cancer throughout the world and to improve the comparability of incidence data. The existence of differences in cancer risk in different populations facilitates the formulation and testing of etiological hypotheses by the Agency and other bodies.

2.1 *WHO/IARC Expert Committee on Cancer Statistics* (Dr C. S. Muir)

The World Health Assembly requested the Director General of WHO to prepare a plan for international cancer control [1]. The planning of national programmes can only be effective if the health services have access to statistics, which indicate as precisely as possible the nature and extent of the cancer problems in their country and whether control measures are effective. The Cancer Unit and Dissemination of Statistical Information Unit of WHO Headquarters, Geneva, and the Agency collaborated in the preparatory work for the Expert Committee, the first to be held jointly by WHO/IARC and the first specifically devoted to all aspects of cancer statistics. As part of the preliminary work, an analysis of previous recommendations of expert committees on statistics in relation to cancer was made.

At a meeting held in Madrid (June 1978), it was noted that WHO had made significant contributions to the classification of malignant disease and to the dissemination and interpretation of incidence and mortality data. The Expert Committee considered that an approach should be made to integrating statistics from various sources, in order to obtain as comprehensive as possible a picture of the cancer situation and the burden it places on medical care resources.

New areas that require urgent attention are the development of guidelines for cancer statistics in less developed countries, the development of criteria for assessing the quality of life after treatment, the up-dating of previous recommendations concerning measurement of survival and the generation of data relevant to studies of the relationship between cancer and the environment. Guidelines are also required for the linkage of data sets at the level of the individual to permit assessment of the health hazards associated with various exposures, including consideration of methods for safeguarding confidentiality.

2.2 *International Classification of Diseases (ICD)* (Ms J. Nectoux)

The Ninth Revision of the ICD has now been published [2] and incorporates the much-needed codes for morphological terms that are compatible with other widely used systems (MOTNAC, SNOMed, SNOP). Tables of equivalence are now being constructed for morphological and anatomical terms that appear in the indices of the 7th, 8th and 9th Revisions of the ICD, to acquaint research workers with the codes assigned in successive revisions.

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[1] Resolution of the 30th World Health Assembly, 1977 (WHA30.41) on 'Long-term planning of international co-operation in cancer research'.

[2] *International Classification of Diseases 1975 Revision*, Geneva, WHO, 1977.

2.3 *Cancer registries*

(a) International Association of Cancer Registries (IACR) (Dr C. S. Muir, Ms S. Whelan)

The Agency continues to act as the secretariat for the Association's activities (RA/73/016). The major collaborative activities comprise the preparation by the Agency, the Cancer Unit of WHO and the IACR of a monograph on cancer registration techniques, which is nearing completion (see section 2.6), joint production of Volume IV of *Cancer Incidence in Five Continents* (see section 2.4) and a study of cancers of the nose, nasal passages, middle ear and accessory sinuses (see below).

The membership of IACR was increased in 1977 by one voting member, Atlanta, Georgia, USA, and the affiliation of four non-voting members: Dijon, France; Munster, Federal Republic of Germany; San Francisco, USA; and Sri Lanka.

A three-day scientific meeting of the Association will be held prior to the XIIth International Cancer Congress in Buenos Aires, on the theme 'Quality Control in the Cancer Registry'. The programme includes examination of quality control problems in in-put and out-put operations and in clinical follow-up. Quality control problems in developed and in developing countries and at central registries receiving information from peripheral sources will also be considered. There will be a panel discussion on completeness of registration as well as a session to hear proffered papers.

Table 2. Age-adjusted incidence rates (AAR) for ICD rubric 160 and relative frequency of each anatomical sub-site within ICD rubric 160, expressed as a percentage of the total rubric, by sex, for selected registries for the period 1968-72

Registry	Nose and nasal cavities (ICD 160)		Nose and nasal cavities (ICD 160.0)		Eustachian tube and middle ear (ICD 160.1)		Accessory sinuses (ICD 160.2,8,9)		Maxillary sinus[b] (ICD 160.2)	
	AAR		Relative frequency (%)		Relative frequency (%)		Relative frequency (%)		Relative frequency (%)[b]	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
AMERICA										
Brazil, Sao Paulo	1.7	0.6	20.0	33.3	0.0	8.3	80.0	58.3	87.5	85.7
Canada, Alberta	0.6	0.4	50.0	52.4	15.0	4.8	35.0	42.9	100.0	77.7
Cuba	0.9	0.5	67.6	65.1	3.4	7.2	29.0	27.7	90.2	91.3
USA, Connecticut	0.7	0.4	61.0	37.2	3.4	11.6	35.6	51.2	76.2	81.8
ASIA										
India, Bombay	1.5	1.0	10.9	5.6	5.0	6.5	84.2	88.0	87.1	91.6
Israel	0.7	0.4	62.7	61.3	7.8	0.0	29.4	38.7	93.3	91.7
Japan, Miyagi	2.5	1.4	3.6	0.0	0.0	0.0	96.4	100.0	94.0	96.4
Japan, Osaka	2.6	1.4	2.8	2.7	1.9	0.7	95.3	96.6	96.7	100.0
EUROPE										
Finland	1.2	0.6	28.8	26.5	6.4	13.3	64.8	60.2	80.2	79.7
Norway	0.9	0.4	22.7	29.0	1.7	0.0	75.6	71.0	71.1	75.5
Spain, Zaragoza	0.4	0.2[a]	50.0	66.7	10.0	33.3	40.0	0.0	50.0	0.0
UK, Birmingham	0.8	0.4	26.2	23.9	9.2	14.8	64.6	61.4	82.1	77.8
Yugoslavia, Slovenia	1.0	0.4	25.0	17.4	0.0	4.3	75.0	78.3	94.4	88.9

[a] Rate based on less than 10 cases
[b] Expressed as a percentage of all accessory sinus neoplasms (ICD 160.2, 8, 9)

Cancers of nose, nasal passages, middle ear and accessory sinuses (Ms J. Nectoux)

Data on malignant neoplasms of nose, nasal passages, middle ear and accessory sinuses (ICD rubric 160), by subrubric and histological type, were requested from cancer registries affiliated with the International Association of Cancer Registries. Some 58 registries responded. The geographical distribution of the disease, including variation in the proportions of the various anatomical subsites and histological types, are being analysed. Japanese registries show a consistent, relatively 'high' incidence (over 3 per 100 000 per annum for males) of ICD rubric 160, most of which is due to neoplasms of the maxillary sinus (Table 2). These findings appear to warrant a study of the case-control type. The proportion of nose and nasal cavity neoplasms was very high in Connecticut, USA; Cuba; parts of Canada; Israel; and Zaragoza, Spain; this finding also requires further investigation.

(*b*) *Caspian Cancer Registry* (see report of the Teheran Research Centre, page 140)

(*c*) *Singapore Cancer Registry* (see report of the Singapore Research Centre, page 134)

(*d*) *Jamaica Cancer Registry* (Professor S. E. H. Brooks: RA/72/014)

The Agency continues to provide minimal financial support to this registry.

(*e*) *Cancer registration in Dakar* (Professor C. Quenum)

A population cancer registry was initiated in Dakar, with the assistance of the Agency, in 1969[3]. Between 1969 and 1974, lists of cancer cases were sent annually to the Agency, where the information was processed.

An initial methodological study explored the various biases likely to occur in cancer material collected in an African country. Duplication is frequent, due to the multiplicity of registration sources and to the inclusion of prevalent cases seen in succeeding years; this is more likely to occur for tumours of lymph nodes, bladder, skin and breast than for other sites. The inclusion of nonresident cancer cases can only be avoided by carefully checking the residence of recorded patients. Of the 4 766 cancer cases entered in the registry, 601 duplicates were eliminated; the remaining 4 165 cases included 1 894 residents of the Cap Vert province, who served for the calculation of incidence rates.

A method was devised for estimating the relative frequency of tumour sites in the various geographic and ethnic groups, using the distribution of the neoplasms seen in the Cap Vert province as a standard. The most frequently observed cancer sites in this province and their age-standardized rates are shown in Table 3. More detailed analysis of this material is underway.

(*f*) *Cancer registration in Latin-speaking countries* (Dr A. J. Tuyns)

The Agency partially financed (RA/78/008) the third meeting of the group for the epidemiology and registration of cancer in Latin-speaking countries (Professor E. Anglesio,

[3] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 28.

Table 3. The ten most frequently observed cancers in the province of Cap Vert, Senegal (1969-1974)

	MALES					FEMALES				
Rank	ICD No. (8th Rev.)	Localization	Number of cases	% of total	Age-stand.[a] rate per 100 000	ICD No. (8th Rev.)	Localization	Number of cases	% of total	Age-stand.[a] rate per 100 000
1	155	Liver	378	36.8	25.0	180	Cervix uteri	182	21.0	16.9
2	172-173	Skin	140	13.6	10.0	174	Breast	127	14.7	11.6
3	200	Lympho-reticulo-sarcoma	58	5.6	3.5	155	Liver	116	13.4	8.9
4	151	Stomach	44	4.3	3.6	172-173	Skin	99	11.4	7.8
5	171	Connective tissue	39	3.8	2.7	183	Ovary	52	6.0	4.1
6	188	Bladder	36	3.5	3.0	200	Lympho-reticulo-sarcoma	23	2.7	1.2
7	185	Prostate	36	3.5	4.3	151	Stomach	20	2.4	2.0
8	191	Brain	28	2.7	1.6	171	Connective tissue	19	2.2	1.6
9	196	Sec. neoplasms of lymph nodes	28	2.7	2.2	188	Bladder	17	2.0	1.5
10	201	Hodgkin's disease	23	2.2	1.1	181	Chorionepithelioma	16	1.9	0.9

[a] Standardized to the African Standard Population

Piedmont Cancer Registry, Turin, Italy; Mr L. Raymond, Geneva Cancer Registry, Switzerland; Dr A. J. Tuyns). The 1978 meeting was held in Zaragoza, Spain, under the chairmanship of Professor E. Zubiri (Zaragoza Cancer Registry). Attention was focused on the evaluation of registration. Various registries reported on present work, and a progress report was presented on the preliminary work carried out for the planning of an international study of laryngeal cancer, involving six of the registries in the Group (see section 3.2 *c*).

(*g*) *Advice to cancer registries and other bodies*

An increasing number of requests for advice and assistance are received by the Unit, some of which are referred by the International Union Against Cancer and the Cancer Unit of WHO. Specifically, advice was provided to the following countries:

Algeria: Further exploitation of existing data on cancer frequency and improvement of the record-keeping system (Professor A. Yaker, Chief, Laboratory of Pathology, Mustapha Hospital, Algiers).

Australia: A short talk on cancer registration, followed by discussion, was given at a meeting of the Director of Health for South Australia and other Health Commissioners (Adelaide). Many aspects of cancer registration were discussed in relation to the new registry which has recently been established in Tasmania (Dr L. F. Young, Department of Health Services, Hobart).

France: Dr A. J. Tuyns provided advice as to the presentation of the first incidence figures for 1975 obtained by the cancer registry in the Department of Bas-Rhin (Dr P. Schaffer, Faculty of Medicine, Strasbourg)[4].

In the Department of Côte d'Or, Dr C. Klepping and Dr J. Faivre (University Hospital of Dijon) run a registry limited to cancers of the gastrointestinal tract. During 1976 and 1977, 913 cases were registered. Close contacts are maintained with this registry, where several publications are in preparation.

Another population-based registry is in operation in the Department of Doubs (Professor S. Schraub, University of Besançon). Preliminary incidence data are now available[5]: urban-rural differences for laryngeal and lung cancer have been demonstrated. These have been discussed with Dr C. S. Muir.

Plans are underway to establish a new population-based registry in the Department of Isère (Dr R. Schaerer, University Hospital of Grenoble); the Unit is assisting in its development.

Indonesia: The possibilities for cancer registration in Jakarta were discussed with Dr Sokeojo Saleh and with Professor Julie Sulianti Saroso, Director of Medical Research, and uses of cancer registration were discussed with senior medical scientists in Jakarta. The hospital-based registry in the university hospital was visited. Dr Soeripto discussed malignant trophoblastic disease on the basis of information from the hospital-based cancer registry in Yogjakarta.

Portugal: A population-based cancer registry in operation in Viana do Castelo in the north of the country (Dr Carvailho, Centro de Actualizaçao de Estudos Medicos) was visited by Dr A. J. Tuyns and a temporary adviser, Mr L. Raymond (Geneva Cancer Registry). There is evidence of an excess of gastric cancer in this area.

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[4] Schaffer, P., Cayemittes, P. A., Arfeux, F. & Kuntzmann, Y. (1978) *Bull. Cancer*, **65**, 9–18.

[5] Klingler, J.-M. G. (1978) *Registre des Tumeurs du Doubs, 1976*, Thèse No. 78–68, Université de Franche-Comté, Besançon, France.

Hospital-based cancer registries in Lisbon and Porto were also visited. It is planned to establish a further population-based registry in the south of the country, and contacts have been established with local members of the medical profession.

Switzerland: The section of cancer registration and epidemiology of the Swiss League against Cancer, under the chairmanship of Professor A. Delachaux (Lausanne), coordinates the work of the six population-based cancer registries that operate in Switzerland. An independent Swiss Association of Cancer Registries is now being formed and the statutes prepared; Dr A. J. Tuyns acts as consultant to this Group, which held a meeting at the Agency in November 1977.

In addition, many enquiries were answered about the chapter on neoplasms in the *International Classification of Diseases* and about the availability of information on the geographical distribution of various cancers.

(*h*) *Computer teaching exercise*

In the workshop and training course on Cancer Registries and Occupational Cancer held in Lyon in 1975[6], the practical work included investigation of an imaginary industrial hazard; the purpose of the exercise was to provide 'instant experience'. On the basis of information about a possible industrial hazard in a factory, students decided on the appropriate methods of investigation, and the computer then supplied the data in the form requested.

It was decided to extend the exercise towards interactivity, allowing for several applications to the computer for additional information or for further processing, thus giving a closer simulation of an actual situation. An agreement (RA/76/018) was made with Dr J. A. H. Waterhouse (Birmingham and West Midland Regional Cancer Registry, UK) to undertake this work, which is being supported by the National Cancer Institute (Bethesda, MD, USA). The analytical sections of the programme have been reviewed and rewritten by Ms J. Fewings[7]. Mr T. M. Sorahan[7] is rewriting the synthetic section, in order to construct a factory population which conforms to whatever outline parameters are set, in terms, for instance, of its overall size at various periods during the calendar years of its existence and the sizes of its subsections, and which is consistent with the mortality-age rates of the district in which it is situated during the same calendar years. Both recruitment to the factory and natural wastage will thus be governed by the vital statistical rates prevailing at the time, and allowance will be made for the distortion of rates of morbidity and mortality for certain diseases, in order to represent the impact of a specific hazard.

2.4. Cancer Incidence in Five Continents, *Volume IV* (Dr C. S. Muir, Ms S. Whelan)

The first meeting of the editorial board for the next volume in this series, planned to appear in 1981, was held in Lyon in March 1978; Professor K. Shanmugaratnam (Singapore Cancer Registry) replaced Dr P. Correa as the representative of the International Association of Cancer Registries. Data will be received from contributing registries between January and September 1979. The basic format and content of the book will remain essentially the same as that of Volume III and will give age-specific and age-standardized incidence rates by site and sex; however, the number of four-digit rubrics for which age-standardized incidence rates are given will be increased to 56.

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[6] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 28.
[7] From the Birmingham and West Midland Regional Cancer Registry, UK.

The existing computer programmes are being rewritten at the Birmingham and West Midland Regional Cancer Registry (Dr J. A. H. Waterhouse, Ms J. Powell) to incorporate modifications in the layout and content of data, and a programme is being devised to check the consistency of several sets of data received from the same registry, e.g., numbers of cases in a given age-group for four-digit rubrics and the relevant three-digit rubrics.

An important place will continue to be given to reliability of data, and extensive enquiries are now being made into variations in registry coding practices. The tables on histological verification of diagnosis, the percentage of registrations based on a death certificate only and correlations with available mortality data will be repeated.

It is anticipated that between 15 and 20 additional registries will be represented in Volume IV, and this will significantly increase the geographical coverage.

2.5 *Commentary on* Cancer Incidence in Five Continents (Dr M. Stukonis)

The three volumes in the *Cancer Incidence in Five Continents* series cover a period of approximately 15 years[8]. The data contained therein consist of a series of tabulations with virtually no commentary, and the significance of the data is not immediately apparent. Work has therefore begun on a monograph that will present the data, including changes over time, in a series of diagrams and charts supported by a brief explanatory text designed for use by medical administrators, non-specialist scientists and informed laymen.

By a rearrangement of the computer tapes, tables were made of the rank order for world-standardized, truncated and cumulative cancer incidence rates; the relative distribution of selected cancer sites within certain population and age groups; the time trends of world-standardized, truncated and cumulative rates; time trends for age-specific incidence rates; sex ratios with time trends; and comparison of ratios of cancer incidence rates for selected sites. These tables are now being used in the preparation of the commentary.

The analysis of this material was discussed with the staff of the cancer registries in Birmingham, UK, Norway and Denmark as well as with the Cancer and Dissemination of Statistical Information Units of WHO, Geneva.

An Internal Technical Report entitled *Cancer Incidence Cumulative Rates – An International Comparison based on Volumes I, II and III of Cancer Incidence in Five Continents* has been completed[9]. This comprises extensive basic tables and an analysis of the findings by site and sex, including time trends.

Discussions were held with the Mathematics Department of the University of Namur, Belgium (Dr G. Schifflers) on methods of data presentation and on the nature of computer graphic output to be employed in the commentary.

2.6 *Cancer registration and its techniques* (Dr R. MacLennan)

There is increasing awareness of the contribution which cancer registries can make to many aspects of cancer control, including epidemiological studies, evaluation of survival and planning of

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[8] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 39.
[9] International Agency for Research on Cancer, *IARC intern. tech. Rep.* No. 78/002.

health services. As the Agency has frequently been approached to give advice on the establishment and running of such registries, a monograph on this topic has now been written [10, 11]. Prepublication copies of the monograph have been requested by cancer registries now being established in Australia, India, Italy, Spain and elsewhere.

2.7 *Ratio studies*

The Agency continues to foster the collection of relative frequency data from cancer institutes and pathology laboratories in regions where cancer registration would be difficult and mortality information unreliable or non-existent.

Cameroon (Dr O. M. Jensen, Dr A. J. Tuyns)

Some 2 808 cases of cancer, histologically confirmed by Professor P. Ravisse, Pasteur Institute, Yaoundé (Cameroon), have been analysed [12]. The most frequent cancers were, in males: skin (30 %), malignant lymphomas (13 %) and primary liver cancer (11 %); in females: skin (20 %), uterine cervix (16 %) and breast (10 %). Kaposi's sarcoma comprised 31 % of all male cancers of the body surface. Ethnic differences within the country were described.

2.8 *Clearing-house for on-going research in cancer epidemiology* (Dr C. S. Muir, Ms A. Nagy-Tiborcz, Ms E. Démaret)

The clearing-house for on-going research in cancer epidemiology was created in 1974 by the Agency and the German Cancer Research Centre, Heidelberg, Federal Republic of Germany (Professor G. Wagner, Dr C. O. Kohler, Mr K. Schlaefer: RA/74/003) and operates within the framework of the International Cancer Research Data Bank of the National Cancer Institute (Bethesda, MD, USA).

The goal of the clearing-house is to provide information on on-going studies in cancer epidemiology through the annual *Directory of On-Going Research in Cancer Epidemiology* and by a special searches service. Although 'epidemiology' is interpreted broadly, the clearing-house does not solicit information on clinical trials, diagnosis or mass-screening programmes, unless these include epidemiological evaluation.

The first annual directory [13] contained 622 projects reported from 56 countries; some 2 000 copies were distributed. The 1977 directory [14] contained 908 projects from 70 countries; about 3 000 copies were distributed to principal investigators, ministries of health, medical journals, cancer research centres and cancer registries, to industry, libraries, medical research boards, research workers and individuals. The content of the 1977 directory has been analysed in some detail in the introduction to the 1978 directory [15]. Studies were reported from 70 countries, but over half were from the USA (32.4 %), the UK (13.8 %), Canada (5.3 %) and Japan (4.1 %).

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[10] International Agency for Research on Cancer (1976) *Annual Report, 1976,* Lyon, p. 31.

[11] International Agency for Research on Cancer (1977) *Annual Report, 1977,* Lyon, p. 31.

[12] Jensen, O. M. & Tuyns, A. J. (1978) *Rev. Epidémiol. Méd. Soc.* (in press).

[13] Muir, C. S. & Wagner, G., eds (1976) *Directory of On-going Research in Cancer Epidemiology, 1976,* Heidelberg, German Cancer Research Centre.

[14] Muir, C. S. & Wagner, G., eds (1977) *Directory of On-going Research in Cancer Epidemiology,* Lyon, International Agency for Research on Cancer *(IARC Scientific Publications No. 17).*

[15] Muir, C. S. & Wagner, G., eds (1978) *Directory of On-Going Research in Cancer Epidemiology,* Lyon, International Agency for Research on Cancer *(IARC Scientific Publications No. 26).*

Statistical studies, largely descriptive, account for 18.8 %, the health effects of industrial exposures for 16.3 %, case-control studies for 14.9 %, and correlation studies for 12.8 %. There are considerable differences in the frequency of study type by region: case-control studies were relatively few in Africa, Australia and eastern Europe, the evaluation of industrial risk was frequent in Canada and in the UK, and statistical studies came often from Africa and South America.

Very few epidemiological studies of cancer of the pancreas and prostate or of malignant melanoma have been carried out, despite their present numerical importance and despite the fact that they seem to be increasing in many parts of the world, even in populations where they have hitherto been considered to be rare.

The clearing-house address list contains some 5 000 names. Mailing for the third directory began in September 1977 and comprised 4 150 letters of invitation to participate; 485 replies were received. The 1978 directory will contain some 1 000 projects from 70 countries.

3. ANALYTICAL EPIDEMIOLOGY

3.1 *Etiological factors in œsophageal cancer*

(*a*) *France* (Dr A. J. Tuyns). See section 3.2 *a*.

(*b*) *Caspian littoral* (Dr N. E. Day, Dr J. Kmet). See report of the Teheran Research Cancer (page 140).

3.2 *Studies on alcohol and cancer* (Dr A. J. Tuyns)

The Agency, with the support of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Rockville, MD, USA), initiated an extensive research programme on the relationship between consumption of alcoholic beverages and various types of cancer. An extensive review of pertinent literature on this subject has now been incorporated in the report *Alcohol and Health* prepared by the NIAAA for the US Congress. A French adaptation of this review has been prepared and published as an IARC Monograph[16].

At the fifth annual review meeting (Lyon, March 1978), the final results of prospective studies of brewery workers in Denmark and Ireland (see section 3.3 *b*) and the most recent findings of retrospective case-control studies on oesophageal cancer in Brittany and Normandy were presented. A progress report on the retrospective case-control study on hepatic diseases in Geneva was also given.

Two new programmes were presented: the study of laryngeal cancer in various countries of Southern Europe, which will start in autumn 1978; and a study to be undertaken in Belgium on cancers of the digestive tract in relation to various dietary factors, including alcohol consumption, the further development of which will depend on whether national funds can be obtained.

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[16] Tuyns, A. J. (1978) *Alcool et Cancer*, Lyon, International Agency for Research on Cancer (in press).

(*a*) *Œsophageal cancer in Brittany and Normandy* (Dr A. J. Tuyns)

These studies continue in collaboration with Dr G. Péquignot, Nutrition Section of the French National Institute of Health and Medical Research (INSERM) (RA/75/015). The intake of beverages and of various food items was studied in œsophageal cancer cases and in the population controls previously used in Brittany for the determination of risks related to alcohol and tobacco consumption[17]; detailed results of this analysis have now been published[18]. The overwhelming role of alcohol consumption was confirmed. Only minor differences were observed between cases and controls with regard to food intake; in particular, there was no indication of deficiencies of vitamins or proteins among cases. This contrasts with the situation observed in Iran, where the restricted diet is under suspicion as a contributory factor. These findings point once more to the diversity of environmental patterns which may determine a high incidence of œsophageal cancer[19] (see p. 140).

In Normandy, not only œsophageal cancer cases but also persons with cancer of other segments of the digestive tract and larynx are being interviewed.

A preliminary analysis of a first series of 327 œsophageal cancer cases (312 males and 15 females) and 914 hospital controls (869 males and 45 females), matched for age and sex, has been undertaken; the hospital controls were interviewed before it was decided that for methodological reasons only population controls would be used in future. Analysis was limited to risks related to alcohol consumption in males.

Crude relative risks were calculated, as well as relative risks adjusted for total tobacco consumption, using the Mantel-Haenszel method; these are shown in Table 4. The regression line was found to be very close to that described previously for cases from Ille-et-Vilaine, confirming the important, dose-related effect of alcohol in the causation of œsophageal cancer in the west of France.

Table 4. Œsophageal cancer study in Calvados (France): relative risks in relation to alcohol consumption

Total daily average consumption of ethanol in grams per day	No. of cases of Œsophageal cancer	No. of hospital controls	Relative risks	
			Crude	Adjusted for smoking
0-20	20	228	1.00	1.00
21-40	20	208	1.10	1.11
41-60	33	157	2.40	2.54
61-80	41	123	3.80	3.59
81-100	52	55	10.78	9.83
101-120	38	39	11.11	10.90
121-140	27	25	12.31	11.28
141+	81	34	27.16	23.26

Further, there was an indication that not all alcoholic beverages are equally dangerous: cider or brandy made from cider may carry an additional risk. This finding requires further investigation and emphasizes the need for parallel biological and laboratory investigations.

[17] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, pp. 33–35.
[18] Tuyns, A. J., Péquignot, G. & Jensen, O. M. (1978) *Bull. Cancer*, **65**, 59–64.
[19] Tuyns, A. J., Péquignot, G. & Jensen, O. M. (1978) *Front. Gastrointest. Res.* (in press).

Substantial progress has been made in laboratory investigations undertaken over the last five years. It is now evident that the small amounts of nitrosamines detected in various alcoholic beverages cannot alone explain the œsophageal cancer incidence levels observed in Brittany and Normandy. Additional investigations seem to indicate the presence of mutagenic components in these beverages, and this finding is being explored further (see p. 110).

An experiment in which animals were exposed for two years to various types of local alcoholic beverages, initiated by Professor J. Y. Le Talaer (Department of Biology, François Baclesse Centre, Caen), with the assistance of Dr A.-M. Mandard (Department of Pathology of the same Centre), is now being terminated.

The possibility that carcinogenic nitrosamines are synthesized endogenously from nitrites in the saliva and in the gastric juice has been explored. The formation of salivary nitrite was found to be highly dependent on exogenous dietary nitrates; there was no difference in the capacity to form nitrites between œsophageal cancer patients and controls[20].

Dr Mandard is pursuing her studies on œsophagi collected at necropsy from cancerous and other patients (see p. 56).

(*b*) *Alcohol in relation to other diseases* (Dr A. J. Tuyns)

The investigations on alcohol and cancer have provided an opportunity to study other alcohol-related diseases. In the study carried out in Ille-et-Vilaine with Dr G. Péquignot, interviews with a group of patients with ascitic cirrhosis showed that the logarithm of the risk of ascitic cirrhosis is a linear function of daily intake of alcohol in grams. It was also established that in that particular French department, some 93% of all ascitic cirrhoses could be attributed to the use of alcoholic beverages[21]. This finding is of considerable public health significance.

In another study in Rouen, based on the same study design and also carried out with Dr G. Péquignot (RA/77/028), the role of tobacco, alcohol and diet is now being studied in relation to acute myocardial infarction.

(*c*) *Cancer of the larynx in southern Europe* (Dr A. J. Tuyns, Dr L. Pla-Bernal, Dr J. Estève)

Preliminary analysis of the literature indicates the existence of a correlation between national levels of alcohol consumption and mortality from laryngeal cancer in males, whereas there is no such correlation with tobacco consumption. More refined analysis of this material is now underway.

In western Europe, there are sharp contrasts in the distribution of mortality from cancer of the lung and from cancer of the larynx, although both are related to tobacco smoking. In the UK and The Netherlands, mortality from lung cancer is very high, whereas mortality from cancer of the larynx is comparatively very low. In Italy, France and Spain, the mortality figures for laryngeal cancer in males are three times higher than those observed in the UK, while lung cancer mortality is much lower. These differences are probably due to the fact that in southern Europe the consumption of alcohol in the form of wine and other beverages is higher than that in northern Europe. It has also been suggested that the tobacco most commonly smoked in these countries,

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[20] Lowenfels, A. N., Tuyns, A. J., Walker, E. A. & Roussel, A. (1978) *Gut*, **19**, 199–201.
[21] Péquignot, G., Tuyns, A. J. & Berta, J. L. (1978) *Int. J. Epidem.* (in press).

so-called 'black' tobacco, may be more carcinogenic to the larynx than the blond type smoked in the North.

As this mortality trend was reflected in incidence figures from Piedmont (Italy), Zaragoza (Spain) and Geneva (Switzerland), a multiregional study on laryngeal cancer was organized: a retrospective case-control study has now begun in Turin and Varese (Italy), Zaragoza and Pamplona (Spain) and Geneva[22]. Groups of patients in Calvados and Paris (France) will also be incorporated into the study.

Three groups of factors will be investigated:

– consumption of alcohol in quantitative and qualitative terms, measured by means of the dietary questionnaires used in previous studies on cancer of the œsophagus (see section 3.2 *a*).

– smoking, in terms of amount, duration and type of tobacco smoked, etc.

– occupational exposures, derived from an extensive occupational history.

Controls for the study will constitute a representative sample of the general population. The study is expected to take four years.

Various difficulties were examined by the Planning Committee: the diverse regional diets, identification of trade marks of cigarettes smoked over the last 20 years, many of which are no longer on the market, and the design of the occupational questionnaire. The various questionnaires have now been drawn up in French, Spanish and Italian. A seminar held in Lyon from 22–31 May 1978 to train interviewers in the various techniques and questionnaires to be used in the investigation was attended by some 20 participants.

3.3 *Large-bowel cancer* (Dr R. MacLennan)

The considerable geographical variation in the second most common cause of death from cancer in males and females in Europe, North America and Australia, is being exploited by means of collaborative international studies in countries with population-based cancer registration. The Agency was represented at a workshop held in Wellington, New Zealand, in 1977, under the auspices of the Medical Research Council of New Zealand, where diet and colon cancer were discussed. There has subsequently been considerable interest among investigators in New Zealand in population studies of diet and faecal characteristics, in large-bowel pathology at autopsy and in the precise anatomical distribution of cancer in the large bowel.

(*a*) *Intestinal metabolic activity in large-bowel cancer* (Dr R. MacLennan, Dr O. M. Jensen)

Although the type and quantity of food and drink consumed are believed to determine the risk of colo-rectal cancer, diet as such is clearly insufficient to explain the occurrence of the disease. Most of the food eaten by high-risk populations is believed to be non-mutagenic, and further metabolism is believed to be necessary for colo-rectal carcinogenesis: bacterial metabolites of bile acids produced in response to a high fat intake are postulated as promoters of colo-rectal cancer, but the initiators of carcinogenesis are unknown. It has been proposed that dietary fibre has a protective

[22] Principal investigators and collaborating institutions are: Dr B. Terracini, Department of Anatomy and Histopathology, University of Turin, Italy (RA/78/017); Dr F. Berrino, National Cancer Institute, Milan, Italy (RA/78/018); Dr A. Zubiri, Cancer Registry of Zaragoza, Zaragoza, Spain (RA/78/015); Dr A. del Moral Aldaz, Health Department of Navarra, Pamplona, Spain (RA/78/016).

effect, by diluting the intestinal contents and, possibly, by modifying bacterial or other types of metabolism in the intestine. The Agency has been able to extend the scope of investigators in national laboratories[23] by providing access to populations with greater contrast in incidence than are available nationally, and by assisting in the study design, organization and collection of data and biological material in a standard manner in each population.

Due to the possible protective role of dietary fibre suggested by previous work of the IARC Intestinal Microecology Group in Denmark and Finland[24], accurate assessment of dietary intake is now being given much greater emphasis in further field studies in Denmark (University of Aarhus: RA/77/027) and Finland (Social Insurance Research Institute, Helsinki: RA/77/030). In the earlier investigations, rural Finnish and urban Danish populations were compared; current studies[25] contrast urban and rural populations in both Denmark (Copenhagen, Them) and Finland (Helsinki, Parrikala).

The rates of colo-rectal cancer among migrant groups in Australasia are currently being documented in Australia and New Zealand.

(*b*) *Beer and large-bowel cancer* (Dr O. M. Jensen, Dr R. MacLennan)

Two historical cohort studies have been conducted among brewery workers in Copenhagen and Dublin, who are allowed a daily free ration of the brewery product[26]. In Copenhagen, there were excess risks of laryngeal, lung and œsophageal cancer but no increased risk for large-bowel neoplasms, whereas in Dublin there was a significant excess (at least two-fold) of rectal cancer. Observed and expected mortality rates for the Dublin workers for certain cancer sites are shown in Table 5. The Dublin brewery workers produce stout manufactured from malted barley which is roasted at a high temperature; tests of the mutagenicity of such stouts and of other types of beer are currently being carried out by Dr T. Sugimura, National Cancer Centre, Tokyo.

(*c*) *Dietary fibre methodology* (Dr R. MacLennan)

Dietary fibre comprises the polysaccharides and lignins that are not digested by the enzymes secreted in the human digestive tract; it includes pectic substances, hemicelluloses, cellulose and lignins. Fibre is heterogeneous in content and diverse in chemistry, and it is likely that the different categories of dietary fibre have different metabolic effects[27] and may differ in their associations with disease. The study of such possible associations is, however, severely handicapped at present by lack of information about the fibre content of common foods in different countries. The Agency, in conjunction with the European Economic Community, sponsored a working group (Lyon, December 1977) to bring together workers who are concerned with analysing the fibre composition of foods and with disease patterns in different populations, mainly in Europe.

Information is now becoming available on the fibre composition of a wide range of foodstuffs, and it is important to ensure that analysts from different countries agree on the most appropriate method for measuring dietary fibre; this would facilitate the comparability of studies in different

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[23] Including the Bacterial Metabolism Research Unit, Colindale, UK; the Medical Research Council Dunn Nutrition Unit, Cambridge, UK; the Department of Clinical Bacteriology, University of Uppsala, Sweden.

[24] IARC Intestinal Micro-ecology Group (1977) *Lancet, ii,* 207.

[25] In collaboration with the Department of Medicine, St Elizabeth Hospital, Copenhagen, Denmark; the Institute of Hygiene, University of Aarhus, Denmark; and the Social Insurance Research Institute, Helsinki, Finland.

[26] International Agency for Research on Cancer (1977) *Annual Report, 1977,* Lyon, pp. 37–38.

[27] Cummings, J. H., Southgate, D. A. T., Branch, W., Houston, H., Jenkins, D. J. A. & James W. P. T. (1978) *Lancet, i,* 5–9.

countries. During the course of meeting it became apparent that many different systems for measuring dietary fibre have been developed over the last two years and that the problem of analysis is extremely complex. Only analyses relating to British foods were available in a comprehensive manner, although there was considerable information on Danish and American foods. The working group concluded that it was necessary to arrive at an agreed approach for analysing fibre in foods and at recommended criteria to be used for the analysis of dietary fibre. The recommendations include abandoning the use of 'crude fibre' both as a term and as an analytical procedure. A collaborative programme was formulated in which standard batches of five foods (bran, potato powder, dried apple, a rye crispbread and citrus pectin) would be supplied by the Dunn Nutritional Laboratory in Cambridge, UK to collaborating laboratories in Europe and North America. The results of further analytical work will be discussed at an EEC sponsored meeting to be held in Cambridge at the end of 1978. Following international agreement, the methods will be applied to the measurement of dietary fibre in all foods commonly consumed in Europe and North America, to enable a better understanding of dietary fibre intakes in different populations and groups. It will thus be possible to use food tables to estimate fibre intake, rather than undertake laboratory analysis on an *ad hoc* basis in every study. This is particularly important in the study of the possible protective role of dietary fibre in colon cancer (see section 3.3 *a*).

Table 5. Expected number of cancer deaths for certain sites among brewery workers 1964-1973 if they had the same risk as the populations[a] of Dublin County Borough and other urban and rural areas in the years 1969 and 1971-1975 inclusive[b]

Cancer site	Expected deaths (1964-1973)				Actual brewery deaths 1964-1973 inclusive	Actual brewery deaths 1954-1963 inclusive
	All Ireland	Dublin County Borough	Other urban areas	Rural areas		
Oesophagus	4.1	6.9	4.8	3.4	5	5
Small intestine, incl. duodenum	0.3	0.5	0.5	0.3	—	1
Large intestine, except rectum	11.2	12.6	13.9	10.2	16	16
Rectum and recto-sigmoid junction	6.5	8.4	8.1	5.7	15[c]	17
Liver and intra-hepatic bile ducts	1.7	2.5	1.4	1.7	4	3
Gallbladder and bile ducts	0.7	1.1	0.8	0.7	1	1
Pancreas	6.2	7.5	5.9	6.0	6	11
Peritoneum & retro-peritoneal tissue	0.3	0.3	0.4	0.2	—	—
Unspecified digestive organs	0.2	0.5	0.1	0.2	—	—
Total	31.2	40.3	35.9	28.4	47	54

[a] Populations based on the 1971 national census; no breakdown of deaths was available for 1970.
[b] From Dean, G., MacLennan, R., McLoughlin, H. & Shelley, E. (submitted for publication).
[c] $P < 0.01$.

(*d*) *Large-bowel pathology in autopsy series* (Dr R. MacLennan)

This collaborative study[28] seeks to correlate variation in possible precursor or associated pathology with variation in cancers of the colon and rectum, and will hopefully provide clues to

[28] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 39.

histogenesis or to common etiological factors. Collection of autopsy material has now been completed in the low-incidence rural area of Kuopio, Finland, and histological examination of polyps is being undertaken by Dr E. Koskela (University of Kuopio). The protocol developed for these studies was distributed to investigators in Baghdad, Iraq (Dr K. Qassab), Christchurch, New Zealand (Dr R. J. Stewart) and Sydney, Australia (Dr E. Hurst), and is available on request.

(*e*) *Sub-site distribution of cancer of the large bowel* (Dr O. M. Jensen, Dr R. MacLennan)

A pilot study to develop a suitable protocol has been completed in Copenhagen and Oslo and is also being tested in Christchurch, New Zealand (Mr G. W. Holland, New Zealand Cancer Society). In each region, attempts are being made to document the exact site of all cancers that occur in geographically defined populations. This is done in collaboration with regional cancer registries.

3.4 *Smoking, chewing and drinking habits* (Dr R. MacLennan)

Much more needs to be known about the epidemiology of risk factors, both in relation to studies of etiology and in planning and assessing cancer prevention. Further collaboration in the documentation of habits of possible relevance to oral, pharyngeal, hypopharyngeal and laryngeal cancers in south-east Asia has been initiated. A similar survey to that in northern Thailand[29] has been conducted in Rangoon (Dr Thein-Hlaing, Department of Medical Research) and other areas of Burma. The Agency assisted in data processing. Advice on a less comprehensive investigation in Sri Lanka was given to Dr S. Sivayoham (Unit of Epidemiology, Department of Health). When the results of the Burmese surveys become available, it is proposed to proceed further with a collaborative international study of risk factors related to the high incidence of cancer of the hypopharynx found in Assam, Burma and northern Thailand.

3.5 *Lung cancer in Chinese* (Dr R. MacLennan)

The high incidence of adenocarcinoma (11.9 per 100 000[30]) in Cantonese women in Singapore is not associated with smoking[31]. This has been confirmed in a collaborative study of Hong-Kong Cantonese organized by Dr M. Colbourne (Department of Community Medicine, University of Hong-Kong: RA/77/010).

However, the etiological factors responsible for this high incidence of adenocarcinoma are not known. As Cantonese women have different cooking methods from other Chinese, it was postulated that either the modern cooking fuels used or the higher temperatures encountered in unventilated urban kitchens are related to the high risk. Spray and mist arising during stir-fry Cantonese cooking were collected onto glass fibre membranes, and these together with deposits on exhaust fans from Cantonese restaurants, have been tested for mutagenic activity by Dr M. Nagao, National Cancer Centre Research Institute, Tokyo. Other types of collection are planned.

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[29] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 40.

[30] Law, C. H., Day, N. E., & Shanmugaratnam, K. (1976) *Int. J. Cancer*, **17**, 304–309.

[31] MacLennan, R., Da Costa, J., Day, N. E., Law, C. H., Ng, Y. K. & Shanmugaratnam, K. (1977) *Int. J. Cancer*, **20**, 854–860.

3.6 *Lung cancer in Cuban women* (Dr R. MacLennan, Dr O. Joly)

In the initial phase of a case-control study of women with lung cancer in Havana, less than 30% of cases diagnosed had histological confirmation of the disease and cell typing. Attempts are being made to increase the proportion that is histologically typed, to obtain more information about differences in risk by cell type for light and dark tobaccos. Following this initial feasibility phase, the study will be extended to include male cases. This work is undertaken in collaboration with the Institute of Oncology and Radiobiology, Havana (RA/77/106), and is financed by the National Cancer Institute, USA.

3.7 *Primary liver cancer* (Dr A. J. Tuyns)

In collaboration with Dr P. Sizaret and Miss N. Martel (Interdisciplinary Programme and International Liaison Unit), an investigation of alpha-fetoprotein levels in various groups of healthy individuals in Asia, Africa and Europe has been completed[32]. Levels increased with age in all groups examined but were much higher in the African groups than in the Asian and European ones, the difference being particularly marked in the younger age groups. These findings are consistent with the hypothesis that young Africans are exposed to various agents that cause alterations in the liver which lead to the formation of alpha-fetoproteins. A viral origin for this injury was hypothesized several years ago, following a study of prevalence rates of HB ag. in sera collected in the Ivory Coast[33]. In European populations, the insult is more likely to be of toxic origin, probably alcohol; it also takes place at a much later age.

In a complementary study on changes over time in alpha-fetoprotein levels in the population of the Ivory Coast[34], it has been shown that these are minimal over six months. It is still not known whether normal individuals with the highest observed levels of alpha-fetoproteins (which are still far lower than those observed in confirmed cases of primary liver cancer) have a higher risk of eventually developing primary liver cancer.

A review of current information about etiological factors in primary liver cancer in Europe and other parts of the world has been prepared[35].

3.9 *Industrial exposure*

(*a*) *Health risks from man-made mineral fibres* (Dr R. Saracci, Dr J. E. H. Milne, Dr O. M. Jensen)

(i) *Production industries*

The study is financed by the Joint European Medical Research Board of the Comité international de la Rayonne et des Fibres Synthétiques (CIRFS) and the European Insulating

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[32] Sizaret, P., Martel, N., Tuyns, A. J. & Reynaud, S. (1977) *Digestion*, **15**, 97–103.

[33] Tuyns, A. J., Rive, J., Zuckerman, A., Sizaret, P., Serie, F., Kone, I. & Berrino, F. (1974) *Med. Afrique Noire*, **21**, 507–512.

[34] Martel, N., Tuyns, A. J. & Sizaret, P. (1977) *Digestion*, **16**, 128–137.

[35] Tuyns, A. J. (1978) *Actual. Pharm.* (in press).

Manufacturers Association (EURIMA) and is directed by the independent Scientific and Technical Committee of the board. The Committee includes representatives of the Agency, of the Institute of Occupational Medicine, Edinburgh, UK and of the Medical Research Council Pneumoconiosis Unit, Cardiff, UK. Dr E. Bolinder, Medical Adviser to the Swedish Trade Union Confederation, has received a mandate from the International Confederation of Free Trade Unions to represent organized labour on the committee.

CIRFS and EURIMA supplied a nominal roll of the 72 factories in their organization, which are situated in 15 countries. Visits have been made systematically to plants in Austria, Belgium, Denmark, the Federal Republic of Germany, Finland, France, Greece, Italy, Norway, Spain, Sweden, Switzerland, The Netherlands, Turkey and the UK. Data were obtained from each plant about numbers of workers, fibre type, method of manufacture, the year production started, availability and quality of personnel records and facilities for follow-up. In some, but not all, plants, measurements of mean fibre diameter were available.

On the basis of these data, an assessment was made for each factory as to its suitability for involvement in a historical cohort study: 13 factories, located in seven countries, have been selected (Table 6). A period of 20 years was considered to be a minimum for historical follow-up, in view of the long latent period between first occupational exposure and the associated neoplasms for other fibre-induced cancers (e.g., mesothelioma induced by asbestos).

Table 6. List of plants in historical cohort study of health effects of employment in man-made mineral fibre production factories

Country	Type of fibre	Approximate present work force	Year records commenced	Collaborating epidemiological investigator
Denmark	Rockwool	450	1943	Dr J. Clemmesen
Finland	Glasswool	200	1941	Dr L. Teppo
France	Continuous filament	1 100	1950	Dr M. Esquevin
Norway	Glasswool	150	1935	Dr E. Pedersen
Norway	Rockwool	80	1940	Dr E. Pedersen
Norway	Rockwool	70	1950	Dr E. Pedersen
Norway	Rockwool	70	1955	Dr E. Pedersen
Sweden	Glasswool	300	1933	Dr P. Westerholm
Sweden	Rockwool	130	1942	Dr P. Westerholm
Sweden	Rockwool	400	1940	Dr P. Westerholm
UK	Glasswool	1 100	1955	Professor E. D. Acheson
UK (Northern Ireland)	Continuous filament	350	1956	Professor E. D. Acheson
Federal Republic of Germany	Glasswool	120	1952	Mr J. Weissker

Investigators from each country, for the most part associated with cancer registries, have agreed to cooperate in the study, assuming responsibility for the direct supervision of data collection at individual factories and for the follow-up of workers; the Agency provides overall supervision and coordination. A meeting was held under the auspices of the WHO Regional Office for Europe, Copenhagen, in April 1978, during which detailed consideration was given to a protocol for data collection, taking into account the results of an initial trial of document sorting, abstraction and follow-up at each factory. This revised protocol is being used as the basis for the collection of data, which begins during the second half of 1978.

Close collaboration has been established with the Institute of Occupational Medicine, Edinburgh, UK (Dr H. Walton, Mr J. Dodgson), whose team of industrial hygiene specialists is conducting the environmental survey at each factory. Measurements of airborne fibre concentration and characterization of fibre size distribution are carried out by a systematic sampling plan. It is anticipated that this large-scale international study will be completed by early 1981.

(ii) *User industries*

Higher concentrations of fibres are likely to be associated with certain uses of man-made mineral fibre products, such as in building (insulation of walls, roofs, etc.), construction and demolition, than occur in the production industry. An investigation of workers in these occupations would thus also be desirable, in order to detect possible cancer risks arising from their use. Several factors could, however, complicate this type of investigation: there may be exposure to other carcinogens, such as asbestos, and the exposure may be discontinuous. Work is organized in small units with high mobility, and follow-up of exposed persons would consequently be difficult. The feasibility of conducting such a study is being examined in Sweden (Dr A. Englund, Medical Adviser to the Foundation for Occupational Safety and Health in the Construction Industry 'Bygghälsan'), where man-made mineral fibres have been used relatively widely for at least two decades in the building industry.

(*b*) *Detection of occupational risk by case-control studies* (Dr R. Saracci, Dr J. Cooper, Dr N. E. Day, Dr J. Siemiatycki, Ms D. Magnin)

Cohort studies, historical or prospective, are traditionally undertaken when a substance or occupational exposure is suspected of being associated with an elevated cancer risk. A large number of exposed and nonexposed (or less exposed) people are followed to determine which of them develop cancer. In the case-control approach, people who have already developed cancer are investigated to determine their previous occupational exposures. A pilot study on the feasibility of conducting such an investigation in the Lyon area is presently underway (Dr J. J. Fabry, Claude Bernard University). This includes a comparison of the effectiveness of different data collection instruments (self-administered questionnaire *vs* semi-structured interview), and an assessment of the validity of information on occupational history collected in this way by comparing it with existing governmental records of occupational history.

(*c*) IARC Monographs of the Evaluation of the Carcinogenic Risk of Chemicals to Humans (Dr R. Saracci)

Dr Saracci continues to provide epidemiological advice to this programme, which in the last year included both the compilation of monographs on specific chemicals and the preparation of partially revised criteria for evaluation of the compounds. The lack of epidemiological information for many of the compounds considered indicates the need for a more systematic approach to this problem (see page 78).

As a follow-up to the monograph on chlorinated dibenzodioxins and related compounds, an *ad hoc* international working group, convened by IARC and the National Institute of Environmental Health Sciences (Research Triangle Park, NC, USA), examined the prospects and problems of long-term epidemiological studies in population groups exposed, occupationally or accidentally, to dibenzodioxins or dibenzofurans (see page 83).

(*d*) *Cancer mortality in relation to occupation and social class* (Dr W. P. D. Logan)

This historical review of trends and the relationship between cancer, occupation and social class is based on the *Decennial Occupational Cancer Mortality Supplements* of the Registrar General of England and Wales from 1851 to 1971 and is funded by a generous grant from the National Cancer Institute of the USA. Access to the material and considerable help have been given by Dr A. Adelstein and Dr J. Fox (Office of Population Censuses and Surveys, London).

The method of occupational mortality analysis employed by the Registrar General has been to aggregate deaths, classified by sex, age, cause and occupation, during three or five years around each decennial population census and to relate these deaths to the corresponding occupational populations enumerated at the census. After the 1911 *Supplement,* individual occupations were combined, on the basis of an assessment of the social standing of each occupation, into five social classes, namely: I Professional, II Intermediate, III Skilled, IV Semi-skilled and V Unskilled occupations.

The main cancer sites can be followed throughout the period, despite successive revisions of the ICD. In the analysis published in 1911, cancers were not broken down by site, but mortality indices for 16 sites were published subsequently in a statistical journal. In each subsequent *Supplement,* mortality data by age and (since 1931) by sex were tabulated for about 30 cancer sites.

To supplement published standardized mortality ratios, serial sex- and age-specific death rates for all sites (œsophagus, stomach, intestine, rectum, lung, breast, cervix uteri, other uterus and leukaemia) have been computed; in addition, cumulative rates for the age-span 25–64 (which assumes that no other causes of death were operating), working life time mortality risk, lost years of expected working life and equivalent mean age at death were calculated.

Table 7 indicates the type of results obtained for each site examined (mortality at ages 25–64 in 1951 is taken as 100).

Table 7. Cancer of the lung; trends in mortality, 1921-1971, by social class (SC[a])

	Men		Married women	
	SC I & II	SC IV & V	SC I & II	SC IV & V
1921	7	5	—	—
1931	19	16	35	34
1951	*100*	*100*	*100*	*100*
1961	110	147	124	160
1971	101	157	176	286

[a] I Professional occupations
II Intermediate occupations
III Skilled occupations
IV Semi-skilled occupations
V Unskilled occupations

4. BIOSTATISTICS (Dr N. E. Day)

Dr J. Estève joined the section in October 1977, and has proved an invaluable addition to the staff. This increase in personnel has resulted in a greater emphasis on independent work. There is a widespread lack of adequate biostatistical support in international cancer research; in response to

this need, the biostatistics section will further the development of appropriate methods, disseminate statistical methodology by the publication of monographs and provide, on suitable occasions, statistical expertise either by direct collaboration or by the provision of consultants.

4.1 *Development of statistical methods for use in cancer epidemiology*

(*a*) *Case-control studies* (Dr N. E. Day, Dr N. E. Breslow, Mr C. Sabai)

A workshop was held in December 1977, partly financed by the International Union against Cancer, to review both the statistical principles underlying the analysis of case-control studies and the statistical methods available. A preliminary draft of a monograph had been prepared for discussion. Review of this initial version by the workshop participants has led to an authoritative text on the analysis of case-control studies, with sufficient explanatory examples to enable working epidemiologists to use it directly. The final draft is in preparation, and the resulting monograph should be published early in 1979.

Work has continued on the development of methods; and the aspects of methodology that treat the estimation of relative risk are now complete. A paper is in press[36].

(*b*) *Evaluation of screening programmes* (Dr N. E. Day, Mr X. Nguyen Dinh)

Methods for the evaluation of early detection programmes are being developed, with current emphasis on screening for cancer of the uterine cervix. The conclusion of the UICC workshop, held in Toronto, in April 1978, at which the IARC was represented by Drs G. Johannesson (Iceland), A. S. Morrison (Harvard University) and N. E. Day (IARC), was that the value of screening for cervical cancer has been established, but that more information is needed on the degree and frequency of screening required to achieve a given level of benefit.

A collaborative project has been initiated in conjunction with the Cancer Unit, WHO Headquarters, Geneva, and with a number of national and regional centres in Iceland, Finland, Scotland, Norway and Switzerland. The aim is to amass data from high quality screening programmes to resolve questions about the quantitative benefit of a given level of screening. Simultaneously, statistical methods are being developed to estimate the presymptomatic-disease-phase sojourn time distribution and the proportion of false negatives. This project follows earlier collaborative work with the Icelandic Early Detection Clinic (see section 4.3 *c*).

(*c*) *Clustering techniques* (Dr N. E. Day, Ms M. Gonzalez)

In a variety of situations, epidemiologists are interested in the degree to which a certain characteristic aggregates in specific groups of individuals, e.g., neighbourhood clusters of high malarial parasite counts, family clusters of Epstein-Barr virus serological markers or of breast cancer or spatial clustering of Burkitt's lymphoma during different time periods. A number of techniques have been proposed to answer these problems, but many use only a part of the available information. An approach suitable for a range of clustering problems, though not all, is being developed, which uses all of the available information and incorporates covariate values.

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[36] Breslow, N. E., Day, N. E., Sabai, C. & Halversen, K. T. (1978) *Am. J. Epidemiol.* (in press).

4.2 *Œsophageal cancer in Iran* (Dr N. E. Day, Ms A. Ressicaud)

(*a*) *Case-control study of socio-economic and dietary factors* (with Ms P. Cook-Mozaffari, Medical Research Council, Oxford, UK)

The main biostatistical contribution to this study was to ensure, by design and analysis, that positive results were not due to bias and were specific for the œsophagus. The design included construction of proper sampling frames for choosing controls (where necessary, by means of special censuses), inclusion of other tumours in the study, and the reinterviewing of both cases and controls. Methodological developments (outlined in section 4.1 *a*) enabled concentration of analysis, in conjunction with the Department of Biostatistics in the Institute of Public Health Research, University of Teheran (Dr F. Azordegan), on questions of bias.

(*b*) *Studies on opium* (with Mr C. Malaveille, Dr H. Bartsch, Mrs G. Brun, Mrs A. Hautefeuille, in collaboration with Dr N. E. Day and Dr K. Szendrei, Szeged, Hungary)

The testing for mutagenic activity of crude opium and opium pyrolysates is reported on p. 110. Work is now in progress to characterize chemically the active ingredient(s) of the dross and to develop methods that can be used in the field to detect consumption of opium pyrolysis products as opposed to raw opium. The detection of mutagenic activity in urine is thus being explored (other collaborative work in the Iran œsophageal cancer project is described in the report of the Teheran Research Centre, p. 140).

4.3 *Epidemiological studies in Iceland* (Dr H. Tulinius, Dr G. Johannesson, Ms M. Gonzalez, Dr N. E. Day)

(*a*) *Familiarity of breast cancer*

An article is in preparation on the risk of breast cancer among first and second degree relatives. Studies of genetic markers in multiple case families are under consideration.

(*b*) *Assessment of risk associated with reproductive factors for cancers of the breast and ovary*

For cancer of the breast, a fall in risk was associated with first birth, as expected, and also with increase in parity[37]. There are conflicting reports about the effects of parity and age at first birth on the risk for cancer of the ovary[38, 39]; the records of the cervical cancer early detection clinic (see section 4.3 *c*) provide prospective data on risk for ovarian cancer. A paper on these relationship is in preparation.

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[37] Tulinius, H., Day, N. E., Johannesson, G., Bjarnason, O. & Gonzalez, M. (1978) *Int. J. Cancer* (in press).

[38] Joly, D. J., Lilienfeld, A. M., Diamond, E. L. & Bross, I. D. J. (1974) *Am. J. Epidemiol.*, **99**, 109–209.

[39] Newhouse, M. L., Pearson, R. M., Fullerton, J. M., Boesen, E. A. M. & Shannon, H. S. (1977) *Br. J. prev. soc. Med.*, **31**, 148–153.

(*c*) *The early detection clinic for cervical cancer*

The first ten years of operation of the clinic (1965–1974) were associated with a notable decline in mortality from cancer of the cervix, which has become accentuated in subsequent years. An initial analysis of this material has been published[40], and more extensive analyses are underway. The value of the detection clinic as a basis for prospective studies has already been demonstrated in relation to the role of reproductive factors in cancers of the breast and ovary. More extensive utilization is being planned.

4.4 *Cancer of the larynx* (Dr J. Estève, Mr S. Sabai, Ms M. Gonzalez)

Assistance has been given in planning a case-control study in Latin countries, including a course, held at the Agency, to train investigators from the participating countries and to test draft questionnaires. The necessary statistical assistance will continue to be given to coordinate and standardize the study in the different centres.

An international and intranational correlation study has been carried out of the relationship between laryngeal cancer and lung and digestive tract cancers and also with the consumption of tobacco and alcohol. The absence of a correlation between mortality from laryngeal cancer and tobacco consumption on an international scale leads to the supposition that the type of tobacco smoked may be of considerable importance for the incidence of this cancer. Figures of estimated consumption of light and dark tobacco are available for France and Italy and are being analysed. An article on the methodology and results of this study is in preparation (see section 3.2 *c*).

4.5 *Singapore Cancer Registry* (Professor K. Shanmugaratnam, Mr X. Nguyen Dinh, Ms A. Ressicaud)

Extended analysis of the data for the first seven years of operation is in progress; updating to cover a ten-year period is envisaged for next year. Analysis by country of birth and dialect group and trends of incidence with time are being considered.

4.6 *Burkitt's lymphoma (BL)* (Mr P. G. Smith, Dr J. Estève, Ms B. Charnay)

An analysis of the BL data from the West Nile district in Uganda for the years 1961–1975, particularly with regard to time-space clustering, has been published[41]. Assistance has been given in preparation for publication of the results of the main prospective study (see page 67).

The data on the number of malaria parasites per individual in the zones endemic for BL are being analysed in two stages. The first is to determine the effect of age, sex, season, year and place of residence on both the prevalence and the degree of parasitaemia. The second is to examine if there are families or individuals with a greater tendency for high or positive parasite levels than would be expected by chance, taking account of the variables fitted in the first stage. The first stage is nearly complete, the second is underway.

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[40] Johannesson, G., Geirsson, J. & Day, N. E. (1978) *Int. J. Cancer*, **21**, 418–425.
[41] Williams, E. H., Smith, P. G., Day, N. E., Geser, A., Ellice, J. & Tukei, P. (1978) *Br. J. Cancer*, **37**, 109–122.

5. INTERNATIONAL CANCER NETWORK FOR THE CONTINUING EVALUATION OF ENVIRONMENTAL FACTORS (Dr J. Cooper)

The need for an international cancer network to collect in a uniform manner data on cancer and the environment in a small number of contrasting environments was described in the *Annual Report, 1976* [42].

The first Working Group devoted to planning in this area met in Lyon in November 1977. Their recommendations are now being implemented. A check list of registry characteristics and types of data needed has been developed, which should help to assess the existing capabilities for the correlation of environmental factors with cancer incidence in specific registration areas. Meetings have been held with the President of the International Association of Cancer Registries (IACR) to incorporate his suggestions into this data collection protocol and to assure cooperation with the IACR in the data collection activity. A survey of available environmental data has now been carried out in the Birmingham and West Midlands Regional Cancer Registry (Dr J. A. H. Waterhouse). The information sought included, in addition to the more usual items, household expenditure figures, information on industrial profiles and chemical production and use, indices of pollution, market surveys and lists of workers with specific, known chemical exposures. A similar assessment is now being planned in a registration region with quite different environmental and administrative characteristics.

A number of specific feasibility studies for network operation have been initiated, and others are now being planned. Activities already commenced included:

(i) Selection of those chemicals that are well-documented human and/or animal carcinogens and for which it is anticipated that significant human occupational exposure may occur. Specific occupational exposures are being determined for several of these substances.

(ii) Determination of the feasibility of following up such exposed workers. A pilot case-control study has been started in males in the Lyon area, covering a number of cancer types that are likely to have an occupational component in their etiology (see section 3.9 *b*).

(iii) Assessment in Central Anatolia, Turkey (Dr R. Saracci) of the feasibility of rapid response to a mesothelioma epidemic which is apparently unrelated to asbsestos exposure (Dr Y. Baris, Hacettepe University, Ankara, Turkey: RA/78/012 and Dr P. C. Elmes, Pneumoconiosis Research Unit, Medical Research Council, Penarth, UK: RA/78/011).

6. TEXTBOOK ON CANCER EPIDEMIOLOGY

Dr P. Cole, Professor of Epidemiology, Harvard School of Public Health, Boston, USA, was a consultant at the Agency for 11 months from July 1977. During this time he worked on a textbook, *The Epidemiology of the Neoplastic Diseases,* which will be published under Agency auspices. He also prepared papers on the case-control study, basic issues in cancer screening and measures of value of screening tests.

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[42] International Agency for Research on Cancer (1976) *Annual Report, 1976,* Lyon, pp. 24–25.

7. MISCELLANEOUS

In addition to the teaching courses organized by the Agency (see page 115), members of the Unit have participated in several educational seminars. Work proposed or in progress is discussed at weekly staff meetings.

Several members of the staff are on the editorial boards of international cancer journals and are frequently asked to review scientific papers. Acceptance by staff members of chairmanships at carefully selected international meetings has led to increased awareness of the programmes and policies of the Agency.

2. UNIT OF ENVIRONMENTAL CARCINOGENS

Dr L. GRICIUTE (Chief)

1. INTRODUCTION

The Unit continues to elaborate and standardize techniques for the analysis of environmental carcinogens and to measure those substances in environmental samples. The collaborative study on the analysis of *N*-nitrosamines has been continued, and an aflatoxin check sample survey begun. The problems of safety involved in handling *N*-nitrosamines in the laboratory are a new field of study for the Unit.

The fifth working conference on *N*-nitrosamine analysis and formation was held in Durham, USA, August 1977.

Two volumes of the *Manual of Selected Methods of Analysis for Environmental Carcinogens,* one on volatile *N*-nitrosamines[1] and one on vinyl chloride[2], have been prepared for publication.

Various environmental samples, obtained mostly in relation to epidemiological studies—alcoholic beverages, and urine samples collected in areas with endemic urinary bladder cancer—have been analysed in the Agency's laboratory, both for *N*-nitrosamines and for other chemical carcinogens.

In vivo formation of *N*-nitrosamines was studied both in the laboratory, by investigating the role of phenols in nitrosation, and in the field, by determining nitrite levels in salivas of the population of the Caspian littoral with differing œsophageal cancer morbidity.

Collaboration with the Pneumoconiosis Unit of the Medical Research Council (Penarth, UK) and the Institute of Experimental and Clinical Medicine of the Estonian SSR (Tallinn, USSR) on the relation between asbestos and cancer has continued.

A collaborative study with the Oncological Research Centre, Moscow, the Central Institute for Cancer Research, Berlin-Buch, and the Institute of Oncology, Sofia, on the combined action of several chemical carcinogens is designed to elucidate the behaviour of several chemicals occurring in the same environmental sample.

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[1] Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds (1978) *Volume 1: Analysis of Volatile Nitrosamines in Food.* In: Egan, H., ed., *Environmental Carcinogens–Selected Methods of Analysis,* Lyon *(IARC Scientific Publications No. 18).*

[2] Squirrell, D. C. M. & Thain, W., eds (1978) *Volume 2: Vinyl Chloride.* In: Egan, H., ed., *Environmental Carcinogens–Selected Methods of Analysis,* Lyon *(IARC Scientific Publications No. 22).*

2. ELABORATION OF METHODS OF ANALYSIS FOR ENVIRONMENTAL CARCINOGENS

2.1 N-*Nitrosamine analysis and formation*

(*a*) *Collaborative studies* (Mr E. A. Walker, Dr M. Castegnaro)

These studies (see IARC *Annual Reports* 1972–1977) have been extended to a substrate other than tinned meat.

(i) *Volatile* N-*nitrosamines*

A collaborative study of methods for analysis of volatile *N*-nitrosamines in cheese spiked with *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosopiperidine (NPIP) and *N*-nitrosopyrrolidine (NPYR) is almost complete. The same *N*-nitrosamine spectra were analysed as for canned meat. The general conclusions derived at this stage are that:

(1) the methods developed for processed meat are generally applicable to cheese;
(2) chemiluminescent detection systems, such as the Thermal Energy Analyzer (TEA), appear to be preferable; and
(3) an oil distillation procedure for the initial isolation of *N*-nitrosamines from the sample appears to afford the best recovery, particularly of the less volatile *N*-nitrosamines such as NPYR.

(ii) *Nonvolatile* N-*nitrosamines*

A tentative study of methods of analysis for three nitrosoamino acids (nitrososarcosine, nitrosoproline and nitrosohydroxyproline) has been conducted on a standard solution. Two general techniques were employed:

(1) separation by high-pressure liquid chromatography (HPLC), using TEA or ultra-violet detection;
(2) conversion of the acid to a volatile derivative by methylation, silylation or acetylation, and completion of the analysis by gas chromatography, mainly with TEA detection.

The results of this study, shown in Table 8, are generally encouraging; however, two of the 12 laboratories experienced inexplicable difficulty in using the silylation technique. This problem is being investigated.

(*b*) *Studies related to nitrosamine formation* in vivo

With the rapid accumulation over the last few years of data on the environmental occurrence of volatile nitrosamines, it is evident that human exposure in the general environment is extremely low. As a consequence, increasing attention is being given to *in vivo* aspects of research on *N*-nitroso compounds, for which information is still limited.

(i) *The promoting effect of phenols on formation of NDEA* (Mr E. A. Walker, Mrs B. Pignatelli, Dr M. Castegnaro)

Phenolic compounds occur naturally in food in many complex forms; relatively simple phenols may also be present as additives, for example, following preservation with liquid smokes or by smoking. A simple *in vitro* approach is being employed to simulate *in vivo* situations. A detailed kinetic study of the formation of NDEA has shown that the promoting effect of phenol can be

Table 8. Comparative analysis of three nitrosoamino acids

Laboratory No.	Method[a]	*N*-Nitrososarcosine (6.37 μg)[b]	*N*-Nitrosoproline (3.28 μg)[b]	*N*-Nitrosohydroxyproline (3.63 μg)[b]
1	TLC	[c]	3.29	5.02
4	Methylation	4.73	2.58	2.74
6	Methylation/ acetylation-TEA	9.62	4.01	2.99
7	HPLC-TEA	6.97	3.59	3.57
8	Methylation-TEA	5.70	2.80	[c]
10	HPLC-UV	7.20	3.30	2.20
11	HPLC-UV	5.78	3.97	4.09
13	HPLC-UV	6.30	3.31	3.53
16	HPLC-TEA	6.52	3.26	3.27
17	Silylation-TEA	5.00	3.10	3.20
20	Silylation-FID	5.50	3.30	2.40
21	Differential pulse polarography	5.78	3.15	3.27
Overall mean		6.28	3.31	3.30
Standard deviation		1.34	0.42	0.78
Corresponding coefficient of variation		21.3%	12.7%	23.6%

[a] TLC – thin-layer chromatography; TEA – thermal energy analyser; HPLC – high-pressure liquid chromatography; UV – ultraviolet; FID – flame-ionization detector
[b] Amount placed in each tube
[c] Laboratory unable to quantify results

attributed to its rapid conversion to *para*-nitrosophenol, which acts as the actual catalyst. The reaction mechanism shown in Figure 2 has been suggested on the basis that first order kinetics were found for all three reactants—nitrite, amine and *para*-nitrosophenol. *meta*-Nitrosophenol, which cannot exist in the quinone form, does not catalyse the reaction. A value of 5.22×10^6 mol^{-2} l^2 min^{-1} was calculated for the pH-dependent rate constant at 37°C. Reaction rates were found to be affected considerably by total ion concentration. As a first approximation, the relative rates of formation for the catalysed and uncatalysed reactions in the region of pH 4 were given by:

$$\frac{\text{rate (catalysed)}}{\text{rate (uncatalysed)}} = \frac{1 + k'' \text{ [}para\text{-nitrosophenol]}}{k' \text{ [nitrite]}} \simeq \frac{70\text{[}para\text{-nitrosophenol]}}{\text{[nitrite]}}$$

where k'' and k' are experimentally determined rate constants.

N-Nitrosophenol may be preformed in smoked bacon from phenol and nitrite, or in smoke from nitrosation of phenol by nitrite present in saliva. Using values taken from the published literature for typical concentrations of phenol in smoked bacon and of nitrite in saliva, assuming that all of the phenol would be nitrosated rapidly, it was calculated that under the anacid conditions of the stomach after consumption of a meal the rate of nitrosation of any diethylamine present could be increased by a factor of about 140. It is reasonable to assume that similar promoting effects would operate on other nitrosatable amines in the gastric juice. Thus, rapid nitrosamine formation would tend to increase the available nitrosamine during the passage of food through the digestive tract.

In extending this work to the dihydric phenols, resorcinol, which readily forms a dinitroso compound, was found to be an even more effective catalyst than phenol. On the other hand, both catechol and hydroquinone, which are very susceptible to oxidation, react with nitrite to form

quinones which do not contain the *C*-nitroso group and function only as inhibitors of nitrosamine formation. This difference is demonstrated in Figure 3.

A similar situation pertains with the trihydric phenol, pyrogallol (1,2,3-trihydroxybenzene), which is also extremely susceptible to oxidation and acts as an inhibitor. Phloroglucinol, the symmetrical trihydroxybenzene, is more stable and acts as a powerful promoter. A number of naturally-occurring phenols are being investigated: preliminary results on gallocatechin, an essential constituent of tea tannins, reveal this to be a powerful promoter of nitrosamine formation.

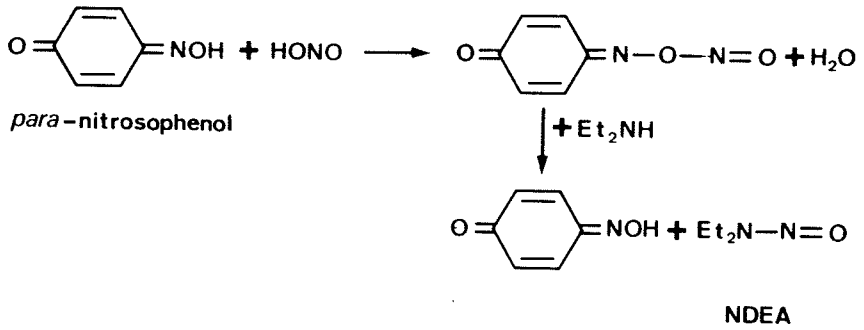

Fig. 2 Reaction mechanism for formation of *N*-nitrosodiethylamine (NDEA) in the presence of phenol

(ii) *Nitrite in saliva—possible relevance to* in vivo *formation of* N-*nitroso compounds* (Dr M. Castegnaro, Mr E. A. Walker, in collaboration with Professor R. Preussmann, Dr G. Eisenbrand and Dr B. Spiegelhalder, Institute of Toxicology and Chemotherapy, Heidelberg, Federal Republic of Germany)

Nitrite and nitrosatable amines are required for the formation of nitrosamines. Determination of all possible nitrosatable amines in the digestive tract is at present impractical; however, determination of nitrite in saliva, the main source of nitrite in humans, is a practical field technique and offers, in principle, a measure of the potential for *in vivo N*-nitrosamine formation which may be used to compare individuals and population groups.

The nitrite concentration in saliva depends directly on the initial nitrate content in the salivary flow. Since salivary nitrate concentration correlates directly with the amount of nitrate ingested, the diet is the major factor governing the nitrite content of saliva[3]. The extent of the conversion of nitrate to nitrite, on the other hand, depends on the activity of the nitrate-reducing bacteria in the oral cavity.

To measure the nitrate-conversion capacity of an individual's saliva it is necessary to standardize the experimental conditions by administering known amounts of nitrate and determining nitrite in the saliva at hourly intervals for up to eight hours. This procedure is very time-consuming and unsuited to field studies; the kinetics of reduction when nitrate is added to human saliva were therefore investigated *in vitro* in Heidelberg, as an alternative approach.

A standard solution of nitrate containing 800 mg/l was added to separate aliquots of saliva, which were then incubated at 37°C for varying periods up to eight hours. The amount of nitrite formed in a given time was plotted for each of 10 different individuals.

[3] Spiegelhalder, B., Eisenbrand, G. & Preussmann, R. (1976) *Food Cosmet. Toxicol.*, **14**, 545–548.

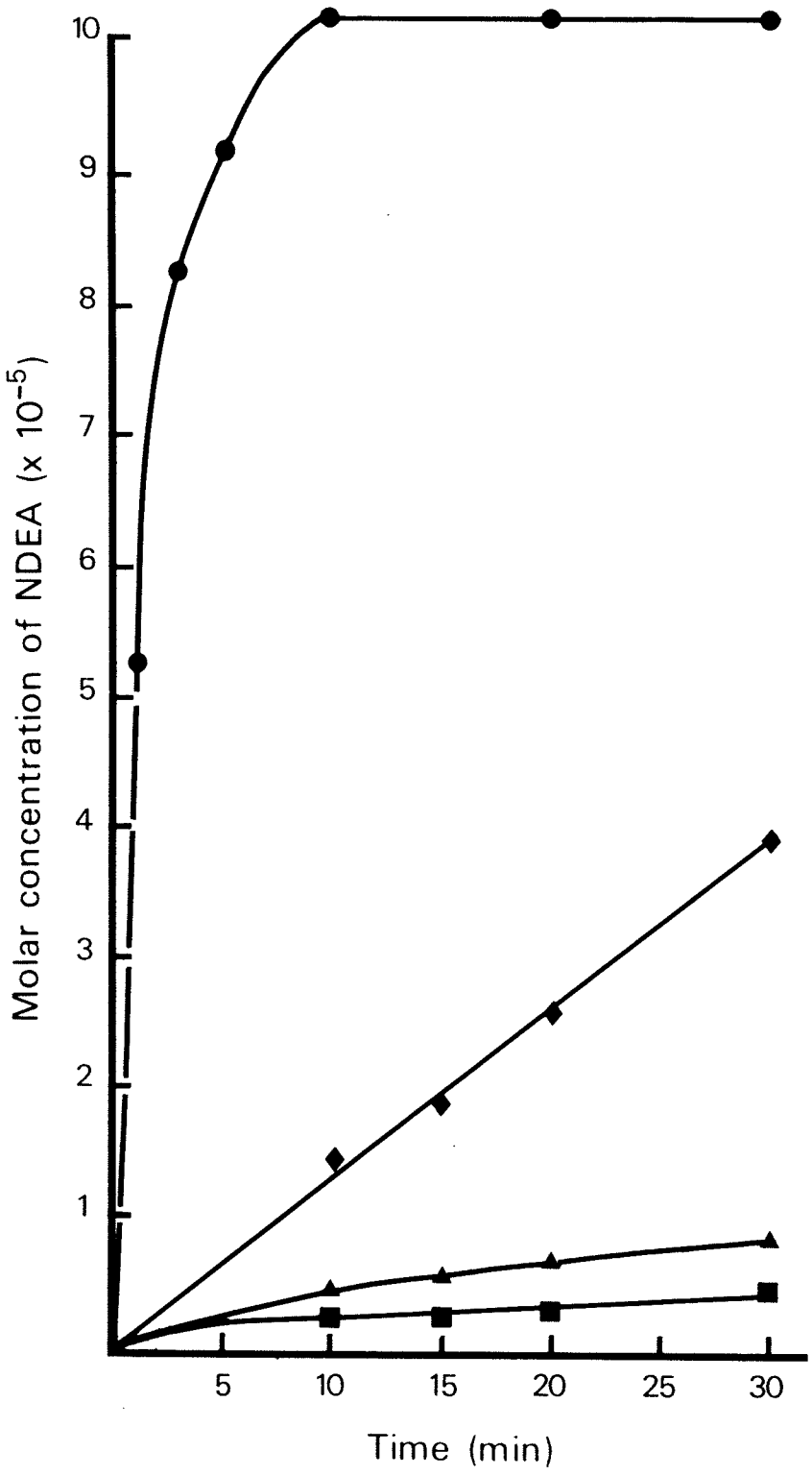

Fig. 3 Nitrosation of diethylamine in the presence of diphenols: ■ = hydroquinone; ▲ = catechol; ◆ = no diphenol; ● = resorcinol

The conversion capacities of a highly active saliva sample and of a less active one are compared (Fig. 4), using three different nitrate concentrations. With the active sample, maximum concentration was reached in 4–5 hours; the subsequent decrease was probably due to reduction of nitrite

to ammonia by nitrite-reducing bacteria. The nitrate-nitrite conversion patterns were very similar when nitrate solutions of 3 200 and 6 400 mg/l were used.

On the basis of these experiments, a screening technique was devised for measuring the nitrate-reducing capacity of saliva. The saliva sample is first analysed for nitrite, then 1 ml of a 3 200 mg/l solution of nitrate is added to each of two separate 1 ml sample aliquots, which are then incubated, one for 2 and the other for 5 hours. The nitrite formed is then determined in each. Three values at 0, 2 and 5 hours were then sufficient to give the profile of the time/reduction curve.

A pilot study was carried out on salivary nitrite levels and nitrate-reducing capacity in village population groups in regions of high and low œsophageal cancer incidence in the Caspian littoral of Iran.

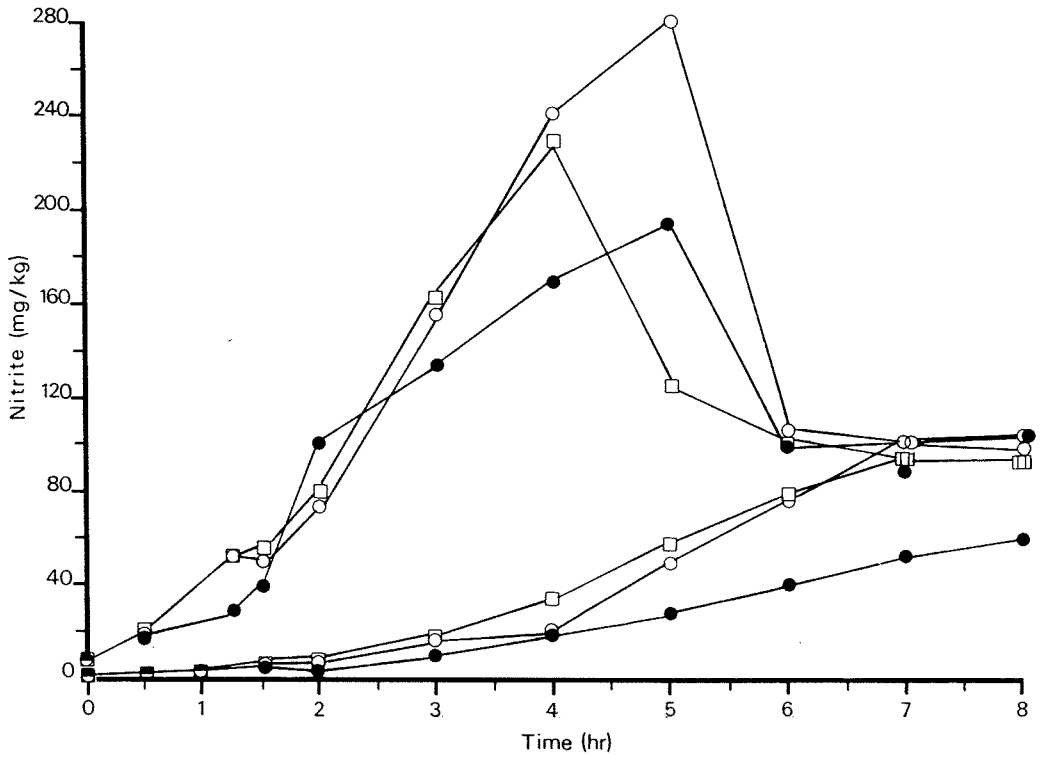

Fig. 4 Conversion of nitrate to nitrite by an active saliva sample (upper 3 curves) and a less active sample (lower 3 curves). Three concentrations of nitrate were used, 1 600 ppm (●), 3 200 ppm (□) and 6 400 ppm (○)

A detailed report of the results of the pilot study was presented at the Third International Symposium on Oncology in Teheran, 1978; these many be summarized as follows:

(1) Salivas of 350 individuals from three villages (two high-incidence—Peshkamar and Khorand—and one low-incidence—Goorab Zarmick) were examined.

(2) No consistent difference was found in the median values for nitrite in saliva between high and low morbidity areas for populations as a whole.

(3) When subdivided into age groups, higher nitrite levels tended to be found in the lower age group (5–10 years) than in older groups. This feature may be more marked in the high-incidence area (Figs 5, 6); however, the population size within each age group was insufficient for statistical evaluation.

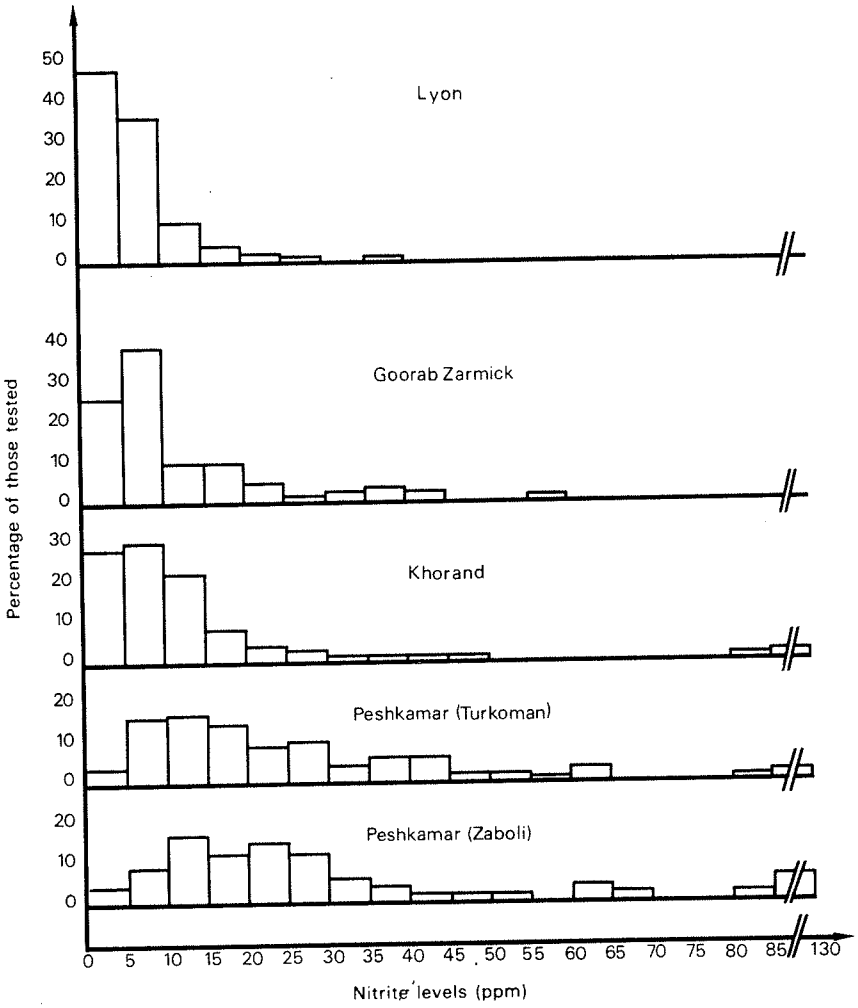

Fig. 5 Nitrite levels in the saliva of population groups in Lyon, France and in areas of the Caspian littoral of Iran with high and low incidence of oesophageal cancer (all age groups)

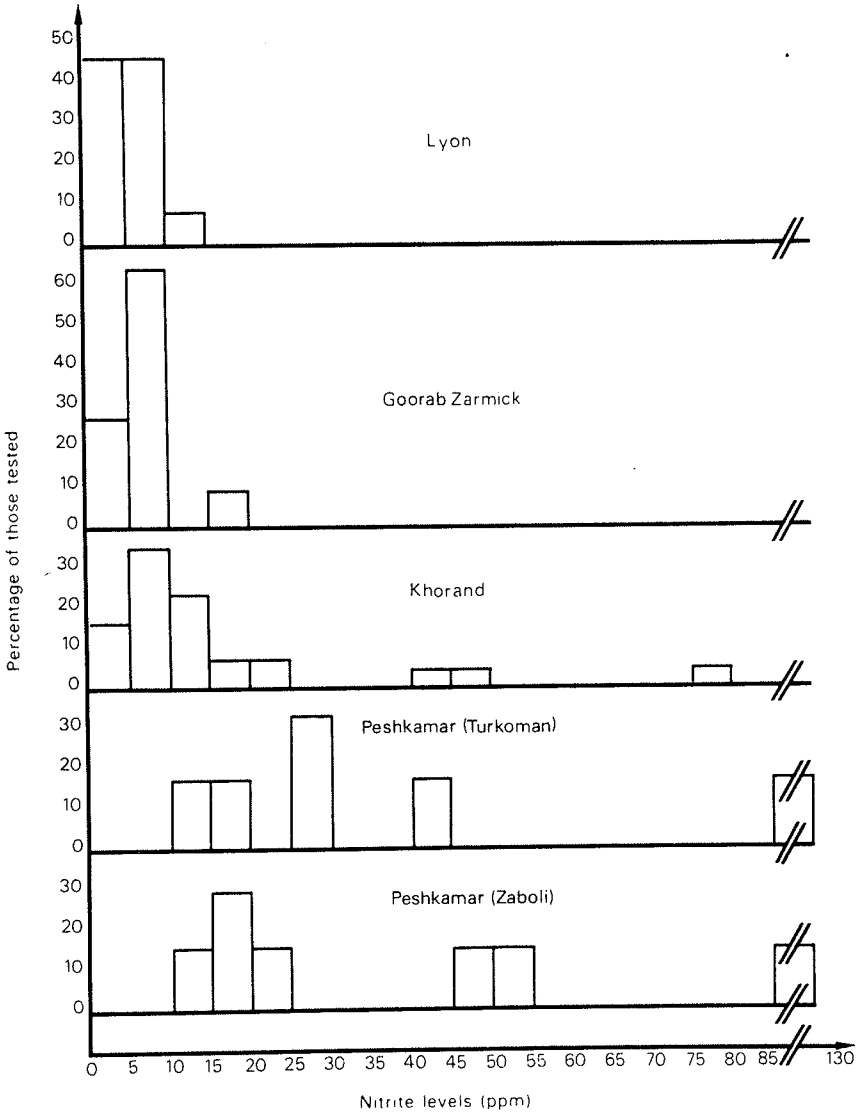

Fig. 6 Nitrite levels in the saliva of population groups in Lyon, France and in areas of the Caspian littoral of Iran with high and low incidence of oesophageal cancer (5-10 year age group)

(4) A few exceptionally high levels (> 100 mg/l, *versus* normal average levels of 7 mg/l reported for Europe and USA) were found in the high-incidence villages.

(5) The nitrite distribution in an immigrant group of different ethnic origin than the indigenous Turkoman population in the high-incidence village of Peshkamar was essentially the same as that of the latter. At the present time no reliable cancer statistics are available for this group, which migrated largely from the Zabol area near Afghanistan.

(6) A general survey of dental status, carried out in parallel with the saliva sampling, indicated that this was in no way related to nitrite levels.

(7) Results from studies of nitrate to nitrite conversion in saliva were difficult to interpret, since for the regions as a whole the rate of conversion was considerably faster than that found for the European population on which the experimented protocol was based. Thus, instead of increasing to a maximum in about 5 hours, the maximum nitrate concentration was frequently achieved in less than 2 hours.

(8) Similar studies were carried out among adults and children in Heidelberg and Lyon, in order to have comparative data. In Lyon, in the study which was conducted among both adults and schoolchildren, no evidence was found of a similar age distribution of salivary nitrite levels to that found in the Caspian littoral (see Figs 4, 5), nor did the nitrate-reducing capacity differ from the general pattern found in Heidelberg. The nitrite content of salivas from 166 children between the ages of 3 and 14 studied in Heidelberg showed a mean value of 3.9 mg/l. Eight children had no nitrite in their saliva, and the highest value, found in one child only, was 22 mg/l. Essentially the same results were obtained in the Lyon study of 168 children, where the average value found was 3.2 mg/l; two children had no detectable nitrite, and the highest value, found in one child only, was 13 mg/l. In contrast to the Iranian study, all salivary incubation tests confirmed the steady increase over 5 hours, as illustrated in Figures 3 and 4.

In order to establish whether or not there is an age distribution of salivary nitrite in the populations of the Caspian littoral of Iran, an intensive study has been made, using three villages in the high-incidence area and two in the low-incidence area (so that the original villages plus one new village in each area were covered) and during a different season from that of the first study. Measurements of diurnal and daily variations of nitrite levels were also included; approximately 2 600 samples of saliva were investigated in all. The results are being analysed statistically.

(*c*) *Safety in handling* N-*nitrosamines and their solutions* (Mr E. A. Walker, Dr M. Castegnaro, Mrs B. Pignatelli, Mrs L. Garren)

It has been demonstrated[4] that *N*-nitrosamines, particularly NDMA, and their solutions rapidly penetrate the types of rubber and plastic gloves used in laboratories. It was shown subsequently[5] that this penetration may be reduced by wearing two pairs of surgical gloves, one

[4] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 53.

[5] Walker, E. A., Castegnaro, M., Garren, L. & Pignatelli, B. (1978) In: Walker, E. A., Castegnaro, M., Griciute, L. & Lyle, R. E., eds, *Environmental Aspects of* N-*Nitroso Compounds*, Lyon *(IARC Scientific Publications No. 19)*, pp. 535–543.

over the other. Best results are obtained when the inner glove is first coated with a barrier cream or talc before putting on the second glove. It has been found, in practice, that wearing two pairs of gloves does not significantly hinder manipulative ability in the analytical laboratory. Table 9 gives a comparison of the barrier effect of the different systems when gloves containing physiological saline are exposed to NDMA from a 10 μg/l solution in methylene chloride; these solutions were used to simulate penetration of a solution in an organic solvent into the perspiration which collects rapidly within a glove during use.

Table 9. Comparison of protection given by single and double glove systems

System	% NDMA which penetrated in 20 min
single glove	11.8
double glove	6.0
double glove with talc	2.5
double glove with barrier cream	1.1

(*d*) *Working conference on analysis and formation of* N-*nitroso compounds*

A working conference on *N*-nitroso compounds in the environment was held at the University of New Hampshire, Durham, New Hampshire, USA, in August 1977. The meeting was attended by 170 participants from 11 countries. As the number of papers offered exceeded the time available for discussion, an editorial board (Dr M. Castegnaro, Dr J. A. Cooper, Dr G. Eisenbrand, Dr T. Gough, Dr L. Griciute, Dr R. Preussmann, Dr P. L. Schuller, Dr G. M. Telling, Mr E. A. Walker and Dr C. L. Walters) was established to select the 50 most appropriate papers. Reports given at the meeting included information on environmental occurrence of *N*-nitrosamines in food, human biological fluids and other environmental samples, their sources and formation. Problems in safe handling of *N*-nitrosamines in the laboratory were also discussed. Following the workshop, sub-committees of invited members met to draw up reports and recommendations for future work. One aspect that was strongly emphasized was the need for epidemiological studies related to the environmental occurrence of *N*-nitrosamines.

(*e*) *Research training*

Dr B. Kowalski, from the Veterinary Research Institute, Pulawy, Poland, was a recipient of an IARC Research Training Fellowship. He spent three months in the Unit before going to the Food Research Division, Health and Welfare Canada, Ottawa. Dr Kowalski received training in techniques for the detection of *N*-nitrosamines. He was also involved in studies related to *in vivo* formation of *N*-nitrosamines.

2.2 *Aflatoxin check sample survey* (Mr E. A. Walker, Dr M. Castegnaro, Mr G. Toussaint, Miss B. Baker)

During the period 1971–1972, two international check sample surveys were held[6, 7], the purpose of which was to encourage standardization of techniques and to enable analysts to evaluate their data in comparison with others. As the result of requests that the series be continued, the Agency was asked to undertake organization of further studies. These are being carried out in collaboration with the original aflatoxin check sample survey committee (Dr F. B. Coon, Dr A. D. Campbell, Dr E. J. Boon, Dr F. J. Baur).

For the study, bulk supplies of naturally-contaminated raw peanut butter, roasted peanut butter and white corn meal were collected by the Committee for individual distribution by the Agency; standard aflatoxins were supplied by Dr A. E. Pohland of the US Food and Drug Administration. Participants were requested to carry out analysis for aflatoxins B_1, B_2, G_1 and G_2, using their preferred methods. Two further samples, peanut meal and yellow corn, are foreseen for the next stage. At present, 160 laboratories have elected to participate in this study; the countries involved include Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Czechoslovakia, the Democratic People's Republic of Korea, Denmark, the Dominican Republic, the Federal Republic of Germany, Finland, France, the German Democratic Republic, Guatemala, Hungary, India, Indonesia, Iran, Israel, Italy, Jamaica, Japan, Malaysia, Nigeria, the Philippines, Poland, Romania, Spain, Sweden, Switzerland, The Netherlands, Tunisia, the UK, the USA, Venezuela and Yugoslavia.

Results from the first three samples are currently being received, and, when all participants have reported, the results will be evaluated statistically and circulated, together with the input data. Participants will be able to identify their own results by a laboratory code number.

2.3 Manual of Selected Methods of Analysis of Environmental Carcinogens (Dr L. Griciute, Mr E. A. Walker)

Volume 1 of the *Manual—Volatile* N-*Nitrosamines*—has just been published[8]. The third meeting of the editorial board (Chairman: Professor H. Egan, Laboratory of the Government Chemist, London) was held in Lyon in November 1977. The draft of Volume 2—*Vinyl Chloride*—was presented by Mr D. C. M. Squirrell, Mr W. Thain and Dr W. R. Eckert and accepted after a number of remarks. It was reviewed by the authors after the meeting and is now ready for publication[9].

At the same meeting, the analytical methods available for mycotoxins (Mr L. Stoloff, Food & Drug Administration, USA) and known plant carcinogens (Dr L. Griciute, IARC) were reviewed. Neither group of substances was considered, for different reasons, to be of first priority in the near future. The next priority would be polycyclic aromatic hydrocarbons, and a meeting of the

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[6] Coon, F. B., Baur, F. J. & Symmes, L. R. L. (1972) *J. Ass. Off. anal. Chem.*, **55**, 315–327.

[7] Coon, F. B., Baur, F. J. & Symmes, L. R. L. (1973) *J. Ass. Off. anal. Chem.*, **56**, 322–327.

[8] Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds (1978) *Volume 1: Analysis of Volatile Nitrosamines in Food.* In: Egan, H., ed., *Environmental Carcinogens – Selected Methods of Analysis,* Lyon *(IARC Scientific Publications No. 18).*

[9] Squirrell, D. C. M. & Thain, W., eds (1978) *Volume 2: Vinyl Chloride.* In: Egan, H., ed., *Environmental Carcinogens – Selected Methods of Analysis,* Lyon *(IARC Scientific Publications No. 22).*

Table 10. Volatile *N*-nitrosamine content of alcoholic beverages

Beverage	No. of samples tested	*N*-nitrosodimethylamine				*N*-nitrosodiethylamine				*N*-nitrosodi-*n*-propylamine			
		Max. value (μg/l)[a]	Average (μg/l)	No. of positive samples	%	Max. value (μg/l)[a]	Average (μg/l)	No. of positive samples	%	Max. value (μg/l)[a]	Average (μg/l)	No. of positive samples	%
Farm apple brandy	94	10	0.66	41	44	0.9	0.04	9	10	0.5	0.01	3	3
Commercial apple brandy	39	3.6	0.38	20	51	2	0.15	14	36	2.6	0.13	9	23
Clear spirits	9	2.2	0.49	4	44	4.8	0.5	6	67	—	—	0	—
Whisky	8	0.7	0.26	6	75	0.4	0.1	3	38	0.4	0.09	2	25
Rum	17	3	0.24	7	41	0.2	0.05	5	29	0.2	0.02	2	12
Cognac and Armagnac	12	1.6	0.33	8	67	0.9	0.15	5	42	0.3	—	1	8
Cider	21	1.8	0.22	6	29	2.2	0.19	2	10	1.1	—	1	5
Wine	33	0.6	0.05	5	15	0.3	—	1	3	—	—	0	—
Beer	35	8.6	1.8	34	97	0.8	0.06	3	9	—	—	0	—

[a] Including samples with nondetectable levels of nitrosamines

review board (Dr H. Kunte, Dr P. Bogovski, Dr J. Jacob) for the volume on these substances was held in February 1978. A draft of the volume is being prepared for consideration by the editorial board in November 1978. Other priorities will be decided at the meeting.

3. ANALYSES OF ENVIRONMENTAL SAMPLES

3.1 *Carcinogens in alcoholic beverages* (Mr E. A. Walker, Dr M. Castegnaro, Mr G. Toussaint)

(*a*) N-*Nitrosamines*

The range of sample types examined in a study of carcinogens in alcoholic drinks has been extended. Table 10 gives the values for NDMA, NDEA and *N*-nitrosodi-*n*-propylamine (NDPA) found most persistently.

N-Nitrosomethylvinylamine (NMVA), the detection of which was reported earlier[10], has been found to occur in low levels in a small number of home-made samples only. Difficulties experienced in handling this compound during analysis suggest that it may be unstable in apple brandy and is probably present only in freshly-distilled samples. This aspect will be investigated further; these samples, although widely consumed, are difficult to obtain: fresh distillates are not consumed by the general population but only on farms.

Forty samples of local beers collected by Dr S. J. van Rensburg from regions of high and low œsophageal cancer incidence in the Transkei are also being analysed.

(*b*) *Polycyclic aromatic hydrocarbons (PAHs)*

Using a thin-layer chromatography (TLC) method, a number of farm samples of apple brandy collected at an earlier date were shown to contain benzo(α)pyrene. This was confirmed in one sample by Dr G. Grimmer, of the Biochemisches Institut für Umweltcarcinogene, Hamburg, Federal Republic of Germany, using a gas chromatography (GC) method. Further TLC analysis on these samples showed that the benzo(α)pyrene levels of about 5–10 μg/kg had diminished over the two-year period of cold-room storage: it had disappeared completely in some samples and was only just detectable in others. This was confirmed using the same GC method as that employed by Dr Grimmer. Although the TLC method is a useful screening test for benzo(α)pyrene, it is less accurate and less informative than the GC method; however, the clean-up procedure required for the latter method is very time-consuming. To overcome this, a technique has been developed which employs high-pressure liquid chromatography (HPLC) for clean-up and GC for detection and quantitation; the use of HPLC considerably reduces the time taken for clean-up and has the additional advantage that the PAH fraction collected is sufficiently free from background interference to allow direct measurement of benzo(α)pyrene, using fluorescence detection. For benzo(α)pyrene, the limit of detection by GC is 1 μg/l and by fluorescence detection 0.2 μg/l,

[10] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 56.

compared with 5 μg/l by TLC. A number of alcohols have been examined using the technique described: levels of benzo(α)pyrene were generally of the order of 0.5 μg/l or less. Since PAHs are ubiquitous in the environment, these low levels would correspond to the general environmental background.

(*c*) *Studies on the biological activity of apple brandies* (in collaboration with Professor J. Y. Le Talaer, Dr A. M. Mandard and Miss C. Loquet, François Baclesse Regional Centre, Caen, France)

The testing for mutagenicity of apple brandies and other alcoholic beverages (whisky, cognac, rum, armagnac) has been continued, using the Ames test on mutants of *Salmonella typhimurium* with and without metabolic activation[11]. The results were presented as the doctoral thesis of Miss C. Loquet at the University of Caen in December 1977.

No mutagenic activity was detected when alcohols were tested *per se*, but when they were separated into alcoholic, aqueous and solid residual fractions, 37% of home-brewed apple brandies, 11% of industrial apple brandies and 18% of other alcoholic beverages were slightly mutagenic (i.e., 2–4 times more mutants than in control cultures), with or without metabolic activation. Because of the low level of mutagenicity, it was impossible to establish dose-response curves.

No correlation was established between mutagenic activity and analytical data on known chemical carcinogens.

Eighty percent of alcohols that were spiked with different levels (1–1 000 ppm) of NDMA and NDEA showed slight mutagenic activity (up to twice as many mutants as controls), according to concentration of *N*-nitrosamine, when tested by the plating technique (Table 11). The highest concentration, 1 000 ppm, was still too low to produce any mutagenic activity in an aqueous solution.

Testing for possible carcinogenicity of apple brandy in rats is still in progress.

Table 11. Mutagenic activity of alcohol spiked with various concentrations of *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) in *Salmonella typhimurium* TA 100 (means of two experiments)[a]

ALCOHOL % / NDMA NDEA (ppm)	5	10	20	40	60	80
1					1.15	1.5
5				1.4	1.35	1.35
10				1.3	1.35	1.4
50				1.4	1.35	1.4
100			1.25	1.75		1.65
1 000		1.65	1.5	1.35	1.1	1.8

[a] Expressed as $\frac{\text{mean number of mutants in test}}{\text{mean number of mutants in controls}}$

[11] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, pp. 57–58.

3.2 *Carcinogens in experimental animal feed* (Mr E. A. Walker, Dr M. Castegnaro, Mr G. Toussaint)

All experimental animals, including control groups, may be exposed to low levels of chemical carcinogens if these are present in the diet; the effect of such low levels is not known. Regular analysis for volatile *N*-nitrosamines, PAH and aflatoxins is being carried out in the Agency's laboratory on feed from its own animal house and on that from four collaborating laboratories, providing a check on quality and the compilation of data which may be used to evaluate the effect on animals of such exposure.

(*a*) N-*Nitrosamines*

For analysis of *N*-nitrosamines, the procedure involving oil distillation with subsequent determination by GC/TEA was used; results were confirmed by GC/MS. Levels of *N*-nitrosamines found in experimental animal feed were in general similar to those reported in food, such as processed meats, for human consumption, (Table 12). A paper has been submitted for publication.

Table 12. *N*-Nitrosamine levels in animal feed

Nitrosamines detected[a]	Nominal % of samples containing the nitrosamines in the concentration ranges (μg/kg)[b]				Highest nitrosamine level found (μg/kg)
	All ranges	0.5-1	1-10	> 10	
NDMA	91	7	75	9	54
NDEA	51	24	23	4	65
NDPA	15	8	7	0	2
NDBA	9	1	8	0	6
NPIP	19	4	8	7	300
NPYR	16	8	7	1	11

[a] NDMA: *N*-nitrosodimethylamine
NDEA: *N*-nitrosodiethylamine
NDPA: *N*-nitrosodipropylamine
NDBA: *N*-nitrosodibutylamine
NPIP: *N*-nitrosopiperidine
NPYR: *N*-nitrosopyrrolidine

[b] Total number of samples: 87

(*b*) *Polycyclic aromatic hydrocarbons*

Using a suitably modified extraction and clean-up technique (the method employed for alcoholic beverages, involving preparative TLC followed by two-dimensional TLC), benzo(α) pyrene has been determined in a number of animal feeds. The results, which have been confirmed using the HPLC/GC technique described in the section on alcohol, are given in Table 13.

(*c*) *Aflatoxins*

The 'mini-column' technique[12] has been adapted for screening samples of animal feed; the method is rapid and has a limit of detection of 5 μg/kg. No evidence of contamination has been found in any of the feeds examined.

[12] Anon. (1975) *J. Ass. Off. anal. Chem.*, **58**, 393–394.

3.3 N-*Nitrosamines in various environmental samples* (Mr E. A. Walker, Dr M. Castegnaro, Dr L. Griciute)

(*a*) N-*Nitrosamines in urines* (in collaboration with Dr A. A. El-Aaser and Dr M. M. El-Merzabani, Cancer Institute, Cairo University, Cairo; Dr R. M. Hicks, School of Pathology, Middlesex Hospital Medical School, London; Dr C. L. Walters, British Food Manufacturing Industries Research Association, Leatherhead, UK)

The suggestion that the *N*-nitrosamines formed in infected urines are one of the causes of endemic urinary bladder cancer in bilharziasis patients[13] is being investigated.

Table 13. Polycyclic aromatic hydrocarbons (PAH) in animal feed—analysis by thin-layer chromatography (TLC)[a]

Country of origin	Anthracene and phenanthrene (μg/kg)	Fluoranthrene and pyrene (μg/kg)	Chrysene and benz(*a*)anthracene (μg/kg)	Benzo(*a*)pyrene (μg/kg)	Benzo(*e*)pyrene (μg/kg)	PAH with < 5 rings (μg/kg)
USSR[b]	10	25	ND	10	ND	trace
USSR	25	25	ND		3	trace
France[c]	50	50	ND	2	1	trace
France	5	15	ND	2	ND	ND
France	5	5	ND	ND	ND	ND
France	3	25	3	ND	ND	ND
France	10	10	ND	1.5	ND	trace
IARC	1.5	5	1.5	ND	1.5	trace
IARC	10	10	ND	2		ND
IARC	2	10	ND	ND	ND	ND
Bulgaria[d]	3	10	ND	1.5	ND	ND
German	2	5	ND	1	ND	ND
Democratic	3	3	ND	1.5	ND	ND
Republic	50	50	ND	10	10	trace

[a] Due to the length of clean-up step in TLC estimation, results are given with a precision of ± 20%.
[b] The Oncological Research Centre, Moscow (Dr V. Turusov)
[c] Centre Régional François Baclesse, Caen, France (Professor J. Y. Le Talaer)
[d] Institute of Oncology, Sofia (Dr I. Chernozemsky)
[e] Central Institute for Cancer Research, Academy of Sciences of GDR, Berlin-Buch (Dr B. Teichmann)
ND – not detected

Analysis was carried out on the urines of five groups of people in Egypt: patients with bladder cancer, patients with bilharzial cystitis, patients with no diagnosed pathology living in areas where bilharziasis is endemic, 'normal' subjects and patients with cancer at other sites, e.g., breast cancer. The urine extracts were prepared in the Cancer Institute, Cairo University, Cairo. NDMA, NDEA, NPIP and NPYR were detected: levels of NDMA varied between 0.1 and 43.6 μg/l, and levels of other *N*-nitrosamines ranged from 0.02 to 2.6 μg/l; only one sample was free from *N*-nitrosamines (a patient with bilharzial cystitis). TEA analysis indicated the possible presence in some samples of unidentified *N*-nitroso compounds, but at very low levels when evaluated as total volatile *N*-nitrosamines. The difference in levels between the five groups does not appear to be highly significant.

[13] Hicks, R. M., Gough, T. A. & Walters, C. L. (1978) In: Walker, E. A., Castegnaro, M., Griciute, L. & Lyle, R. E., eds, *Environmental Aspects of N-Nitroso Compounds*, Lyon (*IARC Scientific Publications No. 19*), pp. 465–475.

These are considered to be pilot studies; it is anticipated that this collaborative work will be published. In view of the fact that the optimal conditions for preservation of *N*-nitrosamines in biological fluids, notably in urines, are not known, a collaborative research agreement (RA/77/023) has been proposed to Professor R. Preussmann, Heidelberg, Federal Republic of Germany, for studies on this problem.

(*b*) N-*Nitrosamines in tobacco smoke*

A contract has been signed with Professor R. Truhaut (Laboratoire de Toxicologie et d'Hygiène Industrielle, Faculté des Sciences Pharmaceutiques et Biologiques de Paris-Luxembourg, Paris), in conjunction with the Society for the Industrial Exploitation of Tobacco and Matches (SEITA), for a study of *N*-nitrosamines in smoke condensates from various French tobaccos. This work is in progress.

(*c*) N-*Nitrosamines in formulations with amidopyrine*

Samples of pharmaceutical formulations containing the drug amidopyrine have been obtained from a number of local pharmacies and from a manufacturer; many of these have been found to contain NDMA. Results for the formulations purchased in pharmacies are summarized in Table 14. Relatively high levels of *N*-nitrosamines were found, particularly in tablets: levels in individual tablets from the same box could vary by a factor of 10, and in two boxes of tablets purchased from pharmacies, levels as high as 36 mg/kg (ppm) and 90 mg/kg were found.

Table 14. Levels of *N*-nitrosodimethylamine (NDMA) in amidopyrine-containing formulations

Type of sample	Number of samples	NDMA detected (μg/kg)	
		Max. level	Min. level
Syrup	6	300	4
Drops	8	25	1
Suppositories	4	380	200
Tablets	21	900[a]	30

[a] Exceptionally high levels, 36 000 and 90 000 μg/kg, of NDMA were found in two boxes of tablets

3.4 *Polycyclic aromatic hydrocarbons in bread*

Three samples of bread from Turkey submitted for analysis (Dr Day) and three samples of bread from Iran which had been stored under deep-freeze conditions in the laboratory were analysed for PAH, using the HPLC-GC method developed in the laboratory. All samples showed traces of benzo(α)pyrene, mainly in the order of 2 μg/kg. The levels were very similar to those previously found by Dr Grimmer[14] in the samples from Iran using the longer GC method; this demonstrates the reliability of the HPLC-GC screening technique (Table 15).

[14] Grimmer, G. (1977) *J. natl Cancer Inst.*, **59**, 1127–1138.

Table 15. Analysis of polycyclic aromatic hydrocarbons[a] in bread using a high-pressure liquid chromatography/gas chromatography technique

Country of origin	Anthracene & phenanthrene	Fluoranthrene	Pyrene	Benzo(*a*)pyrene[c]
Turkey	(*b*)	ND	ND	< 1
Turkey	ND	ND	ND	1.3
Turkey	(*b*)	9	9.5	< 2
Iran	(*b*)	41	23.5	< 2.5
Iran	(*b*)	27.5	17	< 2.5
Iran	(*b*)	19	11.5	2.5

[a] Analysis was made for the entire group, but only those mentioned were detected.
[b] Found in large amounts
[c] Limit of detection depends on size of sample
ND – not detected

3.5 *Preparation of samples from epidemiological studies for mutagenicity testing* (Dr M. Castegnaro)

A number of opium samples of different types collected in Iran for mutagenicity testing by the Unit of Chemical Carcinogenesis have been extracted, using various solvent systems. The same samples were also separated into acid, basic and neutral fractions. The objective is to use the combined approach of mutagenicity testing and subfractionation to isolate and chemically identify the mutagenic compounds.

4. STUDIES ON THE RELATIONSHIP BETWEEN FIBROUS MINERALS AND PARTICULATES AND CANCER

4.1 *Medical Research Council Pneumoconiosis Unit, Llandough Hospital, Penarth, UK* (RA/78/007)

Principal investigator: Dr J. C. Wagner

It was agreed that the scope of this study should be widened to cover all fibrous minerals and particulates.

(*a*) *Physics and chemistry* (Dr F. D. Pooley, Department of Mineral Exploitation, University College, Cardiff, UK)

(i) *Tremolite*

The role of tremolite asbestos fibre in the causation of disease is being investigated. These studies began in 1969 when it was demonstrated that tremolite fibres were present in the lungs of people who developed mesotheliomas in Cyprus and that this fibre was a major contaminant of the chrysotile deposit being mined in that country. Subsequently, tremolite was detected in the lungs of

Canadian chrysotile miners. Recently, it has been shown that a material containing more than 90% tremolite is used to stucco houses in an area of Turkey where calcified asbestotic plaques have been found. Dr Pooley has found that there are three main forms of tremolite that are either used as a commercial product or which contaminate chrysotile deposits. One form is flake-like and nonfibrous; one type of this fibre is mined in California. The other two forms are fibrous; a coarse fibrous type that occurs in Canadian mines is the same as that used as a stucco in Turkey, and a fine fibre variety is found in the chrysotile mines in Cyprus. Animals have been inoculated intrapleurally with all three forms of fibre at the MRC Pneumoconiosis Unit. So far, the only completed experiment is a study in 32 rats with the Californian material; this did not produce mesotheliomas.

Analysis of the material collected in the 1976 mesothelioma survey and the 1977 asbestos exposure study in the UK is being continued; more than 1 400 cases have been collected so far. In addition, lung samples from the Canadian and the United States mesothelioma studies organized by Professor A. McDonald (McGill University, Montreal, Canada) are being received, and it is hoped that this material will have been analysed and correlated with occupational exposures and clinical information for presentation at a meeting in Lyon planned for 1979. Pathologists will examine the tissues to establish the nature of any tumour present, and the incidence and grading of asbestosis in the lung tissue will be recorded.

(ii) *Zeolites*

A detailed analysis of rock and dust samples from the Turkish villages of Tuscoy and Karain, in which mesotheliomas occurred, and from other areas demonstrated that a fibrous form of zeolite, known as eronite, appeared only in the samples from the two villages. Eronite, a fibrous aluminium silicate, is formed when hot volcanic ash falls into water; it seemed unlikely that these fibres would be found in only two locations, as zeolites are distributed universally and occur wherever volcanic tuff has been deposited. During the last five years, zeolite has gained in industrial importance, and deposits are being mined in many countries.

Information has been received about a number of mesotheliomas that have occurred in Maharashtra Province in India; the initial report suggested that these tumours were associated with the burning of sugar cane. A preliminary investigation was undertaken by Dr J. Ball, a consultant chest physician, and Mrs I. Ashton, from the MRC Pneumoconiosis Unit. They received much help from Professor S. G. Deodhare, Pathology Department at Miraj Medical College. Relatives, or surviving patients with mesothelioma, were visited; histological data were obtained; and dust samples were taken from places of work and residence. So far, three of the six cases of mesothelioma have been confirmed. The sugar cane in the area grows on a large zeolite deposit, but, as yet, no fine fibrous material has been identified in the numerous samples that were obtained.

In view of the possibility that mineral fibres from burnt sugar cane play a part in the development of the tumours, a preliminary survey in the Carribean seemed justified. Three islands were chosen: Barbados, an island which is non-volcanic in origin and has produced sugar cane for hundreds of years; St Vincent, a volcanic island where an eruption occurred in 1902, undoubtedly depositing a large amount of zeolites; and the island of Dominica, a volcanic island on which zeolite is actually crushed and exported as 'pumice'. In addition, the southern half of the island is covered with a thick layer of ash from the eruption of Mount Pele on Martinique in 1902. These three islands were visited by Dr J. C. Wagner and Dr M. M. F. Wagner in March 1978. Contact was made with both medical personnel and environmental scientists.

With the advice of geologists from the Overseas Development Corporation in London, further information is being obtained about the zeolite deposits on these islands. There are numerous other sites where zeolites should occur, and arrangements are being made for their collection.

(*b*) *Experimental pathology*

(i) *Animal studies*

The studies on rock wools, glass wools and slag wools are continuing. Experiments are in progress in which rats have been exposed, both by the intrapleural route and by inhalation, to a number of samples of man-made mineral fibre. The results of initial studies will be presented at a meeting in September 1979.

Experimental studies have been undertaken on other man-made mineral fibrous dust and particulates, including insulation materials prepared from calcium silicate and ceramic materials, and the finer forms of polyvinyl chloride particles. Other centres are concerned in these studies, and it is planned to obtain a comprehensive review of the findings.

(ii) In vitro *studies*

Effect of mineral dust and fibres on macrophages: Cytotoxicity to macrophages was determined by examining the release of a cytoplasmic enzyme, which gave a measure of cell death. Five different crystalline silica samples and Cab-O-Sil (amorphous silica) were the most cytotoxic dusts. UICC asbestos samples—crocidolite, amosite, anthophyllite and chrysotile—were less active but had broadly similar cytotoxicities. Fine glass fibre (Code 100), quartz fibres, glass powder and various other man-made mineral fibres all caused lung fibrosis in inhalation studies. On the other hand, magnetite and diamond dust, which are virtually inert, were not cytotoxic to macrophages. Milled UICC crocidolite was less active than the parent material and was also less fibrotic.

Superfine chrysotile and brucite, also two fibrotic materials, did not kill macrophages, but these dusts (and UICC chrysotile) caused the selective release of lysosomal enzymes from macrophages.

Cytotoxic activity of mineral fibres: At the MRC Pneumoconiosis Unit, studies have been undertaken on activities of mineral fibres in reducing the cloning efficienty of V79-4 cells (a Chinese hamster lung-cell line). Activity against these cell lines is correlated to some degree with the tumorigenicity of the mineral fibres in intrapleural inoculation experiments. In general, the fibres which produce tumours *in vivo* are also cytotoxic *in vitro,* whereas non-tumorigenic fibres and mineral dusts are not cytotoxic *in vitro.*

When using glass fibres that were subjected to size separation and amphibole asbestos samples that were ball-milled for different periods of time, the fibres that exerted cytotoxic effects *in vitro* were those longer than 6.5 μm (90 % confidence limits = $\pm$ 2.1 μm). This figure should be compared with Stanton's threshold figure of ≥ 8 μm, which was derived from experiments *in vivo.*

The response of the V79 cell line to the cytotoxic effects of a series of mineral dusts and fibres is different from that of mouse peritoneal macrophages. For example, isometric silica particles and glass powder are inactive in the cell lines but strongly cytotoxic to macrophages; however, silica presented as fibres of suitable dimensions is cytotoxic to V79-4 cells.

Further work is necessary to determine the role that fibre diameter plays in cytotoxicity *in vitro.*

(iii) Immunology

Continuing study of workers at high risk after exposure to asbestos in a UK dockyard has shown that those with small opacities (ILO 1/1 classification) and who smoke have increased markers of 'activated' T lymphocytes. There is no evidence of altered immunity among those with pleural change. Patients with mesothelioma show only a decreased number of lymphocytes. No aberrant distribution was found in 250 men with pleural changes and/or small opacities who were tissue typed for HLA A and B loci. Tissue typing on patients with mesothelioma is still being carried out.

(c) Epidemiology

Mortality studies on previoulsy defined groups from the same dockyard are being correlated, and the follow-up studies are being continued.

Dr P. C. Elmes, Professor J. C. McDonald (London School of Hygiene and Tropical Medicine, London), Dr J. C. Wagner, Dr F. D. Pooley (Department of Mineral Exploitation, University College, Cardiff, UK) and Mr G. Berry, were invited to attend an African Asbestos Symposium in October 1977, where recent studies in southern Africa were described. The importance of undertaking a detailed survey of the Tswana population living in the vicinity of Kuruman, many of whom had worked in crocidolite mines, was emphasized by the team; they offered to help with this study, since the information obtained from it will be most important in determining the relative properties of the different types of asbestos fibre.

Table 16. Effect of phenols extracted from Estonian oil shale generator tar on benzo(*a*)pyrene- and asbestos-induced lung carcinogenesis in Wistar rats by intratracheal instillation

Test substances in polyglucin	Initial no. of animals	Effective no. of animals	No. of animals that died during the experiment	No. of animals at histological investigation	No. of animals alive at 30 April, 1978
Benzo(*a*)pyrene	60 30 ♂ 30 ♀	49 23 ♂ 26 ♀	20 11 ♂ 9 ♀	18 9 ♂ 9 ♀	40 19 ♂ 21 ♀
Asbestos dust	60 30 ♂ 30 ♀	54 25 ♂ 29 ♀	11 8 ♂ 3 ♀	10 7 ♂ 3 ♀	49 22 ♂ 27 ♀
Phenols	60 30 ♂ 30 ♀	60 30 ♂ 30 ♀	12 5 ♂ 7 ♀	12 5 ♂ 7 ♀	48 25 ♂ 23 ♀
Benzo(*a*)pyrene and phenols	80 40 ♂ 40 ♀	57 29 ♂ 28 ♀	33 18 ♂ 15 ♀	31 16 ♂ 15 ♀	47 22 ♂ 25 ♀
Asbestos dust and phenols	80 40 ♂ 40 ♀	73 36 ♂ 37 ♀	21 12 ♂ 9 ♀	20 11 ♂ 9 ♀	59 28 ♂ 31 ♀
Controls	40 20 ♂ 20 ♀	37 18 ♂ 19 ♀	6 2 ♂ 4 ♀	6 2 ♂ 4 ♀	34 18 ♂ 16 ♀
Polyglucin					
No treatment	40 20 ♂ 20 ♀	39 19 ♂ 20 ♀	3 2 ♂ 1 ♀	3 2 ♂ 1 ♀	37 18 ♂ 19 ♀

4.2 *Investigation on the synergistic action of phenols extracted from Estonian oil shale generator tar on benzo(a)pyrene-induced and asbestos-induced lung carcinogenesis in Wistar rats*[15] (Dr A. Vösamäe, Laboratory of Morphology, Institute of Experimental and Clinical Medicine, Tallinn, Estonian SSR: RA/74/011)

Experiments using intratracheal instillation, started in April 1977, were finished in July 1977. At present, 12 months from the beginning of the experiments, 106 out of 420 rats have died (Table 16); many of the deaths (33 out of 80) occurred in those that received benzo(α)pyrene and phenols. Tissue specimens from respiratory organs, liver, kidney, spleen, stomach, head, female genital organs and other organs and tissues that showed gross pathological lesions were taken from 100 of 106 autopsied rats for histological examination. Preparation of microscope slides is in progress.

5. CARCINOGENICITY TESTING OF DAPSONE (Dr L. Griciute)

Testing of the anti-leprosy drug dapsone[16, 17] has been completed. Survival rates of the experimental animals were high; and various tumours occurred in both experimental and control groups of animals, mostly during the second year of the experiment. Overall tumour morbidity was not very different among the groups, but some unusual tumours occurred in treated rats: fibrosarcomas and angiosarcomas of the spleen were seen, mostly in males, and cancers of the thyroid in males and females. Spleen tumours were related to spleen fibrosis, which was detected in numerous dapsone-treated rats; no similar changes were observed either in the positive, benzo(α)pyrene-treated, or negative control groups of rats or in mice. Hyperplastic nodules of the thyroid epithelium were detected in numerous dapsone-treated and benzo(α)pyrene-treated rats; there were no lesions of this kind in mice, but several haemangiosarcomas of the liver were observed.

It is noteworthy that both mesenchymal tumours and spleen fibrosis were also observed in numerous male rats in the experiment carried out by the team at the National Cancer Institute, USA[18]; spleen tumours and thyroid tumours also occurred in male rats in Dr Bergel's experiment[19]. In our experiments, dapsone was found to be slightly carcinogenic: unusual tumours occurred during the second year of life in both species studied.

6. INVESTIGATION ON THE COMBINED ACTION OF SEVERAL CHEMICAL CARCINOGENS (Dr L. Griciute, in collaboration with Dr V. Turusov, Oncological Research Centre, Moscow; Dr B. Teichmann, Central Institute for Cancer Research, Berlin-Buch; and Dr I. Chernozemsky, Institute of Oncology, Sofia).

Environmental samples are usually contaminated with low levels of several chemical carcinogens. For the evaluation of analytical data, it is therefore essential to have information on

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[15] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 66.
[16] International Agency for Research on Cancer (1976) *Annual Report, 1976*, Lyon, p. 60.
[17] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 67.
[18] National Cancer Institute (1977) *NCI Carcinogenesis tech. Rep. Ser. No. 20.*
[19] Bergel, M. (1973) *Acta Leprologica*, 53, 11–24.

the effects of concomitant exposure to several carcinogens. There is some epidemiological evidence that the combined action of several known carcinogens or of known with presumed carcinogens is greater than that of a single carcinogen (e.g., asbestos and smoking, strong alcohols and smoking); however, the available experimental data are both poor and contradictory.

A collaborative study in four laboratories on the combined action of several chemical carcinogens has been started, using the same experiment protocol:

(a) C57 BL mice are used;
(b) analogous experimental and control groups are tested;
(c) three well-known environmental carcinogens, benzo(α)pyrene, *N*-nitrosodiethylamine and aflatoxin B_1, from the same batch, are administered at low, marginally-active doses; and
(d) the animal feed from all four laboratories is analysed periodically for benzo(α)pyrene, volatile *N*-nitrosamines and aflatoxin B_1 by the Unit.

It is anticipated that the data from this study give a clearer idea of the action of this combination of carcinogens. Other experiments, involving the application of other carcinogens, could be planned within the framework of this collaboration.

3. UNIT OF BIOLOGICAL CARCINOGENESIS

Dr A. GESER (Acting Chief)

1. INTRODUCTION

Etiological studies of Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) continued to be the main occupation of the Unit throughout the year.

The testing of 14 sera collected in the West Nile, Uganda, from BL patients prior to onset of the tumour[1] showed that anti-Epstein–Barr virus (EBV)/viral capsid antigen (VCA) activities were significantly increased in BL candidates years before appearance of the tumour. This finding supports one of the hypotheses being tested. In some cases, the EBV/VCA titres were not raised before manifestation of BL, and the presence of the EBV genome could not be demonstrated: in order to establish whether a form of BL exists in Africa that is not EBV-associated, and also to increase the confidence of the serological findings, it was decided that BL detection in the child cohort which was bled in the West Nile between 1972 and 1974 should be continued through 1979.

The geographical association between high incidence of malaria and BL continues to be confirmed in studies in the West Nile district of Uganda, as well as in Mara region, Tanzania. In the malaria intervention trial which is being carried out in North Mara to test the hypothesis that the association between malaria and BL is a causal one, excellent cooperation is being obtained from the population, and the prevalence of malaria is being reduced in children of 0–10 years old.

In Singapore, a prospective study was initiated to investigate the etiological role of EBV in NPC. Approximately 5 000 Chinese males will be bled and followed for five years to see whether the EBV antibody profile in persons who subsequently develop NPC differs from that of people who do not.

Laboratory activities support both the BL and NPC field programmes: besides banking and serological testing of field specimens, the laboratory is involved in more basic research activities, such as improvement of EBV serological techniques, characterization and purification of EBV antigens, virological studies to evaluate the etiological role of EBV in NPC, and the preparation and distribution of reference sera and lymphoblastoid cell lines.

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[1] de-Thé, G., Geser, A., Day, N. E., Tukei, P. M., Williams, E. H., Beri, D. P., Smith, P. G., Dean, A. G., Bornkamm, G. W., Feorino, P. & Henle, W. (1978) *Nature*, **274**, 756–761.

2. ETIOLOGICAL STUDIES OF BURKITT'S LYMPHOMA (Dr A. Geser)

2.1 *Prospective study of Burkitt's lymphoma in the West Nile district, Uganda*

East African Virus Research Institute, Entebbe, Uganda
Principal investigator: Dr L. G. Mukwaya

Burkitt's lymphoma field station, Arua, Uganda
Principal investigator: Dr G. Olwit

Kuluva Hospital, Arua, Uganda
Principal investigator: Dr E. H. Williams

(*a*) *Case detection*

The child cohort which was bled in the West Nile district between 1972 and 1974 is now 5–13 years old and may be expected to yield another five to seven cases before the end of 1979. It has therefore been decided to continue case detection in the West Nile throughout 1979, in order to obtain the maximum number of pre-bled BL cases.

Since last year, two more 'pre-bled' BL cases have been found in the West Nile, but these have not yet been tested. The total number of BL cases detected in the entire West Nile district in 1977 was seven, and, up to June 1978, six new cases had been found this year. On the whole, the rate of 'pre-bled' BL cases has been lower than expected (16 instead of 30). In order to see whether the reason for this might be that in recent years the people in the West Nile report less frequently to local health services, an investigation of records at dispensaries and health centres was made. The results showed that attendance was about 20% less in 1977 than in 1976, whereas there was no decline from 1975 to 1976, and large numbers of out-patients are still attending clinics everywhere in the district. The decline in attendance rate is too small to account for the deficiency of 'pre-bled' BL cases. In order to investigate the possibility that migration and deaths have depleted the cohort which was bled four to six years ago, a new survey of the study population in the West Nile is being made. A sample of 1 000 children has been selected from the register of those who were bled, and these are now being revisited to ascertain how many are still at risk for developing BL.

(*b*) *EBV-free BL in Africa*

It was mentioned in the previous *Annual Report*[2] that three of the nine 'pre-bled' BL cases which were examined for EBV-DNA did not contain measurable amounts of the EBV genome. A preliminary review of these cases has now revealed that one of them was not a BL by histological criteria; it was included because the clinical findings were strongly suggestive of BL. In another, the EBV genome has now been found to be present, in spite of the initial negative report. There is thus only one EBV-free tumour among those submitted to hybridization testing; the whole question of the frequency of non-EBV-associated BL tumours in Africa would thus appear to require revision. A study is planned on the basis of both new and old BL cases from the West Nile district, from which suitable material is available for hybridization testing.

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[2] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 76.

(c) *Antibodies to viruses other than the EBV in BL patients and controls*

In order to determine whether the elevation of antibody titres which was observed in pre-bled BL patients before and after tumour onset is specific for the EBV, the sera from pre-bled and other BL patients and age-matched controls were tested for antibodies to herpes simplex virus (HSV), cytomegalovirus (CMV), measles virus (MV) and adenovirus type 5 (post-BL sera only). Dr Feorino, Atlanta, GA, USA, tested for antibodies to HSV (immunofluorescence, IF), CMV (IF) and measles virus (complement fixation, CF), whereas testing for anti-adenovirus activities was carried out by Dr Chardonnet, INSERM, Lyon, using the IF method.

Table 17. Prevalence and geometric mean titres (GMT) of positive antibody titres to herpes simplex virus, cytomegalovirus and measles virus among pre-bled Burkitt's lymphoma (BL) patients and controls in the West Nile district, Uganda

Virus	Examinees		Number examined	Those with titres ⩾ 10	
				prevalence (%)	GMT
Herpes simplex virus	Pre-BL	cases	14	86	15.0
		controls	67	81	14.5
	Post-BL	cases	14	86	14.1
		controls	14	86	12.6
Cytomegalo-virus	Pre-BL	cases	11	91	34.8
		controls	57	95	30.2
	Post-BL	cases	14	93	19.0
		controls	14	100	20.0
Measles virus	Pre-BL	cases	10	40	16.8
		controls	58	57	21.3
	Post-BL	cases	14	36	13.2
		controls	14	71	15.2

Table 18. Prevalence and geometric mean titres (GMT) of positive antibody titres to herpes simplex virus, cytomegalovirus, measles virus and adenovirus 5 among post-bled Burkitt's lymphoma (BL) patients and their controls in the West Nile district, Uganda

Virus	Examinees	Number examined	Those with titres ⩾ 10	
			prevalence (%)	GMT
Herpes simplex virus	BL cases	15	87	13.1
	controls	15	87	15.3
Cytomegalo-virus	BL cases	15	100	21.9
	controls	15	100	19.1
Measles virus	BL cases	15	53	15.4
	controls	15	73	12.9
Adenovirus type 5	BL cases	14	100	65.6
	controls	15	100	69.6

The results obtained for the pre-bled BL cases and their controls are shown in Table 17: for HSV and CMV, the proportion and geometric mean of positive titres (GMT) were similar in BL patients and controls, both before and after tumour manifestation. For MV, the proportion and GMT of positive titres were higher in the controls both in pre- and post-sera; this excess of positive measles antibodies in the controls approaches statistical significance, but it is not easy to see what it means in immunological terms.

The results of HSV, CMV, MV and adenovirus antibody testing of sera from the BL cases who were not bled before tumour onset and their controls are shown in Table 18. The difference between BL cases and controls is slight only, both in terms of prevalence and GMT of positive antibody titres, for all four viruses, and none of them attain statistical significance.

These findings indicate that only EBV antibodies are elevated in BL patients, and that this virus maintains a specific and unique relationship with BL. The elevated EBV antibody titres in BL patients are thus not just the result of a general alteration of the immunological response in BL patients.

(*d*) *Malaria parasites in BL patients before ('pre') and after ('post') tumour onset*

In the prospective study in the West Nile, slides from all children who were bled in the initial survey and again from children who developed BL were examined for the presence of malaria parasites. The results for slides collected from pre-bled BL cases before as well as after tumour occurrence, and from age-matched controls, are summarized in Table 19. It can be seen that 80% of pre-bled BL patients had parasites in the blood, *versus* 71% of the controls; this difference is not statistically significant, and the high levels merely reflect the fact that the children live in a hyperendemic area. The geometric mean counts of parasites (positive children only) were also similar in BL patients (240) before onset of the tumour and in controls (269). Slides obtained after the tumour occurred showed a somewhat lower prevalence of parasitaemia in patients (50%) than in controls (68.8%), but this difference is not significant. However, the occurrence of malaria in a series of 38 other BL patients found in the West Nile between 1973 and 1975 was significantly lower (37%) than that prevailing in the controls (77%). It is not clear what this lower prevalence of parasitaemia in BL patients means; it is possible that more anti-malarial treatment was given to these children, who had been ill for some time before their BL was diagnosed.

Table 19. Prevalence of malaria parasitaemia and geometric mean of parasite counts in positive slides from Burkitt's lymphoma (BL) patients and controls made before ('pre') and after ('post') diagnosis of BL in West Nile district, Uganda

Examinees		Number examined	No. with parasite[a]			% with both	Geometric mean count in positive cases
			Falc.	Mal.	Both		
BL	pre-	15	12	—	12	80.0	240.17
	post-	14	6	1	7	50.0	133.32
Controls	pre-	14	8	2	10	71.4	269.94
	post-	16	9	2	11	68.8	210.44

[a] Falc.: *Plasmodium falciparum*
Mal.: *Plasmodium malariae*

The fact that the BL patients did not reveal a higher malaria burden prior to tumour development than did the control children does not favour the hypothesis that malaria causes BL. It must, however, be appreciated that malaria parasitaemia varies drastically from day to day in children living in hyperendemic areas, and that a single examination could hardly be expected to give a significant difference between BL candidates and controls, even though such a difference may exist at some time prior to BL onset.

2.2 *Cofactors in the etiology of Burkitt's lymphoma*
Shirati Mission Hospital, Musoma, Tanzania
Principal investigator: Dr G. Brubaker

In the search for cofactors in the etiology of BL, malaria remains the most likely candidate, in view of the close geographical correlation between hyperendemic malaria and high incidence of BL.

Malaria suppression is being carried out in North Mara (Tarime district), Tanzania, in order to see whether the incidence of BL can be reduced by reducing malaria from the present hyperendemic to mesoendemic levels. The malaria suppression scheme was fully implemented in all villages (*ujamas*) in North Mara by September 1977. Approximately 90 000 children, aged 0–10 years, now receive chloroquine tablets twice monthly, and the continuous malaria survey which is built into the study shows that the prevalence of malaria parasitaemia is being reduced in the area.

South Mara (Musoma district), where no village-wide chloroquine distribution has yet been introduced, serves as a comparison area. The prevalence of malaria parasitaemia and the incidence of BL are monitored continuously by the research team in both North and South Mara. Only three BL cases were detected in 1977 in North Mara and five in South Mara. This low incidence of BL in North Mara—which has continued into 1978—poses a difficulty for the research scheme, since it began too early to be attributed to the malaria suppression; it may consequently be necessary to continue the trial longer than planned in order to show whether or not the chloroquine distribution has an effect on BL incidence.

The level of chloroquine sensitivity of the local *falciparum* parasites will be monitored for the duration of the project in order to see whether prolonged antimalarial medication induces chloroquine resistence in them. A field adapted method for testing chloroquine sensitivity will be introduced at Shirati Hospital with the help of the WHO Division of Malaria and Other Parasitic Diseases and of Dr Draper from the London School of Hygiene and Tropical Medicine.

In order to investigate whether there is any interaction between malaria infection and antibodies to EBV, sera will be collected from a sample of children undergoing malaria prophylaxis in North Mara, as well as from children in South Mara where no chloroquine distribution is practised.

3. STUDIES ON NASOPHARYNGEAL CARCINOMA

3.1 *Immunogenetic studies in Singapore* (see Report of the Singapore Research Centre)

3.2 *Prospective study of 5 000 Chinese males in Singapore* (Dr A. Geser)

The follow-up study was initiated in 1978 of 5 000 Chinese males living in homes for the aged in Singapore. This study forms an integral part of a prospective study aimed at determining the risk

of liver cancer among chronic carriers of hepatitis B virus. It is organized by Dr Phoon Wai On (Department of Social Medicine and Public Health, University of Singapore), in cooperation with the Unit of Interdisciplinary Programme and International Liaison, IARC, for the purpose of studying the association between hepatitis B infection and liver cancer.

Approximately 5 000 male Chinese over 45 years of age will be bled, and cases of NPC developing in this cohort will be ascertained through the Cancer Registry of Singapore. It is expected that about 15 cases will develop during the 5-year period of follow-up; and the sera collected from these patients before tumour development ('pre-sera'), and a suitable number of control sera, will be tested for EBV activities in the Agency's laboratory.

3.3 *Tunisia*

(*a*) *Sero-epidemiology* (Professor R. Sohier)

A sero-epidemiological survey was carried out among 419 Tunisian people hospitalized in Tunis. The results of EBV/VCA testing (Table 20) show that Tunisian children already have high EBV/VCA antibody levels in the second half year of life (56.5 % infected) and that 100 % of those from five to ten years old have positive anti-EBV/VCA antibodies.

Table 20. Prevalence and geometric mean titres (GMT) of positive Epstein-Barr virus (EBV) antibody titres[a] in sera from Tunisians, by age

Age	VCA titres			EA titres			EBNA titres		
	No.	Prevalence (%)	GMT +	No.	Prevalence (%)	GMT +	No.	Prevalence (%)	GMT +
0- 6 months	26	54	26.9	26	0	0	26	62	30.8
7-12 months	23	48	116.8	23	13	20	23	48	42.6
13-24 months	25	56	124.9	25	16	28.3	25	52	44.5
25-36 months	24	75	97	24	21	11.5	24	71	166.7
37-48 months	10	90	54.4	10	20	14.1	10	100	149.3
5-10 years	61	100	73	61	7	20	61	93	145.2
11-20 years	90	96	61.3	90	13	16.8	90	96	166.4
21-30 years	51	100	57.7	51	8	11.9	51	100	164.4
31-40 years	46	96	75.1	46	11	20	45	96	167.9
41 + years	63	100	80.9	63	18	20	63	100	197.2
All ages	419	89	69.5	419	12	17.7	418	88	142.4

[a] VCA – viral capside antigen; EA – early antigen; EBNA – nuclear antigen

(*b*) *Immunogenetic studies* (Dr H. Bétuel)

Sera collected from 323 multiparous women in Tunisia were tested for HLA antigens at the Blood Transfusion Centre in Lyon, France. The results reveal that six HLA antigens at the A locus (Nos 1, 2, 3, 9, 29 and 30) and seven at the B locus (Nos 5, 7, 12, 13, 17, 21 and 27) occur with higher frequency in Tunisians than in other populations that have been studied. It will now be investigated whether these antigens are more common in NPC patients than in controls in Tunisia.

4. LABORATORY STUDIES (Dr G. Lenoir)

4.1 *Routine serological activities*

This represents the main laboratory activity. The 3 360 sera from the in-depth BL study in Uganda are presently under testing for the three EBV antibody reactivities [VCA, early antigen (EA) and nuclear antigen (EBNA)]; and sera from other related programmes, such as the NPC studies in south-east Asia and north Africa and the BL prospective study, are also being tested.

4.2 *Improvement of serological testing*

(*a*) *Immunofluorescence technique*

At the present time, EA slides are generally prepared from Raji cells induced by superinfection with the P3 HR1 strain of EBV (100 × concentrate). This technique, which requires large-scale virus production and concentration, is costly and time-consuming because of the low capacity of lymphoblastoid cell lines to produce the virus. Induction of EA by a chemical such as IUdR generally results in a percentage of positive cells that is too low for serological use (< 5 %). In collaboration with Dr Tovey, Scientific Institute for Cancer Research (IRSC), Villejuif, France, we have developed new techniques for inducing EA[3], by combining IUdR with mitogens, which permit a consistent induction of a high percentage of EA-positive cells (up to 50%) (see Fig. 7). This facilitates the preparation of EA slides and of EA-soluble antigens that are free of contaminating VCA; the latter are necessary for the development of the micro-Elisa test (see below).

(*b*) *Development of a field-adaptable EBV serological test* (in collaboration with Dr A. Voller, Zoological Society of London)

The micro-Elisa test, a new serological test using alkaline phosphatase-labelled anti-human immunoglobulins, has been applied to the detection of antibodies directed against EBV antigens. The detection of antibodies against EA by this test is easy, and the results correlate well with data obtained by immunofluorescence. Antibodies of the IgA class can be detected with this test, but the detection of IgM appears to be more difficult. For EBV/VCA serology, it is necessary to have VCA antigen extract with very high specific activity; VCA antigens are presently being partially purified for this purpose.

4.3 *Characterization and purification of EBV antigens* (in collaboration with Professor J. Daillie, Dr T. Ooka, Claude-Bernard University, Lyon)

Two groups of antigens are being studied: EBNA and EA. EBNA is the first antigen detectable in cells after EBV infection and is expressed in all EBV genome-carrying cells, both in lymphoblastoid cell lines and *in vivo* in tumour cells such as Burkitt's lymphoblasts or epithelial cells of NPC. The presence of this antigen in a cell correlates with the presence of the viral genome and may be related to its malignant state.

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[3] Tovey, M. G., Lenoir, G. & Begon-Lours, J. (1978) *Nature* (in press).

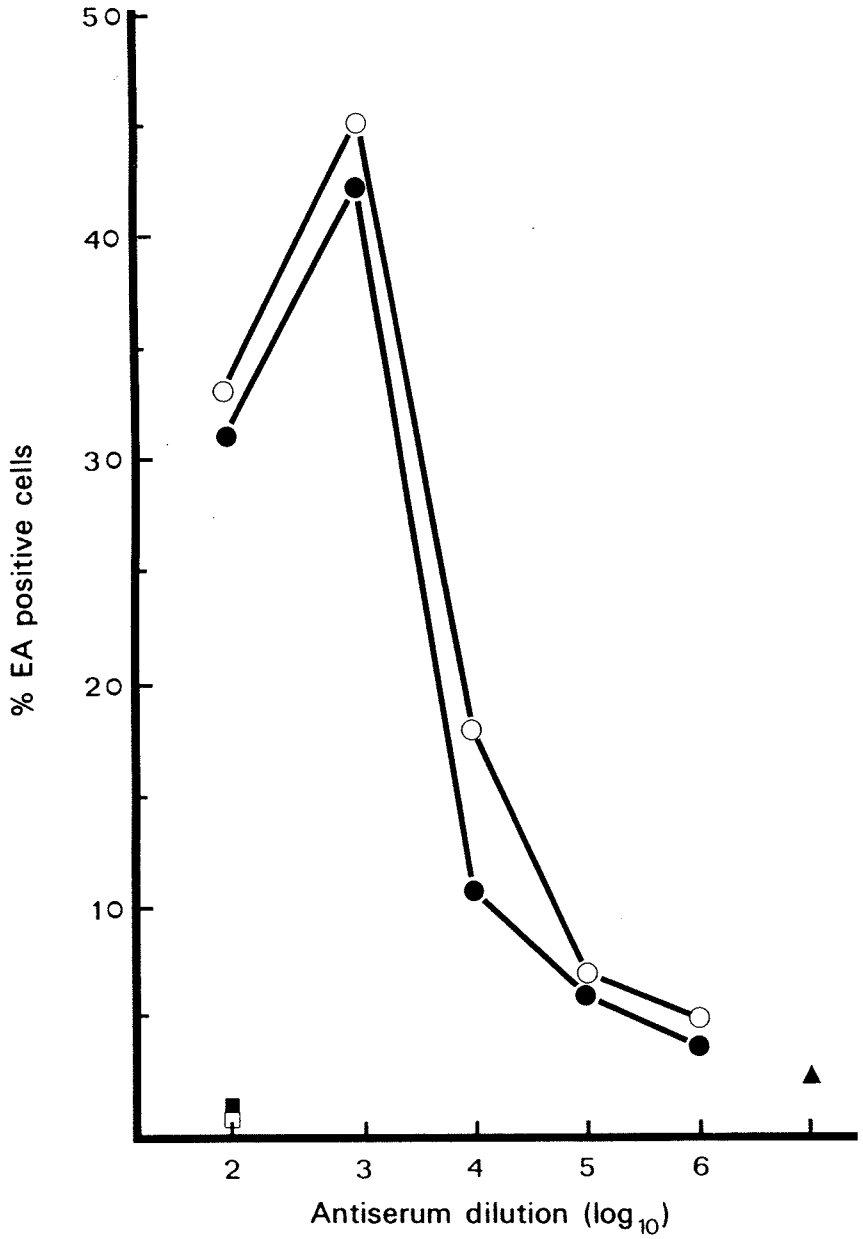

Fig. 7 Induction of early antigen (EA) in cultures of Raji cells treated with various dilutions of anti-immunoglobulins. Cells were cultivated for 72 hours with each dilution of antiserum in the presence of IUdR (25 μg/ml). The number of EA-positive cells was then determined on acetone-fixed smears by direct immunofluorescence; ○ = total human anti-immunoglobulins, ● = anti-IgM, □ = anti-IgA, ■ = anti-IgG, ▲ = IUdR alone

EBNA is partially purified using gel filtration techniques and affinity chromatography. The antigenic molecule, which has a molecular weight of 180 000 daltons in its native form, can be dissociated into smaller components (mol. wt about 60 000) under dissociating conditions. EBNA binds to DNA and may then act as a regulatory protein. A radioimmunoassay for the detection of this antigen in tumour cells will be developed when its purification reaches a satisfactory level.

The characterization of EA is important, since high levels of antibodies directed against them are found predominantly in patients with EBV-related diseases, such as BL and NPC, and not in the general population. We have shown that when lymphoblastoid cells express EA a new DNA

polymerase is induced in those cells[4], and the observed increase in the activity of this polymerase parallels the appearance of EA-positive cells (Fig. 8). This new polymerase has been partially purified by chromatography (Table 21) and can be distinguished from cellular DNA polymerase[4]. It will be interesting to see to what extent the purified enzyme can be defined as an EA polypeptide, and then whether it can be used as purified antigen for serological purposes.

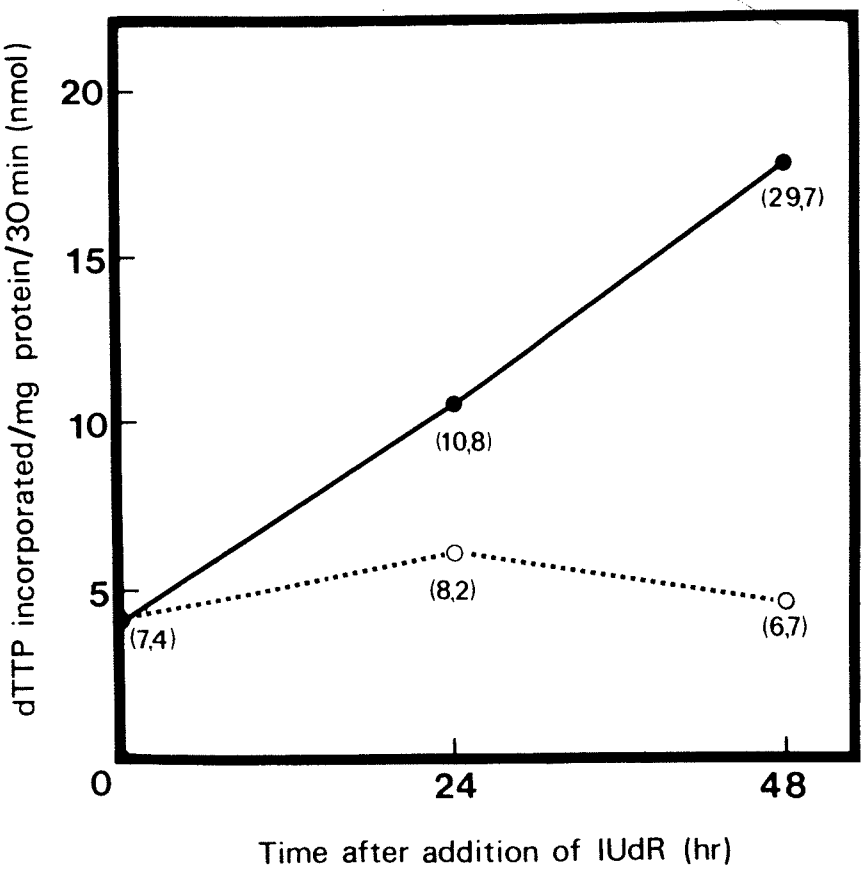

Fig. 8 Kinetics of induction of Epstein–Barr virus (EBV)-induced DNA polymerase activity and early antigen (EA)-positive cells in P3HR-1 cells treated with IUdR. DNA polymerase activity in IUdR-treated cells (●———●) and in untreated cells (○---------○). The percentage of EA-positive cells is indicated in parentheses

Table 21. Purification of Epstein-Barr virus (EBV)-induced DNA polymerase from IUdR-treated P3HR-1 cells

Chromatographic fraction	Total protein (mg)	Total activity (units)[a]	Recovery (%)	Specific activity (units/mg protein)	Purification (fold)
Crude extract	210.0	273.8	100	1.29	
Sepharose 6B	32.2	520.2	189	16.1	13
DEAE-cellulose	2.96	147.4	54	50.0	39
Phosphocellulose	0.099	41.4	15	418.4	326

[a] A unit is defined as 1 nmole of deoxynucleotide incorporated into an acid-insoluble form in 60 min at 37°C.

[4] Ooka, T., Lenoir, G. & Daillie, J. (1978) *J. Virol.* (in press).

4.4 *Virological studies on nasopharyngeal carcinoma* (Mrs C. Desgranges-Blanc)

(*a*) *Association between EBV and NPC*

The previous *Annual Report*[5] stated that EBV-specific IgA antibody titres are elevated in the serum of NPC patients but not in those with BL or infectious mononucleosis. Subsequent studies have shown that both the VCA and EA antibody fractions of the EBV-specific IgA are elevated in NPC patients relative to age-matched controls (Table 22). A study of cancer patients other than NPC with high IgG EBV antibody titres showed (Fig. 9) that 21/46 patients with lung cancer and 6/7 patients with cancer of the nasal fossae had EBV/IgA VCA antibody titres of 10 or more in their sera and that this antibody is thus not unique for NPC patients.

(*b*) *Epithelial infection*

In preliminary studies of the relationship between EBV and the nasopharyngeal mucosa, it was shown that 'normal' mucosa from NPC patients, obtained from the pharyngeal wall opposite the tumour, could be infected with a mixture of two strains of EBV (M81 and P3 HR1). The criteria for infection was that 2–3 % of the cells of the mucous membrane became EBNA-positive[6].

(*c*) *Strain differences*

The question of whether or not there are different strains of wild EBV was approached by studying cell lines immortalized by EBV from different sources. It was found that EBV derived from patients with infectious mononucleosis produce permanent cell lines which are morphologically and immunologically different from those produced by EBV derived from NPC patients[7].

Table 22. Anti-Epstein-Barr virus (EBV) IgG and IgA antibody[a] levels in nasopharyngeal carcinoma (NPC) patients and controls from Hong Kong, Singapore, Tunisia and France

Group	% sera with EBV titre > 10	GMT[b] (positive sera)	Standard error	95% confidence interval
NPC patients (230)				
IgG/VCA	100	900	0.11	771-1050
IgG/EA	89.1	171	0.15	139- 209
IgA/VCA	83.9	103	0.14	85- 126
IgA/EA	56.1	59	0.16	48- 73
Controls (365)				
IgG/VCA	97.5	79	0.08	71- 89
IgG/EA	17.5	17	0.12	15- 20
IgA/VCA	1.7	10	0	— —
IgA/EA	0	0	—	— —

[a] VCA – viral capsid antigen; EA – early antigen
[b] GMT – geometric mean titre

[5] International Agency for Research on Cancer (1977) *Annual Report, 1977*, pp. 80–82.
[6] Desgranges, C. & de-Thé, G. (1977) *Lancet, ii*, 1286–1287.
[7] Desgranges, C., Lavoué, M. F., Patet, J. & de-Thé, G. *In vitro* transforming activity of Epstein-Barr virus (EBV). II. Comparison of M81 and B95-8 EBV strains (submitted for publication).

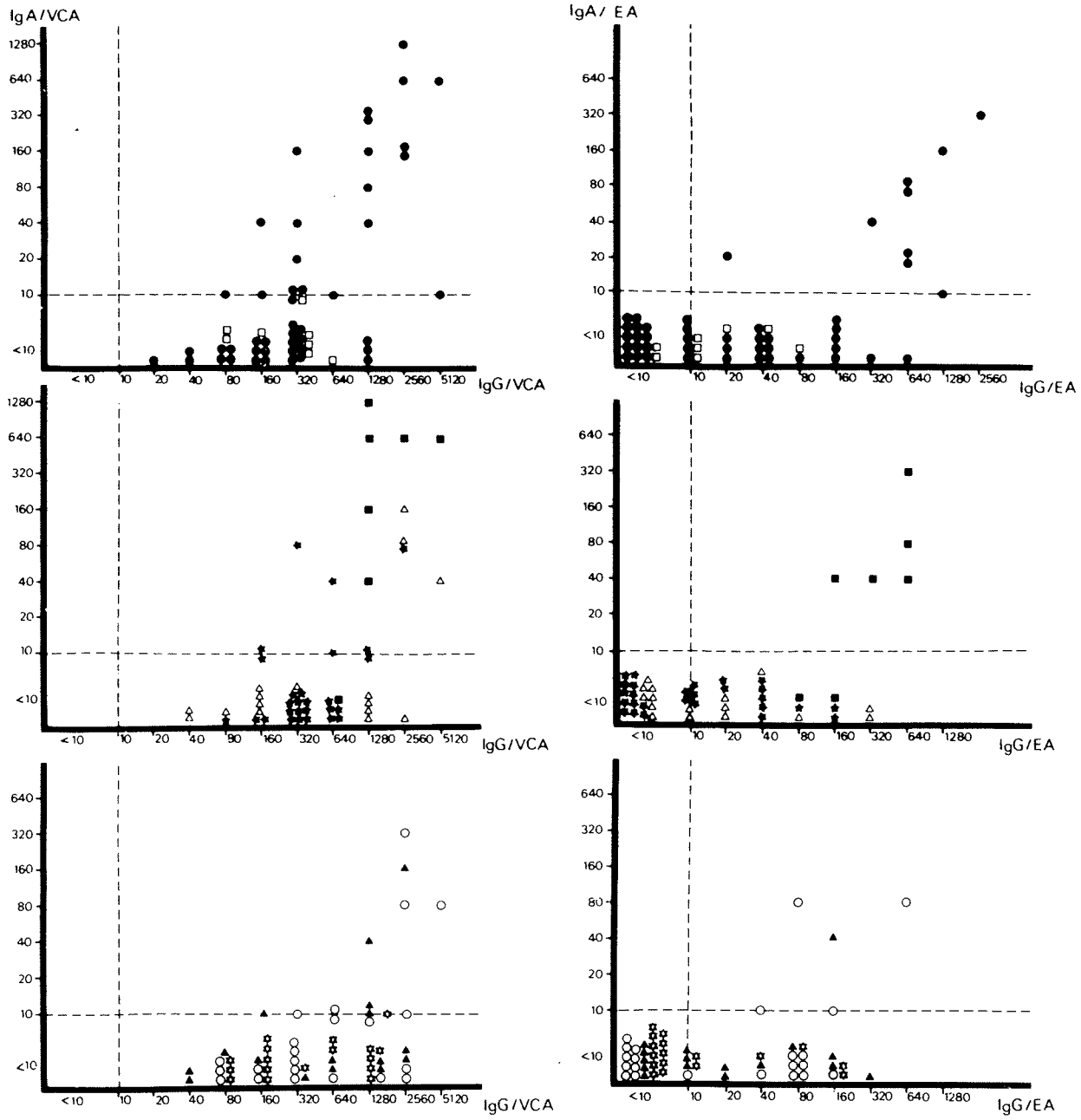

Fig. 9 Epstein–Barr virus (EBV)-IgA sera from tumours other than nasopharyngeal carcinoma; ● = lung carcinoma, □ = lung infections, ★ = laryngeal carcinoma, ■ = carcinoma of the nasal fossae, △ = carcinoma of the head and neck, ○ = Hodgkin's disease, ▲ = reticulosarcoma, ☆ = other tumours

4.5 *References activities (International Reference Programme for Oncogenic Herpes Viruses (IRP-OHV))* (Professor R. Sohier)

The distribution of reference material for use in EBV studies, both in the form of test sera and cell lines, has continued; and the Herpes Advisory Teams (HAT) dealing with simian EB viruses, lymphoblastoid cell lines and the preparation of reference sera are still active.

4. UNIT OF CHEMICAL CARCINOGENESIS

Dr L. TOMATIS (Chief)

1. INTRODUCTION

The activities of the Unit continue to be focused on generating information that can be used for the primary prevention of cancer in humans; it follows two principal directions:

(1) the identification of potentially carcinogenic chemicals in the environment and the evaluation of their carcinogenic risk to humans; and

(2) the development of criteria for a better assessment of the significance of experimental results in predicting similar effects in humans.

Up to September 1978, 19 volumes in the series of *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* have been published or are in press. In them, a total of 420 chemicals have been evaluated. Evidence or a strong suspicion of a causal association with the occurrence of cancer in humans was found for 26 chemicals; for a further 19 chemicals, although some case reports or epidemiological studies were available, no evaluation of the carcinogenic risk to humans was made since the results were inconclusive. The general paucity of epidemiological studies and inadequacies in a number of experimental reports were among the greatest difficulties encountered during the compilation of the monographs.

The Unit is organizing and *ad hoc* Working Group of national and international experts to draft criteria for the carrying out and reporting of long-term, short-term carcinogenicity and related tests, in order to make published results universally acceptable.

A worldwide survey on chemicals being tested for carcinogenicity has been continued, with the aims of avoiding unnecessary duplication of research, of increasing communication among scientists and of making a census of available research facilities as well as of chemicals which are being tested. *Information Bulletin No. 7* was completed in January 1978 and distributed.

The laboratory programme of the Unit involves both intramural and extramural activities. A limited programme of long-term carcinogenicity testing is carried out in Lyon; however, the Unit also coordinates a much larger programme that is being performed in a number of national laboratories. The feasibility of establishing a worldwide network of national laboratories which would collaborate in the carcinogenicity testing of environmental chemicals is being explored. The development and improvement of short-term carcinogenicity and related tests and the investigation of the mechanisms of carcinogenesis with the aim of developing criteria to better assess the significance of experimental results to humans are presently the main research activities of the Unit. This effort involves an intense and growing international collaboration.

2. COORDINATION OF CARCINOGENICITY DATA[1]

2.1 IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans (Dr L. Tomatis, Dr J. E. Huff, Mr J. D. Wilbourn, Mrs C. Partensky)

Implementation of the IARC *Monograph* programme involves three key, sequential steps: (1) the collection of all available data relevant to the assessment of the carcinogenic risk of chemicals to which humans are exposed; (2) the critical analysis and evaluation of these data by Working Groups of international experts in chemical carcinogenesis and related disciplines; and (3) the publication and dissemination of the data, revised and evaluated by these expert panels, as IARC *Monographs*.

Since July 1977, Volumes 16, 17, 18 and 19 of the *Monographs* series have been published or are in press.

Volume 16[2], published in January 1978, contains 32 monographs on some aromatic amines and related nitro compounds, as prepared by a Working Group that met in June 1977. Another Working Group convened in October 1977 to evaluate the carcinogenicity of *N*-nitroso compounds; the 17 monographs were published as Volume 17[3] in May 1978. Volume 18[4], published in October 1978, consists of monographs on polychlorinated biphenyls and polybrominated biphenyls; the meeting to prepare the former took place in October 1977 and that for the latter in June 1978. Volume 19[5], resulting from a meeting held in February 1978, is in press; it contains 16 monographs on monomers, plastics and synthetic elastomers. The chemicals evaluated in Volumes 16, 17, 18 and 19 of the *Monographs* are listed alphabetically in Table 23.

Volume 20, stemming from a meeting on halogenated hydrocarbons held in June 1978, is in preparation. Volume 21 will be the result of a meeting held in November 1978 on natural and synthetic sex hormones; Volume 22 will comprise monographs on sweetening agents and heavy metals which will be considered by a Working Group in March 1979.

A complete inventory of those substances evaluated in Volumes 1–16 of the *Monographs* appears in a recent review of the programme[6]; additionally several editorials about the programme have been written[7, 8, 9].

Over 200 people from 25 countries participated in the first 19 monograph meetings (Table 24). Representatives from the World Health Organization, US National Cancer Institute, Commission of the European Communities, Stanford Research Institute International and other observers from various countries have also attended these meetings. The members and observers who attended the

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[1] The Monograph and Survey Programmes are supported in part by the US National Cancer Institute under Contract No. N01 CP 45608.

[2] International Agency for Research on Cancer (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, **16**, *Some Aromatic Amines and Related Nitro Compounds – Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals*, Lyon.

[3] International Agency for Research on Cancer (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, **17**, *Some* N-*Nitroso Compounds*, Lyon.

[4] International Agency for Research on Cancer (1978) *IARC Monographs on The Evaluation of the Carcinogenic Risk of Chemicals to Humans*, **18**, *Polychlorinated Biphenyls and Polybrominated Biphenyls*, Lyon (in press).

[5] International Agency for Research on Cancer (1978) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, **19**, Monomers, Plastics and Synthetic Elastomers, Lyon (in press).

[6] Tomatis, L., Agthe, C., Bartsch, H., Huff, J., Montesano, R., Saracci, R., Walker, E. & Wilbourn, J. (1978) *Cancer Res.*, **38**, 877–885.

[7] IRPTC (International Register for Potentially Toxic Chemicals) (1978) *IRPTC Bulletin*, **1**, No. 2, 3–4.

[8] Huff, J., Wilbourn, J., Partensky, C. & Tomatis, L. (1978) *Forum for the Advancement of Toxicology Newsletter* (in press).

[9] Anon. (1978) *Chem. Eng. New*, **56**, 30–31.

Working Groups that resulted in Volumes 16, 17, 18 and 19 are listed in Table 25. Lists of the experts who contributed to the preparation of Volumes 1–7[10], 8–11[11] and 12–15[12] have been published previously.

The first 19 volumes in the *Monographs* series comprise 360 monographs, in which evaluations or re-evaluations have been made on 420 chemicals. For 26 chemicals (or industrial processes), a positive association was established between exposure and the occurrence of cancer in humans (Table 26). The type of exposure for which the association was found was occupational for 17 chemicals, iatrogenic for eight and dietary for one; however, the general population may also be exposed to most of these chemicals. The uses and potential routes of exposure for the 420 chemicals are shown in Table 27. For 234 of the remaining 394 chemicals, epidemiological evidence was either non-existent or insufficient to assess their carcinogenicity in humans, but some evidence of carcinogenicity was found in one or more species of experimental animals. For the remaining 160 chemicals, the available data were inadequate for making an evaluation of the presence or absence of a carcinogenic effect in humans or experimental animals.

Table 23. Chemicals evaluated in *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Volumes 16, 17, 18 and 19

Chemical	Volume	Chemical	Volume
Acridine orange	16	*N*-Nitrosomethylvinylamine	17
Acrolein	19	*N*-Nitrosomorpholine	17
Acrylic acid	19	*N*-Nitrosonornicotine	17
Acrylic and modacrylic fibres	19	*N*-Nitrosopiperidine	17
Acrylonitrile	19	*N*-Nitrosoproline	17
Acrylonitrile-butadiene-styrene copolymer	19	*N*-Nitrosopyrrolidine	17
5-Aminoacenaphthene	16	*N*-Nitrososarcosine	17
para-Aminobenzoic acid	16	Nylon 6	19
4-Amino-2-nitrophenol	16	*meta*-Phenylenediamine and its hydrochloride	16
Anthranilic acid	16	*para*-Phenylenediamine and its hydrochloride	16
Benzyl violet 4B	16	*N*-Phenyl-2-naphthylamine	16
Blue VRS	16	Polyacrylic acid	19
Brilliant blue FCF diammonium and disodium salts	16	Polybrominated biphenyls	18
Caprolactam	19	Polychlorinated biphenyls	18
Chloroprene	19	Polyethylene	19
para-Chloro-*ortho*-toluidine and its hydrochloride	16	Polymethylene polyphenyl isocyanate	19
Cinnamyl anthranilate	16	Polymethyl methacrylate	19
N,N'-Diacetylbenzidine	16	Polypropylene	19
2,4-Diaminoanisole and its sulphate	16	Polystyrene	19
4,4'-Diaminodiphenyl ether	16	Polytetrafluoroethylene	19
1,2-Diamino-4-nitrobenzene	16	Polyurethane foams (rigid and flexible)	19
1,4-Diamino-2-nitrobenzene	16	Polyvinyl acetate	19
2,4-Diaminotoluene	16	Polyvinyl alcohol	19
2,5-Diaminotoluene and its sulphate	16	Polyvinyl bromide	19
3,3'-Dichloro-4,4'-diaminodiphenyl ether	16	Polyvinyl chloride	19
2,4'-Diphenyldiamine	16	Polyvinylidene chloride	19
Ethyl acrylate	19	Polyvinyl pyrrolidone	19
Ethylene	19	Rhodamine B	16
		Rhodamine 6G	16

[10] International Agency for Research on Cancer (1974) *Annual Report, 1974*, Lyon, pp. 70–73.
[11] International Agency for Research on Cancer (1976) *Annual Report, 1976*, Lyon, pp. 92–94.
[12] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, pp. 90–92.

Table 23 (continued)

Chemical	Volume	Chemical	Volume
Fast green FCF	16	Streptozotocin	17
Guinea green B	16	Styrene	19
Light green SF	16	Styrene-acrylonitrile copolymer	19
Methyl acrylate	19	Styrene-butadiene copolymer	19
4,4'-Methylene diphenyl diisocyanate	19	Styrene oxide	19
Methyl methacrylate	19	Tetrafluoroethylene	19
1,5-Naphthalene diisocyanate	19	4,4'-Thiodianiline	16
Neoprene	19	2,4-Toluenediisocyanate	19
5-Nitroacenaphthene	16	2,6-Toluenediisocyanate	19
N-Nitrosodi-*n*-butylamine	17	*ortho*-Toluidine and its hydrochloride	16
N-Nitrosodiethanolamine	17	Vinyl acetate	19
N-Nitrosodiethylamine	17	Vinyl bromide	19
N-Nitrosodimethylamine	17	Vinyl chloride monomer	19
N-Nitrosodi-*n*-propylamine	17	Vinyl chloride-vinyl acetate copolymer	19
N-Nitroso-*N*-ethylurea	17	Vinylidene chloride	19
N-Nitrosofolic acid	17	Vinyl pyrrolidone	19
N-Nitrosohydroxyproline	17	2,4-Xylidine and its hydrochloride	16
N-Nitrosomethylethylamine	17	2,5-Xylidine and its hydrochloride	16
N-Nitroso-*N*-methylurea	17		

Table 24. Countries of origin of scientists involved in the preparation of Volumes 1-19 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*

Australia	Japan
Austria	Luxembourg
Belgium	Mexico
Bulgaria	Nigeria
Canada	Norway
Czechoslovakia	Sweden
Denmark	Switzerland
Federal Republic of Germany	The Netherlands
Finland	Union of Soviet Socialist Republics
France	United Kingdom
German Democratic Republic	United States of America
Ireland	Yugoslavia
Italy	

(*a*) *Principles for evaluating the carcinogenic risk of chemicals*

The criteria used for the preparation of the draft monographs, for judging the adequacy of the available data and for evaluating the carcinogenic risk to humans were first established in 1971 and, with minor modifications, were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the IARC *Monographs*. In October 1977, however, a joint IARC/WHO *ad hoc* Working Group of invited scientists (Table 28) from nine countries was convened to update and revise the criteria on which to assess the carcinogenic risk of chemicals to humans and/or experimental animals and on which to evaluate the possible carcinogenic risk that chemicals may pose for humans.

Table 25. Individuals who contributed to the preparation of monographs published in Volumes 16, 17, 18 and 19 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*

Dr J.R. Allen, University of Wisconsin, The Medical School, Department of Pathology, Madison, Wisconsin, USA
Dr B.K. Armstrong, University of Western Australia, Department of Medicine, Nedlands, Western Australia
Dr E. Arrhenius, Environmental Toxicology Unit, University of Stockholm, Wallenberg Laboratory, Stockholm
Dr J. Autian, Materials Science Toxicology Laboratories, College of Dentistry & College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, Tennessee, USA
Dr O. Axelson, Department of Occupational Medicine, University Hospital, Linköping, Sweden
Prof. P. Bannasch, Department of Cytopathology, Institute of Experimental Pathology, German Cancer Research Centre, Heidelberg, Federal Republic of Germany
Dr G. Bochert, Institute of Toxicology and Embryonal-Pharmacology of the Free University of Berlin, Berlin, Federal Republic of Germany
Prof. E. Boyland, London School of Hygiene and Tropical Medicine, London
Dr S.M. Brown, University of California, School of Public Health, Berkeley, California, USA
Dr J.R.P. Cabral, MRC Toxicology Unit, Medical Research Council Laboratories, Carshalton, Surrey, UK
Dr I. Chernozemsky, Institute of Oncology, Medical Academy, Sofia
Dr A.W. Craig, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK
Dr C. Cueto, Jr, Toxicology Branch, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland, USA
Dr J.M. Davies, Division of Epidemiology, Institute of Cancer Research, London
Dr F.K. Dzhioev, N.N. Petrov Research Institute of Oncology, Leningrad, USSR
Dr L. Elbling, Institute for Cancer Research of the University of Vienna, Vienna
Prof. S.S. Epstein, School of Public Health, University of Illinois at the Medical Center, Chicago, Illinois, USA
Dr V.J. Feron, Central Institute for Nutrition and Food Research (TNO), Zeist, The Netherlands
Dr D.H. Fine, Thermo Electron Research Center, Waltham, Massachusetts, USA
Dr L. Fishbein, National Center for Toxicological Research, Jefferson, Arkansas, USA
Dr W.G. Flamm, National Cancer Institute, Bethesda, Maryland, USA
Dr R.C. Garner, Cancer Research Unit, University of York, Heslington, York, UK
Dr R. Gingell, The Eppley Institute for Research in Cancer, The University of Nebraska Medical Center, Omaha, Nebraska, USA
Dr R. Griesemer, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland, USA
Dr E. Kriek, The Netherlands Cancer Institute, Amsterdam
Dr R. Krowke, Institute of Toxicology and Embryonal-Pharmacology of the Free University of Berlin, Berlin, Federal Republic of Germany
Dr K.S. Larsson, Laboratory of Teratology, The Karolinska Institute, Stockholm
Dr W. Lijinsky, Frederick Cancer Research Center, Frederick, Maryland, USA
Prof. N. Loprieno, Laboratory of Genetics, Institute of Anthropology and Human Paleontology, Pisa, Italy
Prof. P.N. Magee, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania, USA
Dr T. Matsushima, Department of Molecular Oncology, The Institute of Medical Science, The University of Tokyo, Tokyo
Prof. U. Mohr, Department of Experimental Pathology, Medical School, Hanover, Federal Republic of Germany
Dr J.A. Moore, Research Resources Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Prof. N. Nelson, Institute of Environmental Medicine, New York University Medical Center, New York City, New York, USA
Dr H.-G. Neumann, Institute of Pharmacology and Toxicology of the University of Würzburg, Würzburg, Federal Republic of Germany
Dr R. Owen, Trades Union Congress, Congress House, London

Table 25 (continued)

Dr G. Parmiani, Division of Experimental Oncology, National Institute for the Study and Treatment of Tumours, Milan, Italy
Dr A.E. Pegg, Department of Physiology, The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania, USA
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Prof. C. Rappe, Department of Organic Chemistry, University of Umeå, Umeå, Sweden
Dr M.D. Reuber, Frederick Cancer Research Center, Frederick, Maryland, USA
Prof. M. Roberfroid, Catholic University of Louvain, Faculty of Medicine, School of Pharmacy, Department of Medical Chemistry, Toxicology and Bromatology, Brussels
Dr K. Sankaranarayanan, Department of Radiation Genetics and Chemical Mutagenesis, Sylvius Laboratories, State University of Leiden, Leiden, The Netherlands
Dr B.W. Stewart, School of Pathology, University of New South Wales, Kensington, New South Wales, Australia
Prof. S.R. Tannenbaum, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA
Dr B. Teichmann, Central Institute for Cancer Research, Academy of Sciences of the GDR, Berlin-Buch, German Democratic Republic
Dr B. Terracini, Institute of Anatomy and Pathological Histology, University of Turin, Turin, Italy
Prof. R. Truhaut, Centre for Toxicological Research, Faculty of Pharmaceutical and Biological Sciences, University René-Descartes, Paris
Dr V.S. Turusov, Cancer Research Center, USSR Academy of Medical Sciences, Moscow
Dr H.A. Tyroler, Department of Epidemiology, The School of Public Health, The University of North Carolina, Chapel Hill, North Carolina, USA
Prof. H. Uehleke, Department of Toxicology, German Health Office, Berlin, Federal Republic of Germany
Dr H. Vainio, Department of Industrial Hygiene and Toxicology, Institute of Occupational Health, Helsinki
Dr S. Venitt, Institute of Cancer Research, Pollards Wood Research Station, Chalfont St Giles, Bucks, UK
Dr E. Vogel, Department of Radiation Genetics and Chemical Mutagenesis, Sylvius Laboratories, State University of Leiden, Leiden, The Netherlands
Dr J.K. Wagoner, Occupational Safety and Health Administration, US Department of Labor, Washington DC
Dr J.S. Wassom, Environmental Mutagen Information Center, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA
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Prof. F. Zajdela, Radium Institute, Faculty of Sciences, INSERM, Unit No. 22, Orsay, France
Dr G. Zetterberg, Department of General Genetics, University of Uppsala, Uppsala, Sweden

Representatives from the World Health Organization

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Dr G. Vettorazzi, Food Safety Unit, WHO, Geneva, Switzerland

Representative from the US National Cancer Institute

Dr S. Siegel[1], Coordinator, Technical Information Activities, Technical Information Resources Branch, Room 3A-06, Landow Building, Carcinogenesis Bioassay Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland, USA

Representative from the Commission of the European Communities

Mrs M.-T. van der Venne, Commission of the European Communities, Health and Safety Directorate, Kirchberg, Luxembourg

[1] Present address: US Environmental Protection Agency, Washington DC

Table 25 (continued)

Representatives from Stanford Research Institute International

Dr O.H. Johnson, Senior Industrial Economist, Chemical-Environmental Program, SRI International, Menlo Park, California, USA

Dr K.E. McCaleb, Director, Chemical-Environmental Program, SRI International, Menlo Park, California, USA

Mrs S. Urso, Research Analyst, Chemical-Environmental Program, SRI International, Menlo Park, California, USA

Representative from the United Nations Environment Programme

Dr H.E. Christensen, International Register of Potentially Toxic Chemicals, United Nations Environment Programme, World Health Organization, Geneva, Switzerland

Observers

Dr W. Freiesleben, Wacker-Chemie Ltd, Munich, Federal Republic of Germany

Dr A.M. Kaplan, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. Du Pont de Nemours & Co., Inc., Newark, Delaware, USA

Dr E. Loser, Institute of Toxicology, Bayer AG, Wuppertal, Federal Republic of Germany

Dr L. Villemy, European Council of Chemical Manufacturers' Federations, Brussels

Dr A. Yamamoto, Visiting Fellow from Japanese Government, Division of Prophylactic, Diagnostic and Therapeutic Substances, World Health Organization, Geneva, Switzerland

The resulting report[13] represents the basis of the Preamble to each volume of the series from Volume 17 onwards.

Subsequently, and following a recommendation made at the meeting in October 1977, another *ad hoc* Working Group (Table 28) met on 24–26 April 1978 in Lyon, to examine critically the available data on those 230 chemicals that had been identified in the first 17 volumes of the monographs as exhibiting some evidence of carcinogenicity in experimental animals. Of these, 111 were judged to have sufficient evidence of carcinogenicity in experimental animals, and, therefore, according to the newly adopted guidelines, these 111 chemicals should be regarded for practical purposes as if they were carcinogenic to humans. The 111 chemicals are listed in Table 29 and in an *IARC Internal Technical Report*[14].

(*b*) *Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans*

From 10–11 January 1978, in Lyon, a joint US National Institute of Environmental Health Sciences/IARC *ad hoc* Working Group (Table 30) discussed the feasibility of coordinating epidemiological studies on the long-term hazards associated with the chlorinated dibenzo-*para*-dioxins and chlorinated dibenzofurans. Nineteen invited scientists from eight countries presented introductory working papers summarizing the most up-to-date and relevant information available from their individual programmes. The greater part of the publication resulting from this meeting[15] comprises reports of epidemiological studies related to episodes of human exposure. It

[13] International Agency for Research on Cancer (1977) *IARC intern. tech. Rep.* No. 77/002, Lyon.
[14] International Agency for Research on Cancer (1978) *IARC intern. tech. Rep.* No. 78/003, Lyon.
[15] International Agency for Research on Cancer (1978) *IARC intern. tech. Rep.* No. 78/001, Lyon.

Table 26. Chemicals or industrial processes associated with the induction of cancer in humans (compiled from Volumes 1-19 of *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*)[a]

1. Aflatoxins
2. 4-Aminobiphenyl
3. Arsenic compounds
4. Asbestos
5. Auramine (manufacture of)
6. Benzene
7. Benzidine
8. *N,N*-Bis(2-chloroethyl)-2-naphthylamine
9. Bis(chloromethyl)ether
10. Cadmium-using industries (possibly cadmium oxide)
11. Chloroamphenicol
12. Chloromethyl methyl ether [possibly associated with bis(chloromethyl)ether]
13. Chromium (chromate-producing industries)
14. Cyclophosphamide
15. Diethylstilboestrol
16. Haematite mining (Radon?)
17. Isopropyl oils
18. Melphalan
19. Mustard gas
20. 2-Naphthylamine
21. Nickel (nickel refining)
22. Oxymetholone (?)
23. Phenacetin
24. Phenytoin
25. Soot, tars and oils
26. Vinyl chloride

[a] The list of 26 chemicals or industrial processes given above should *not* be taken as a thorough compilation of chemicals known to induce cancer in humans. It reflects only those chemicals or industrial processes which have been evaluated in the programme up to now (*IARC Monographs*, Volumes 1-19). Other agents have been designated as human carcinogens: tobacco smoking and, among others, betel-nut chewing, wood dust, certain mineral oils, and so on. Some of these have been scheduled for future consideration.

Table 27. Major use-exposure categories for the chemicals or industrial processes evaluated in Volumes 1-19 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*

Major use or exposure category	Number of chemicals
Industrial chemicals[a]	213
Pharmaceutical preparations and/or veterinary drugs	84
Naturally-occurring substances (environmental and food contaminants)	42
Pesticides	34
Food additives or cosmetic ingredients	31
Miscellaneous chemicals and analogues	7
Industrial processes	5
Industrial by-products and contaminants	4
TOTAL	420

[a] Although the major exposures or uses of these compounds are industrial, environmental contamination and subsequent exposure of the general population may occur, particularly following industrial accidents or because of environmental pollution.

begins, however, with a brief section concerning possible routes of human exposure and an overview of the pertinent chemical characteristics and salient toxicological properties of these structurally similar compounds and ends with recommendations for future activities.

(c) *Environmental factors in human cancer*

These two research studies relate directly to the IARC *Monograph* programme on the evaluation of the carcinogenic risk of chemicals to humans.

(i) *Role of environmental components in the origin of human cancer*
National Institute for Research and Treatment of Tumours, Milan, Italy
Principal investigators: Professor U. Veronesi and Dr F. Berrino

The collaboration with the recently initiated cancer registry, which covers part of the Lombardy Region, will be focused on the verification of etiological hypotheses of human cancer, with special emphasis on occupational exposure. In this respect, the Agency will provide all the data from the programme on the evaluation of the carcinogenic risk of chemicals to humans, and, in particular, information on chemicals for which there is evidence of a carcinogenic effect in humans and/or animals and for which human exposures are known to occur.

Table 28. Members of the Working Groups which met from 3-7 October 1977[1] and from 24-26 April 1978[2] to discuss the criteria for evaluating the carcinogenic risk of chemicals to humans

Dr A. Abbondandolo, Laboratory of Mutagenesis and Differentiation – CNR, Pisa, Italy
Professor E.D. Acheson, School of Medicine, Southampton General Hospital, Southampton, UK
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Dr B.K. Armstrong, University of Western Australia, Department of Medicine, Nedlands, Western Australia
Dr H.A. Bern, Cancer Research Laboratory, University of California, Berkeley, California, USA
Dr D. Bootsma, Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands
Professor E. Boyland, London School of Hygiene and Tropical Medicine, London
Dr A.L. Brown, Department of Pathology and Anatomy, Mayo Clinic, Rochester, Minnesota, USA
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Dr T. Hirohata, Department of Public Health, Kurume University, Kurume City, Japan
Dr D.G. Hoel, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Dr N.K. Hooper, Department of Biochemistry, University of California, Berkeley, California, USA
Dr T. Kawachi, National Cancer Center Research Institute, Tokyo
Dr P.N. Magee, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania, USA
Dr K.E. McCaleb, Chemical-Environmental Program, SRI International, Menlo Park, California, USA
Professor M. Mercier, Catholic University of Louvain, School of Pharmacy, Laboratory for Toxicology and Bromatology, Brussels

[1] International Agency for Research on Cancer (1977) *IARC intern. tech. Rep.* No. 77/002, Lyon.
[2] International Agency for Research on Cancer (1978) *IARC intern. tech. Rep.* No. 78/003, Lyon.

Table 28 (continued)

Professor N.P. Napalkov, N.N. Petrov Research Institute of Oncology, Leningrad, USSR
Professor D. Neubert, Institute for Toxicology and Embryonal-Pharmacology, Free University of Berlin, Berlin, Federal Republic of Germany
Dr M. Newhouse, London School of Hygiene and Tropical Medicine, London
Dr R. Peto, Department of the Regius Professor of Medicine, University of Oxford, Radcliffe Infirmary, Oxford, UK
Professor R. Preussmann, Institute for Toxicology and Chemotherapy, German Cancer Research Centre, Heidelberg, Federal Republic of Germany
Dr I.F.H. Purchase, Central Toxicology Laboratory, Imperial Chemical Industries Ltd, Alderley Park, Cheshire, UK
Dr D.P. Rall, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Professor P. Sartwell, Marblehead, Massachusetts, USA
Dr E. Sawicki, Laboratory Measurements Research Section, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA
Dr M. Schneiderman, Field Studies and Statistics, National Cancer Institute, Bethesda, Maryland, USA
Dr P. Shubik, The Eppley Institute for Research in Cancer, The University of Nebraska Medical Center, Omaha, Nebraska, USA
Dr S. Siegel, Technical Information Resources Branch, Carcinogenesis Bioassay Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland, USA
Dr J.M. Sontag, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Maryland, USA
Dr B.W. Stewart, School of Pathology, University of New South Wales, Kensington, New South Wales, Australia
Dr V.S. Turusov, Cancer Research Center, USSR Academy of Medical Sciences, Moscow

Table 29. Chemicals evaluated in the first seventeen volumes of the IARC *Monographs* for which there is sufficient evidence of carcinogenicity in experimental animals[a]

Compound	IARC *Monograph* volume and page number
Actinomycins	**10**, *29*
ortho-Aminoazotoluene	**8**, *61*
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	**7**, *143*
Amitrole	**7**, *31*
Aramite	**5**, *39*
Azaserine	**10**, *73*
Benz(*a*)anthracene	**3**, *45*
Benzo(*b*)fluoranthene	**3**, *69*
Benzo(*a*)pyrene	**3**, *91*
Benzyl violet 4B	**16**, *153*
Beryllium and certain beryllium compounds[b]	**1**, *17*
BHC (technical grades)	**5**, *47*
ß-Butyrolactone	**11**, *225*
Cadmium and certain cadmium compounds[b]	**2**, *74* **11**, *39*
Calcium chromate	**2**, *100*
Carbon tetrachloride	**1**, *53*
Chlorambucil	**9**, *125*
Citrus Red No. 2	**8**, *101*
Cycasin	**1**, *157* **10**, *121*

Table 29 (continued)

Compound	IARC *Monograph* volume and page number
Daunomycin	**10**, *145*
N,N'-Diacetylbenzidine	**16**, *293*
4,4'-Diaminodiphenyl ether	**16**, *301*
2,4-Diaminotoluene	**16**, *83*
Dibenz(*a,h*)acridine	**3**, *247*
Dibenz(*a,j*)acridine	**3**, *254*
Dibenz(*a,h*)anthracene	**3**, *178*
7H-Dibenzo(*c,g*)carbazole	**3**, *260*
Dibenzo(*a,e*)pyrene	**3**, *201*
Dibenzo(*a,h*)pyrene	**3**, *207*
Dibenzo(*a,i*)pyrene	**3**, *215*
1,2-Dibromo-3-chloropropane	**15**, *139*
3,3'-Dichlorobenzidine	**4**, *49*
3,3'-Dichloro-4,4'-diaminodiphenyl ether	**16**, *309*
Diepoxybutane	**11**, *115*
1,2-Diethylhydrazine	**4**, *153*
Diethyl sulphate	**4**, *277*
Dihydrosafrole	**1**, *170*
	10, *233*
3,3'-Dimethoxybenzidine (*o*-Dianisidine)	**4**, *41*
para-Dimethylaminoazobenzene	**8**, *125*
trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	**7**, *147*
3,3'-Dimethylbenzidine (*o*-Tolidine)	**1**, *87*
Dimethylcarbamoyl chloride	**12**, *77*
1,1-Dimethylhydrazine	**4**, *137*
1,2-Dimethylhydrazine	**4**, *145*
Dimethyl sulphate	**4**, *271*
1,4-Dioxane	**11**, *247*
Ethinyloestradiol	**6**, *77*
Ethylene dibromide	**15**, *195*
Ethylenethiourea	**7**, *45*
Ethyl methanesulphonate	**7**, *245*
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	**7**, *151*
Glycidaldehyde	**11**, *175*
Hexamethylphosphoramide	**15**, *211*
Hydrazine	**4**, *127*
Indeno[1,2,3-*cd*]pyrene	**3**, *229*
Isosafrole	**1**, *169*
	10, *232*
Lasiocarpine	**10**, *281*
Lead acetate	**1**, *40*
Lead phosphate	**1**, *40*
Lead subacetate	**1**, *40*
Merphalan	**9**, *167*
2-Methylaziridine	**9**, *61*
Methylazoxymethanol acetate	**1**, *164*
	10, *131*
4,4'-Methylene bis(2-chloroaniline)	**4**, *65*
4,4'-Methylene bis(2-methylaniline)	**4**, *73*
Methyl iodide	**15**, *245*
Methyl methanesulphonate	**7**, *253*
N-Methyl-*N'*-nitro-*N*-nitrosoguanidine	**4**, *183*
Methylthiouracil	**7**, *53*
Mitomycin C	**10**, *171*

Table 29 (continued)

Compound	IARC *Monograph* volume and page number
Monocrotaline	**10**, *291*
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)-amino]-2-oxazolidinone	**7**, *161*
Nickel and certain nickel compounds[b]	**2**, *126* **11**, *75*
Niridazole	**13**, *123*
5-Nitroacenaphthene	**16**, *319*
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone	**7**, *181*
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	**1**, *181* **7**, *185*
Nitrogen mustard and its hydrochloride	**9**, *193*
Nitrogen mustard *N*-oxide and its hydrochloride	**9**, *209*
N-Nitrosodi-*n*-butylamine	**4**, *197* **17**, *51*
N-Nitrosodiethanolamine	**17**, *77*
N-Nitrosodiethylamine	**1**, *107* **17**, *83*
N-Nitrosodimethylamine	**1**, *95* **17**, *125*
N-Nitrosodi-*n*-propylamine	**17**, *177*
N-Nitroso-*N*-ethylurea	**1**, *135* **17**, *191*
N-Nitrosomethylethylamine	**17**, *221*
N-Nitroso-*N*-methylurea	**1**, *125* **17**, *227*
N-Nitroso-*N*-methylurethane	**4**, *211*
N-Nitrosomethylvinylamine	**17**, *257*
N-Nitrosomorpholine	**17**, *263*
N-Nitrosonornicotine	**17**, *281*
N-Nitrosopiperidine	**17**, *287*
N-Nitrosopyrrolidine	**17**, *313*
N-Nitrososarcosine	**17**, *327*
Oestradiol-17ß	**6**, *99*
Oestrone	**6**, *123*
Oil Orange SS	**8**, *165*
Polychlorinated biphenyls (PCBs)[b]	**7**, *261*
Ponceau MX	**8**, *189*
Ponceau 3R	**8**, *199*
1,3-Propane sultone	**4**, *253*
ß-Propiolactone	**4**, *259*
Propylthiouracil	**7**, *67*
Safrole	**1**, *169* **10**, *231*
Sterigmatocystin	**1**, *175* **10**, *245*
Streptozotocin	**4**, *221* **17**, *337*
Thioacetamide	**7**, *77*
Thiourea	**7**, *95*
Trypan blue (commercial grade)	**8**, *267*
Uracil mustard	**9**, *235*
Urethane	**7**, *111*

[a] Not including chemicals associated with cancer induction in humans (see Table 26).
[b] These groups of compounds have each been counted as one compound but, of course, include several chemicals.

Table 30. Members of the National Institute of Environmental Health Sciences/IARC Working Group on the Long-Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans, Lyon, France, 10-11 January 1978

Dr A.U. Arstila, Department of Cell Biology, University of Jyväskylä, Jyväskylä, Finland
Dr O. Axelson, Department of Occupational Medicine, University Hospital, Linköping, Sweden
Dr P.J. Baxter, Employment Medical Advisory Service, Health and Safety Executive, London
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Professor L. Jirasek, Charles University, 2 Clinic of Dermatology, Prague
Dr G. May, Bolsover, Derbyshire, UK
Dr J.A. Moore, Research Resources Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Dr G.F. Peruzzo, Commissario Straordinario, Uffici della Regione, Seveso (Milan), Italy
Professor F. Pocchiari, Istituto Superiore di Sanità, Rome
Dr A. Poland, McArdle Laboratory for Cancer Research, University of Wisconsin Medical Center, Madison, Wisconsin, USA
Professor C. Rappe, Department of Organic Chemistry, University of Umeå, Umeå, Sweden.
Dr V. Riihimäki, Department of Industrial Hygiene and Toxicology, Institute of Occupational Health, Helsinki
Professor I.J. Selikoff, Mount Sinai School of Medicine, Environmental Sciences Laboratory, New York City, N.Y., USA
Dr R.R. Suskind, Institute of Environmental Health, Kettering Laboratory, University of Cincinnati Medical Center, Cincinnati, Ohio, USA
Dr J.G. Vos, Department of Oncology, Laboratory of Pathology, National Institute of Public Health, Bilthoven, The Netherlands
Dr N. Wald, University of Oxford, Department of the Regius Professor of Medicine, Radcliffe Infirmary, Oxford, UK

(ii) *Correlation between the karyotypes of cancer cells and etiological factors*
Clinical Genetics, University Hospital of Lund, Sweden
Principal investigator: Dr F. Mitelman

This investigation will explore the possibility of relating chromosome patterns in experimental and human tumoural cells to specific etiological factors.

2.2 Survey of Chemicals being Tested for Carcinogenicity (Mrs M.-J. Ghess, Dr J. E. Huff and Dr H. Bartsch)

Due to the long duration and high costs involved in carcinogenicity testing, the Agency, together with the US National Cancer Institute, initiated in 1973 an international questionnaire survey of institutes involved in long-term testing of chemicals for carcinogenicity.

The objective of this project is to survey research in progress on long-term carcinogenicity testing throughout the world. The major aims are, in particular, to avoid unnecessary duplication of research, to increase communication among scientists, and to make a census of available research

facilities as well as of chemicals which are being tested. The collected data are collated, adding synonyms and Chemical Abstract Service Registry Numbers, and are made available in *Information Bulletins* to participating laboratories and to others upon request. The *Bulletins* list chemicals by investigation, animal species and strain, route of exposure, stage of experiments, principal investigators, and references to published reports of completed studies.

Survey results are arranged alphabetically by country, and within each country by city, and within each city by institute. For every institute that reports on long-term experiments, the chemicals being tested (natural and synthetic; pure, technical grades or product formulations; combinations and mixtures) are listed in alphabetical order.

(*a*) *Information Bulletin No. 7*

In February 1977 letters were sent to those 89 institutes that had reported in previous questionnaires; results of this fourth survey appears as *Information Bulletin* No. 7[16]. Data that appeared in *Information Bulletin* No. 6 were updated, with special attention paid to studies that have been completed, to publication of results and in verifying that studies mentioned previously had not been discontinued. Replies were often accompanied by publication reprints of completed studies, names of institutes carrying out long-term testing which were not listed in *Information Bulletin* No. 6, and routine updating of on-going, newly-started or discontinued research projects.

Information Bulletin No. 7 gives data received from 98 institutes in 20 countries on a total of 990 chemicals. Of the 905 projects from 70 countries listed in the IARC *Directory of On-going Research in Cancer Epidemiology 1977*[17], about 300 are wholly or partly concerned with 45 of the 990 chemicals or chemical substances listed in *Information Bulletin* No. 7. A total of 181 published reports on 180 chemicals are also given.

Of the 990 chemicals listed, 334 (34 %) have already been tested, as reported in the latest edition of the *Survey of Compounds Which Have Been Tested for Carcinogenicity*[18]. Thus, 656 (66 %) substances were apparently being tested for the first time.

Of the compounds undergoing long-term carcinogenicity testing, 180 (18 %) have been evaluated in the first 20 volumes of the *IARC Monographs* series. Fifteen of these chemicals or industrial processes have been associated with cancer induction in humans (see section 2.1, Table 26), and 55/180 (31 %) had sufficient evidence[19] of carcinogenicity in experimental animals (see Table 30). About 65 % (639/990) of the chemicals under test are currently being produced and used or are known to occur naturally, whereas 35 % (351/990) are mainly compounds of laboratory interest only. The major use categories[20] of the 990 chemicals listed in *Information Bulletin* No. 7 are given in Table 31 (compare with Table 27).

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[16] Ghess, M.-J., Bartsch, H., Huff, J. E. & Tomatis, L., eds (1978) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*, No. 7, Lyon, 1978.

[17] Muir, C. S. & Wagner, G., eds (1977) *Directory of On-going Research in Cancer Epidemiology 1977*, Lyon *(IARC Scientific Publications No. 17)*.

[18] Carcinogenesis Program National Cancer Institute (1976) *Public Health Service Publication No. 149: 1972–1973*, Washington, DC, US Government Printing Office.

[19] International Agency for Research on Cancer (1978) *IARC intern. tech. Rep.* No. 78/003, Lyon.

[20] Uses of the chemicals were verified using the following sources:

Windholz, M., ed.(1976) *The Merck Index*, 9th ed., Rahway, N. J., Merck & Co., Inc.; Gosselin, R. E., Hodge, H. C., Smith, R. P. & Gleason, M. N. (1976) *Clinical Toxicology of Commercial Products*, 4th ed., Baltimore, Williams & Wilkins Co.; Blacow, N. W., ed. (1972) *Martindale, The Extra Pharmacopoeia*, 26th ed., London, The Pharmaceutical Press; Chemical Information Services, Stanford Research Institue (1976) *1976 Directory of Chemical Producers, United States of America*, Menlo Park, California.

Table 31. Major use categories for chemicals in *Information Bulletin* No. 7 on the *Survey of Chemicals Being Tested for Carcinogenicity*

Rank order	Use category	Number of chemicals[a]
1	No known use and/or production data were found[b]	351
2	Pharmaceutical preparations and/or veterinary drugs	201
3	Industrial chemicals	105
4	Agricultural chemicals and pesticides	85
5	Naturally-occurring substances	79
6	Chemical intermediates	67
7	Chemicals produced but use unknown	66
8	Food and feed additives, flavours and packaging materials	59
9	Cosmetics and perfumes	39
10	Dyes, pigments and printing inks	38
11	Solvents	34
12	Used in the manufacture of plastics and/or rubber	30
13	Minerals and natural fibres	19
14	Contaminants and/or impurities	7
	TOTAL	1180

[a] Certain chemicals fit into more than one use category.
[b] These comprise analogues or derivatives of known carcinogens, potential anticancer drugs, nitrosation products of drugs and other chemicals, and combinations of chemicals with additive or modifying effects.

(*b*) Bulletin *users' form*

A users' form in *Information Bulletin* No. 7 contained a series of multiple-choice questions: the answers to these will influence the development of subsequent *Information Bulletins*. Basically, the survey evaluation consisted of two parts: one involved the overall value and usefulness of the *Bulletins;* the other was a proposal of a series of new data elements with a request that respondents indicate not only whether these entries would be useful but also if they would be willing to supply the requested information. Approximately 75% (165/229) of the *Bulletin* recipients have responded to the survey and to follow-up letters that were posted to all those who did not answer the initial request. The *Information Bulletins* are used regularly, once or twice a month, by all those who returned the evaluation forms, and they have used the information in various ways. Most would like to see more information in the future. The three additions considered most useful for inclusion in the next *Bulletin* are numbers of animals, dose levels and schedules and uses of chemicals. For example, 106 got in touch with other investigators, 64 contacted other institutes, 30 added new chemicals for test, and 36 eliminated chemicals scheduled for test. More than one-half (119/229) wanted a cumulative index of chemicals listed in *Information Bulletins 1–7.*

(*c*) *Future plans*

The survey questionnaire for *Information Bulletin* No. 8 will be posted in October/November 1978 to all previous participants as well as to any newly identified investigators/institutes doing long-term chemical carcinogenicity testing.

From January 1979, all of the questionnaire survey data received from the autumn 1978 mailing will be compiled into *Information Bulletin* No. 8, which will be finalized and distributed during Spring 1979.

2.3 *Carcinogenicity testing*

(*a*) *Aziridine*
Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow
Principal Investigator: Dr V. S. Turusov

Aziridine (ethylenimine) is being tested in rats. This compound can be polymerized to polyethylenimine, a flocculant used in water treatment.

(*b*) *5-Bromodeoxyuridine* (Dr A. Likhachev, Dr V. Ponomarkow)

5-Bromodeoxyuridine was given intraperitoneally to BD-IV rats on days 1, 3, 7 and 21 after birth. Even though the average lifespan was shortened considerably, some preneoplastic lesions were observed in the pancreas and in the kidney. Follow-up experiments have been initiated.

(*c*) *Chloroethylene oxide and 2-chloroacetaldehyde*
National Institute of Health and Medical Research, Orsay, France
Principal investigator: Professor F. Zadjela

In mice, repeated subcutaneous administration of chloroethylene oxide, an ultimate metabolite of vinyl chloride, induced local tumours with a frequency comparable to that of bis(chloromethyl)ether when both compounds were tested at maximal tolerated toxic doses. These two compounds and 2-chloroacetaldehyde were also tested in an initiation-promotion experiment by skin painting in mice. Chloroethylene oxide was the most active compound in producing skin tumours, while 2-chloroacetaldehyde was inactive. The data are being assembled for publication.

(*d*) *Chloroprene (2-chlorobutadiene)* (Dr V. Ponomarkov)

Chloroprene was administered orally to BD-IV rats at weekly doses of 50 mg/kg body weight (bw). Several tumours were observed in treated animals, but not in controls; the total tumour incidence was, however, not statistically different.

(*e*) *Magenta and* para-*rosaniline*
School of Medicine, Hanover, Federal Republic of Germany
Principal investigator: Professor U. Mohr

Syrian golden hamsters and Sprague-Dawley rats were given oral doses of either commercial magenta or *para*-rosaniline twice a week for lifespan. All animals have died or were killed. Histological evaluation is in progress.

(*f*) *Maleic hydrazide* (Dr V. Ponomarkov)

(i) Maleic hydrazide was given to groups of C57BL mice either subcutaneously (in tricaprylin) on days 1, 7, 14 and 21 after birth at a total dose of 55 mg or orally (in olive oil) at a weekly dose of 510 mg/kg bw. Both experiments are completed. Histological evaluation is in progress.

(ii) *National Institute of Public Health, Bilthoven, The Netherlands*
Principal investigator: Dr G. van Esch

Maleic hydrazide did not result in an increased incidence of tumours in treated as compared with untreated control rats. The results are being evaluated and prepared for publication.

(*g*) *Pesticides and drugs*
National Institutes of Public Health, Budapest
Principal investigator: Dr M. Börzönyi

Benlate (butylcarbamoylmethyl-2-benzimidazol carbamate) and carbendazim (methyl-2-benzimidazol carbamate) alone were non-carcinogenic, but in combination with sodium nitrite they produced mainly lymphoid tumours[21, 22], when given either to adult Swiss mice or administered transplacentally. Dodine (*N*-dodecyl guanidine acetate) was nitrosated both *in vitro* and *in vivo* and when administered with sodium nitrite caused various tumours in the offspring[23, 24]. Long-term carcinogenicity testing of other carbamate pesticides, Ficam (2, 2-1, 3-benzodioxol-4yl-*N*-methyl carbamate) and Formetanate (3-dimethylaminomethyleneiminophenyl-*N*-methyl carbamate), are still in progress. The nitrosation of the fungicide Triforine (*N*,*N*'-1,4-piperazine-diyl-bis-2,2,2-trichloroethylidene-bis-formamide) yields 1,4-dinitrosopiperazine. Various tumours arose in Swiss mice treated simultaneously with Triforine and sodium nitrite[25].

Pyridinol carbamate [2,6-pyridinedimethanol bis (*N*-methylcarbamate)], an anti-inflammatory, anti-arteriosclerotic drug, can be nitrosated, and its nitroso derivative was strongly mutagenic in *Salmonella typhimurium* strains TA 1535 and TA 100[26, 27]. Long-term tests are in progress.

(*h*) N-*Phenyl-2-naphthylamine*
School of Medicine, Hanover, Federal Republic of Germany
Principal investigator: Professor U. Mohr

Syrian golden hamsters and Sprague–Dawley rats are given oral doses of *N*-phenyl-2-naphthylamine twice a week for lifespan. The experiment in hamsters is completed, and histological evaluation is in progress. The study in rats is still underway.

(*i*) *Styrene* (Dr V. Ponomarkov)

Styrene monomer in olive oil was given orally to female 0_{20} mice, C57BL mice and BD-IV rats on the 17th day of gestation. Offspring were treated weekly with styrene by stomach tube from weaning. After 100 weeks, an increased and earlier appearance of lung tumours was observed in O_{20} mice. A few tumours rarely seen in controls were observed in BD-IV styrene-treated rats, and a slightly increased incidence of liver tumours was found in C57BL mice. The results provide weak evidence for the carcinogenicity of styrene in O_{20} mice[28].

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[21] Börzsönyi, M. & Pintér, A. (1977) *Neoplasma*, **24**, 119–122.
[22] Surján, A., Börzsönyi, M., Nádasdi, L., Pintér, A. & Csik, M. (1977) *Egészségtudomány*, **21**, 69–75.
[23] Börzsönyi, M., Pintér, A., Surján, A., Török, G. & Sajgó, M. (1977) *Magy. Onkol.*, **21**, 197–206.
[24] Börzsönyi, M., Pintér, A., Nádasdi, L. & Török, G. (1978) *Cancer Lett.* (in press).
[25] Börzsönyi, M., Pintér, A., Török, G., Surján, A. & Nádasdi, L. (1978) In: Walker, E. A., Castegnaro, M., Griciute, L. & Lyle, R. E., eds, *Environmental Aspects of* N-*Nitroso Compounds*, Lyon, *(IARC Scientific Publications No. 19)*, pp. 477–484.
[26] Börzsönyi, M., Ferencz, A., Pintér, A., Nádasdi, L., Kiss, K. & Török, G. (1978) *Int. J. Cancer* (in press).
[27] Ferencz, A., Börzsönyi, M., Pintér, A., Török, G., Nádasdi, L. & Kiss, K. (1978) *Egészségtudomány* (in press).
[28] Ponomarkov, V. & Tomatis, L. (1978) *Scand. J. Work Environ. Health* (in press).

(*j*) *Styrene oxide* (Dr V. Ponomarkov)

Styrene oxide was given orally to O_{20} mice at weekly doses of 600 mg/kg bw. The total incidence of tumours was similar in treated and control O_{20} mice. BD-IV rats were given styrene oxide orally at weekly doses of 100 mg/kg bw. This latter experiment is still in progress.

(*k*) *Vinylidene chloride* (Dr V. Ponomarkov)

Vinylidene chloride (VDC) was given orally to C57BL mice and BD-IV rats at weekly doses of 70 mg/kg bw and 150 mg/kg bw. In mice, the incidence of liver and stomach tumours was increased slightly. In rats, both sexes exhibited small increases in the number of tumours at various sites. However, there was no statistically significant increase in the total number of tumour-bearing animals[29].

3. EVALUATION OF THE SIGNIFICANCE FOR HUMANS OF DATA ON EXPERIMENTAL CHEMICAL CARCINOGENESIS AND THE DEVELOPMENT OF RAPID SCREENING TESTS

3.1 *DNA-repair studies and metabolism of carcinogens*

(*a*) *The role of DNA-repair processes in the carcinogenicity of alkylating agents* (Dr R. Montesano, Dr G. Bannikov, Miss C. Bordet, Miss H. Brésil, Miss G. Planche, in collaboration with Dr G. Margison, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK; Dr A. E. Pegg, The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA, USA; Dr A. J. Likhachev, Professor N. N. Petrov Research Institute of Oncology, Leningrad, USSR; and Dr M. Leng, Centre for Molecular Biophysics, National Centre for Scientific Research, Orléans, France)

(i) *DNA-excision repair capacity of hamster liver*

There is an inverse relationship between the susceptibility of certain organs to the carcinogenic effects of alkylating agents and their capacity to remove some alkylation products, like O^6-alkylguanine, from DNA. This inverse relationship results from the tissue-variable activity of the enzyme(s) responsible for the removal of alkylation damage from DNA.

Although it would not exclude a possible role for RNA alkylation in the process of carcinogenesis, the absence of such excision processes for RNA alkylation products would provide indirect support for the hypothesis that DNA products and their repair play a significant role in the induction of tumours by alkylating agents.

Levels of certain base alkylation products have been measured in Syrian hamster liver rRNA at various times after administration of *N*-nitrosodimethylamine (NDMA) in order to determine whether there is any evidence that such damage might be actively removed, as has been observed for DNA[30]. The amounts of 7-methylguanine, 3-methylcytosine, O^6-methylguanosine and 1-

[29] Ponomarkov, V. & Tomatis, L. (submitted for publication).
[30] Margison, G. P., Margison, J. M. & Montesano, R. (1976) *Biochem. J.*, **157**, 627–634.

methyladenosine in hamster liver DNA were measured over four days after administration of a high and low dose (25 and 2.5 mg/kg bw) of NDMA.

The results show that the relative amounts of these alkylation products are constant with time and dose. The loss of alkylated bases from liver rRNA can be attributed to two factors, (a) cell death and a consequently increased catabolism due to the hepatotoxicity of DMN, and (b) normal rRNA turnover[31]. In addition, as shown in Fig. 10, whereas no changes were observed in the O^6-methylguanine: 7-methylguanine ratio in the rRNA over a period of 96 hours, in the DNA this ratio increased considerably as a consequence of enzymic excision involving various DNA aklylated bases[30].

These results suggest that, in contrast to the observation in liver DNA of the same animal species, there is a lack of specific excision of alkylated bases from rRNA.

In another study[32], the formation and persistence of alkylation products in DNA of hamster liver have been observed after various doses of NDMA (0.01 to 20 mg/kg bw). The results show that the initial degree of alkylation was proportional to the dose administered, and the removal of O^6-methylguanine from DNA occurs only when the initial extent of methylation is low. In fact, little decline in the O^6-methylguanine level was observed after doses of NDMA greater than 0.75-1 mg, indicating that the enzyme(s) responsible for its removal is either saturated or inhibited at these dose levels.

(ii) *Effects of chronic exposure to NDMA on the DNA-excision repair processes in rat liver*

Since the induction of tumours is more frequently the result of a chronic exposure to carcinogens, and in view of the importance of DNA repair in the carcinogenesis process, the effects of chronic administration of NDMA on the various alkylation products in DNA were examined[33].

Table 32 shows the amounts of 7-methylguanine, 3-methyladenine and O^6-methylguanine in liver DNA at various times after administration of ^{14}C-NDMA (2 mg/kg) to normal rats or to rats that had been pretreated for a total of 44 days with the unlabelled carcinogen. As expected, the greatest extent of purine alkylation was in the 7-position of guanine; the amounts of this alkylated base present at different times after administration of NDMA showed some variation in both pretreated and control rats, but the overall levels were generally slightly higher in the pretreated animals.

Detectable amounts of 3-methyladenine were also present in the DNA samples, and after two hours this base initially constituted about 4% of the alkylation at the 7-position of guanine in both control and pretreated groups; but, again, the levels in the pretreated animals were generally slightly higher than in the control animals. By twelve hours, approximately 30 and 40 % of the initial amounts of 3-methyladenine had been lost from DNA in pretreated and control rats, respectively (Table 32). Thus, while the amounts of 7-methylguanine and 3-methyladenine were higher in the liver DNA of pretreated animals, no major differences were observed in the persistence of these alkylation products in control rats and in rats pretreated with multiple doses of NDMA.

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[31] Margison, G. P., Margison, J. M. & Montesano, R. (1978) *Biochem. J.* (in press).

[32] Stumpf, R., Margison, G. P., Montesano, R. & Pegg, A. E. (1978) *Cancer Res.* (in press).

[33] Montesano, R., Brésil, H. & Margison, G. P. Increased excision of O^6-methyl guanine from rat liver DNA after chronic administration of dimethyl-nitrosamine (submitted for publication).

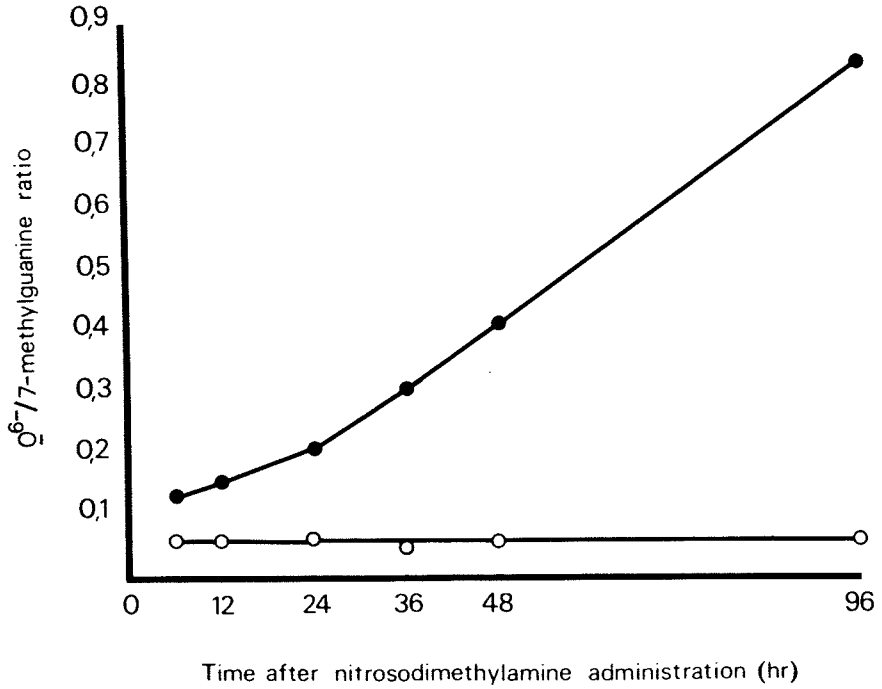

Fig. 10 O^6-Methylguanine: 7-methylguanine ratios in hamster liver nucleic acids at various times after administration of [^{14}C]-nitrosodimethylamine (25 mg/kg; 3.17 mCi/mmol). ● = DNA (taken from Margison, G. P., Margison, J. M. & Montesano R. (1976) *Biochem. J., 157,* 627-634); ○ = RNA (present results)

The situation appeared to be different in the case of O^6-methylguanine. In the control group, the initial value of O^6-methylguanine was approximately three times higher than that in the rats pretreated with NDMA. Although some variation in the levels of this product was also observed, there was a generally more pronounced and rapid reduction in the amounts in the pretreated animals. The difference between the two groups increased with time, and by twelve hours the level of O^6-methylguanine in the liver DNA of pretreated animals was about one-fifth of that of the control animals.

Table 32. Alkylated purines in liver DNA at various times following administration of ^{14}C-*N*-nitrosodimethylamine (2 mg/kg; 5.18 mCi/mmol) to control rats or to rats treated with *N*-nitrosodimethylamine (2 mg/kg daily on weekdays for a total of 44 days)

Time (h)	Radioactivity (dpm/μmol parent base)					
	7-Methylguanine		3-Methyladenine		O^6-Methylguanine	
	Pretreated	Control	Pretreated	Control	Pretreated	Control
2	4395	4325	194	204	138	381
4	5756	4565	190	151	151	410
5	5599	4420	142	127	114	385
6	4946	3519	138	97	98	309
8	5023	4574	93	88	75	374
10	4030	3974	85	70	52	334
12	4875	3667	76	63	67	282

Thus, the chronic administration of low doses of NDMA specifically increases the capacity of the liver to excise O^6-methylguanine from DNA. Studies are underway on the effects of chronic administration of different doses of NDMA, and of the effect of such pretreatments on the rate of DNA synthesis in the liver.

(iii) *Preparation of antibodies to alkylation adducts of nucleic acids*

Studies have been initiated, in collaboration with Dr M. Leng, on the preparation of antibodies which may specifically recognize alkylated bases or nucleosides present in nucleic acids. Antibodies are produced following the immunization of rabbits with protein-nucleoside conjugates[34]. Preliminary results indicate that specific antibodies for the detection of alkylated products in nucleic acids have been obtained.

(*b*) *Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced in rodent or human liver tissues; evidence for oxirane formation by P450-linked microsomal mono-oxygenases* (Dr H. Bartsch, Mr C. Malaveille, Mr A. Barbin, Miss G. Planche)

Since the recognition of vinyl chloride as a human carcinogen, there has been concern about a number of halogen-substituted ethylenes, butadienes and butenes, which are produced in large amounts throughout the world and which have the common structural element of an olefinic double bond(s); these compounds could undergo oxidative metabolism in mammals to yield oxiranes as potentially reactive, mutagenic or carcinogenic intermediates, and for some of which there is a notable lack of carcinogenicity data. The mutagenic and alkylating properties of several such halo-olefins (Fig. 11) and their metabolites, which are released in the presence of rodent and human liver fractions, have been investigated[35]. The mutagenicity (expressed as the number of revertants per μmole of the test compound per hour of exposure) was estimated in *Salmonella typhimurium* TA100 in the presence of a post-mitochondrial mouse liver supernatant by exposure to vapour from one of the following olefins (activity in descending order): 3,4-dichlorobutene-1 > 1-chloro-1,3-butadiene (technical grade) > 2-chloro-1,3-butadiene > vinyl bromide > vinylidene chloride > vinyl chloride. Marginal mutagenicity was detected in the presence of trichloroethylene and 1,1-difluoroethylene, and none with tetrachloroethylene or vinyl acetate. In the plate incorporation assay, 1,4-dichlorobutene-2 was mutagenic *per se*, and the addition of microsomal fraction from human or mouse liver enhanced the mutagenicity.

As an approach to elucidating mechanisms by which vinyl chloride and vinylidene chloride exert their biological activity, we have investigated the effect of pretreating rats with modifiers of hepatic microsomal mono-oxygenases, such as phenobarbital, pregnenolone-16α-carbonitrile, aminoacetonitrile and 3-methylcholanthrene. The resulting increase or decrease in liver microsome-mediated mutagenicity in the presence of these chloroethylenes was compared with reported changes in *in vivo* metabolism and/or toxic responses of these treated animals. Different drug treatments caused very similar changes in liver microsome-mediated mutagenicity in rats, suggesting that similar types of P450-dependent mono-oxygenases catalyse the formation of

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[34] Erlanger, B. F. & Beiser, S. M. (1964) *Proc. natl Acad. Sci. (USA)*, **52**, 68–74.

[35] Bartsch, H., Malaveille, C., Barbin, A. & Planche, G. Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced in rodent or human liver tissues; evidence for oxirane formation by P450-linked microsomal mono-oxygenases (submitted for publication).

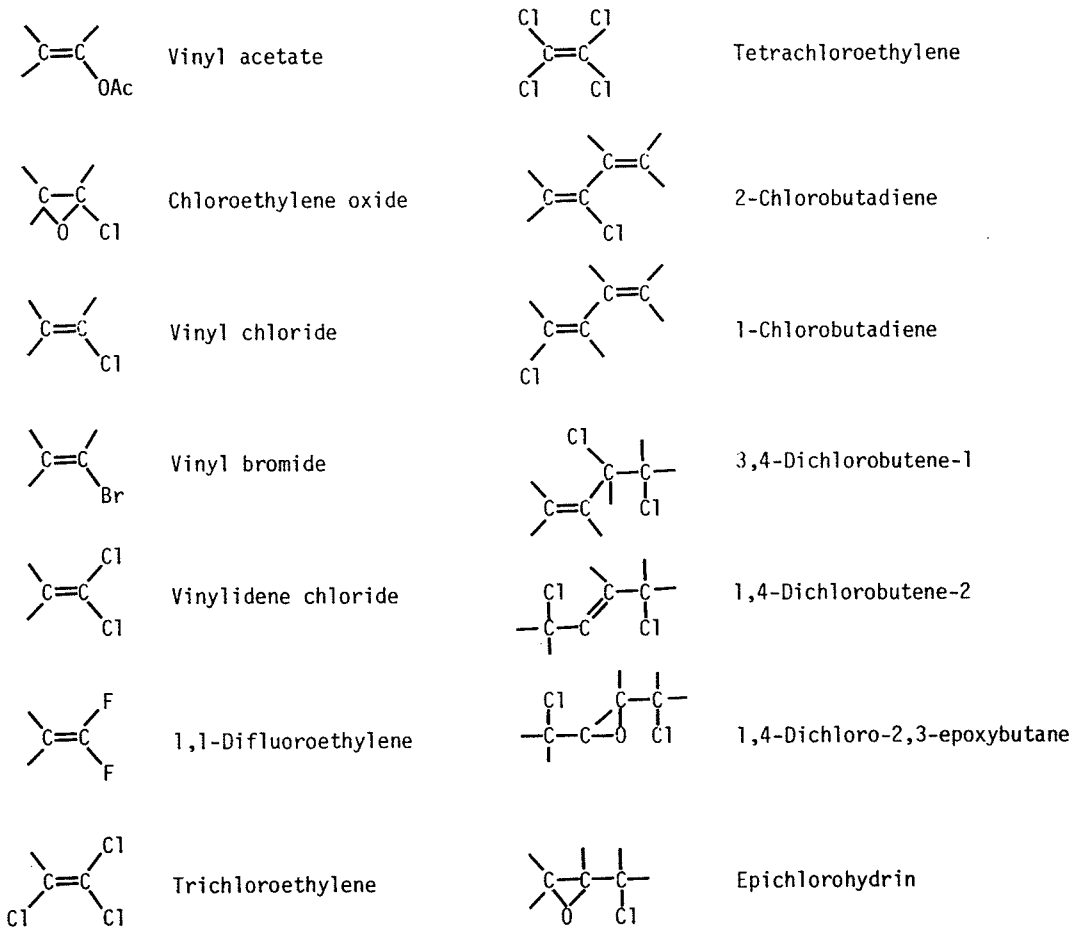

Fig. 11 Chemical structures of halo-ethylenes, chlorobutadienes, dichlorobutenes and related epoxides

mutagenic oxiranes from vinyl chloride and vinylidene chloride. An epoxidation of vinyl chloride, and probably of vinyl bromide, by mouse liver microsomes has been demonstrated previously[36]. These data support the theory of a microsome-dependent oxidation of the double-bond in certain halo-olefins and indicate a common pathway to biologically reactive intermediates.

Good correspondence between mutagenic activity and capacity to induce tumours in animals was observed for most of the halo-olefins or related epoxides tested (Fig. 10): vinyl acetate, which was not mutagenic, does not produce tumours in rats[37]; wehreas the carcinogenic compounds, vinyl chloride, vinylidene chloride, trichloroethylene and 1,4-dichlorobutene-2 or epichlorohydrin, were all detected as mutagens. As an exception, tetrachloroethylene, which produced hepatocellular carcinomas in mice[38], was not found to be mutagenic.

The mouse- and human-liver-microsome-mediated mutagenicity of vinyl bromide and 2-chlorobutadiene indicates their potential carcinogenicity. Although they varied widely in their activity, 1,1-difluoroethylene, 1-chlorobutadiene and 3,4-dichlorobutene-1 were mutagenic; this emphasizes the need for further testing in animals, if human exposure exists.

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

[37] International Agency for Research on Cancer (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, **18**, *Polychlorinated Biphenyls and Polybrominated Biphenyls*, Lyon.

[38] National Cancer Institute (1977) *Carcinog. tech. Rep. Ser.*, **No. 13.**

(*c*) *Metabolic and mutagenicity studies on DDT and 15 of its derivatives* (Miss G. Planche, Mr C. Malaveille, Dr H. Bartsch, in collaboration with A. Croisy, Institute of Chemistry of Natural Substances, Gif-sur-Yvette, France)

The systemic carcinogenic action of dichlorodiphenyltrichloroethane (DDT) and of some its metabolites in inducing tumours only in specific organs of experimental animals suggests that these compounds require metabolic conversion. Using bacterial mutagenicity assays as a method of indicating the possible ultimate reactive form(s) of DDT, 15 identified mammalian metabolites or putative intermediates were tested for their reactivity towards bacterial DNA[39]. Two compounds were found to be mutagenic: in the presence of mouse liver microsomes, 1,1-dichloro-2, 2-bis(*para*-chlorophenyl)ethane (DDD) increased the number of revertants in *Salmonella typhimurium* TA98 strain, and a synthetic acetylated derivative of 1,1-bis(*para*-chlorophenyl)-2,2,2-trichloroethanol (Kelthane: a urinary metabolite in DDT-treated mice) was a direct-acting mutagen in TA100. Synthetic 1,1-bis(*para*-chlorophenyl)ethylene oxide, a probable DDT metabolite, showed alkylating activity toward 4-(4-nitrobenzyl)pyridine, but was not detected as a mutagen. These studies strongly imply the formation of reactive DDT intermediates *in vivo*, which can bind covalently to nucleophilic sites. This supports the proposal that the carcinogenic effect of DDT in rodents may be caused by covalent interaction of its metabolites with cellular macromolecules in target organs, a mechanism which has been demonstrated for other classes of carcinogens.

(*d*) *Mutagenicity of* N-*(α-acetoxy)alkyl*-N-*alkylnitrosamines: model compounds for metabolically activated* N-*nitrosamines* (Miss A. M. Camus, Mr C. Malaveille, Dr H. Bartsch, in collaboration with Dr M. Wiessler, German Research Center Institute for Toxicology and Chemotherapy, Heidelberg, Federal Republic of Germany)

A series of *N*, *N*-dialkylnitrosamines ('alkyl' means an ethyl, methyl and propyl, *n*-butyl or *tert*-butyl group mono-substituted at the α-carbon with an acetoxy group) were tested for mutagenicity in *Salmonella typhimurium* in the presence or absence of a rat liver preparation[40]. The presumed release of methyl, ethyl, *n*-butyl and *n*-propyl carbonium ions from the corresponding α-acetoxy derivatives caused high mutagenicity in bacteria. The results strongly support the hypothesis that α-carbon hydroxylation is a major pathway in the formation of alkylating metabolites from *N*,*N*-dialkylnitrosamines.

(*e*) *Studies on the correlation between microsome-mediated mutagenicities of the 3,4-dihydrodiols of benz(*a*)anthracene, 7-methylbenz(*a*)anthracene and 7, 12-dimethylbenz(*a*)anthracene and the carcinogenic activity of the parent hydrocarbons* (Mr C. Malaveille, Dr H. Bartsch, Mrs G. Brun, Mrs A. Hautefeuille, in collaboration with Dr P. L. Grover and Dr P. Sims, Chester Beatty Research Institute of Cancer Research, The Royal Cancer Hospital, London)

Tissue-mediated mutagenicity tests with *Salmonella typhimurium* strains have been used in studies of the mechanisms of metabolic activation of polycyclic aromatic hydrocarbons to

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[39] Planche, G., Croisy, A., Malaveille, C., Tomatis, L. & Bartsch, H. Metabolic and mutagenicity studies on DDT and 15 derivatives. Detection of the 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethane (DDD) and 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethyl acetate (Kelthane acetate) as mutagens in *S. typhimurium* and of 1,1-bis(*p*-chlorophenyl)ethylene oxide (DDNU-oxide), a likely metabolite, as an alkylating agent (submitted for publication).

[40] Camus, A. M., Wiessler, M., Malaveille, C. & Bartsch, H. (1978) *Mutat. Res.*, **49**, 187–194.

pin-point which particular dihydrodiol derivatives are biological precursors of vicinal diol-epoxides[41]. The results obtained with a series of dihydrodiols derived from 7,12-dimethylbenz(*a*)anthracene strongly support the hypothesis that one or both of the isomeric forms of 3,4-dihydrodiol-1,2-epoxide may be a biologically important metabolite of the parent hydrocarbon *in vivo*[42]. The results of two series of experiments are given in Table 33, in which attempts have been made to compare the mutagenic activities of benz(*a*)anthracene, 7-methylbenz(*a*)anthracene and 7,12-dimethylbenz(*a*)anthracene and their 3,4-dihydrodiols, using a hepatic microsomal fraction from rats pretreated with 3-methylcholanthrene as the activating system[43]. The results indicate that mutagenic activities of the 3,4-dihydro-derivatives were in the order: 7,12-dimethylbenz(*a*)anthracene > 7,12-benz(*a*)anthracene > benz(*a*)anthracene, whereas the mutagenic activities of the hydrocarbons were in the order: benz(*a*)anthracene > 7-methylbenz-(*a*)anthracene > 7,12-dimethylbenz(*a*)anthracene. There was a statistically significant positive correlation between the carcinogenic activity of the hydrocarbons, as measured by the Iball indices, and the mutagenicity of the dihydrodiols, but no good correlation between the carcinogenicity indices and mutagenicities of the parent hydrocarbons. A positive correlation between the binding indices of the three hydrocarbons to cellular DNA of mouse embryo cells (for definition, see footnote *b* to Table 33) and the mutagenicities of the 3,4-dihydrodiols, but not those of the parent hydrocarbons, was also observed. These data suggest that the rate of formation of 3,4-dihydrodiol-1,2-oxides from their precursor diols may determine the extent of DNA binding and the cell-mediated mutagenicity of mammalian cells as well as the carcinogenic activities of benz(*a*)anthracene, 7-methylbenz(*a*)anthracene and 7,12-dimethylbenz(*a*)anthracene.

(*f*) *Carcinogen metabolism by human tissue specimens* (Mrs N. Sabadie, Dr H. Bartsch, Mr C. Malaveille, Miss A. M. Camus, Mrs G. Brun, in collaboration with Dr H. B. Richter-Reichhelm and Professor U. Mohr, School of Medicine and Professor W. Schindler, Lung Clinic, Hanover, Federal Republic of Germany; and Dr A. H. Conney, Department of Biochemistry and Drug Metabolism, Hoffmann-Laroche, Nutley, NJ, USA)

To facilitate the extrapolation of animal data to man, species differences in pathways or in rates of carcinogen metabolism and the magnitude of inter-individual variations are being investigated in liver and lung surgical samples from human subjects. The enzymic capacities of animal or human target tissues to convert several carcinogens into electrophiles were measured *in vitro* using tissue-mediated mutagenicity assays with *Salmonella typhimurium* strains and determination of the specific enzyme activities which are known to be involved in the activation of certain aromatic amines and polycyclic aromatic hydrocarbons. Liver fractions from different human subjects were shown to convert 1,4-dichlorobutene-2, 2-chlorobutadiene-1,3, vinylidene chloride, vinyl bromide and vinyl chloride into mutagens (Fig. 12a), and to convert several cyclic *N*-nitroso compounds (Fig. 12b) into alkylating and mutagenic intermediates. Although large inter-individual variations were observed, the average activity was generally similar to that of mouse or rat liver fractions. However, with *N*-nitroso-*N*'-methylpiperazine, human samples were

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[41] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 102.

[42] Malaveille, C., Bartsch, H., Tierney, B., Grover, P. L. & Sims, P. (1978) *Biochem. biophys. Res. Common.* (in press).

[43] Malaveille, C., Bartsch, H., Tierney, B., Grover, P. L. & Sims, P. (1978) *Abstract, 7th International Congress of Pharmacology, Paris, 1978.*

Table 33. Comparisons of the carcinogenicities of benz[*a*]anthracene, 7-methylbenz[*a*]anthracene and 7,12-dimethylbenz[*a*]anthracene, their binding indices and the mutagenicities of the hydrocarbons and of their 3,4-dihydrodiols

Hydrocarbons	Binding index[a]	Carcinogenicity index[b]	Mutagenicity[c] (revertants/nmol)	
			of hydrocarbons	of 3,4-dihydrodiols
Benz[*a*]anthracene	0.8	5	6	8.5
7-Methylbenz[*a*]-anthracene	16	45	5	33
7,12-Dimethylbenz-[*a*]anthracene	170	95	2.4	80

[a] Binding index is the extent of covalent reaction with DNA of cultured mouse embryo cells (μmol/mol phosphorus) divided by nmol hydrocarbon metabolized per ml of medium (from Duncan, M., Brookes, P. & Dipple, A. (1969) *Int. J. Cancer*, **4**, 813-819).

[b] Carcinogenicity index, taken from Arcos, J.C. & Argus, M.F. (1968) *Adv. Cancer Res.*, **11**, 305-471, corresponds to the average of the Iball indices for sarcoma, epithelioma and papilloma formation in mice.

[c] Mutagenicity data are taken from the slopes of the linear regions of dose-response curves.

up to 40 times more active (Fig. 12b); with aflatoxin B_1, the average activity was less than one-tenth that of rat liver (data not shown).

When hepatic benzo(α)pyrene hydroxylase activity in several samples from different human subjects was plotted against their respective liver microsome-mediated mutagenicity, a statistically significant positive correlation was obtained between the rates of oxidative benzo(α)pyrene metabolism and mutagenicity in the presence of *N*-nitrosomorpholine, *N*-nitroso-*N*'-methylpiperazine or vinyl chloride as substrate[44]. This correlation may be significant for developing methods to evaluate the drug and carcinogen metabolizing capacities of different individuals. Benzo(α)pyrene hydroxylase activity was therefore also measured in normal and neoplastic lung tissue from more than 70 patients[45]. A 60-fold inter-individual variation was noted, and in most cases the rate of benzo(α)pyrene hydroxylation in tumourous lung tissue was lower than in normal tissue from the same patient. When benzo(α)pyrene hydroxylase activity in the tumourous tissue (expressed as % activity of the normal tissue of the same patient) was plotted *versus* the number of cigarettes smoked prior to surgery, a negative correlation was obtained. These interim results suggest that differences in carcinogen metabolism may in part condition the response of individuals exposed to the same level of environmental carcinogens.

3.2 *Chemical carcinogenesis and mutagenesis in cultured cells*

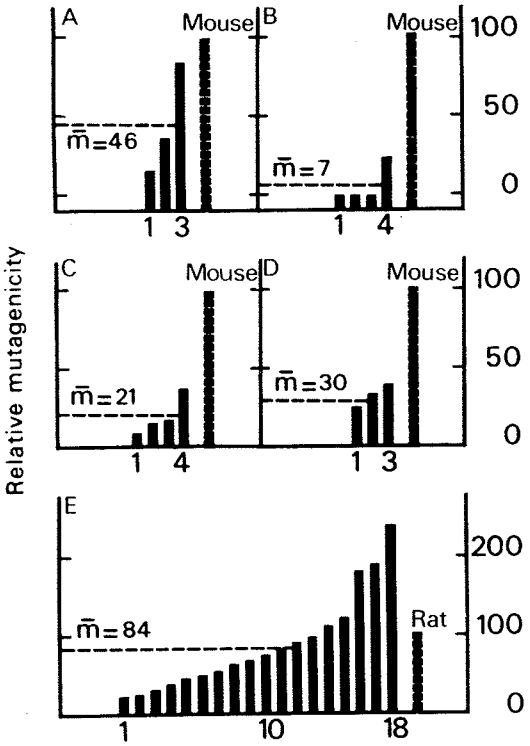
(*a*) *Rat liver epithelial cells* (Dr R. Montesano, Dr T. Kuroki, Dr G. Bannikov, Miss C. Drevon, Mrs L. Saint-Vincent, in collaboration with Dr E. Huberman, Oak Ridge National Laboratory, Oak Ridge, TN, USA and Dr F. Mitelman, University Hospital, Lund, Sweden)

Studies of neoplastic transformation *in vitro* have been carried out mostly with cultures of mesenchymal cells; the question has been raised as to the extent to which these studies are also

[44] Sabadie, N., Malaveille, C., Camus, A. M. & Bartsch, H. Vinyl chloride, *N*-nitrosomorpholine and *N*-nitroso-*N*'-methylpiperazine mutagenicity associated with benzo(*a*)-pyrene hydroxylase activity in human and rat liver *in vitro* (submitted for publication).

[45] Sabadie, N., Bartsch, H., Richter-Reichhelm, H. B., Schindler, W. & Mohr, U. (1978) *Abstract, 7th International Congress of Pharmacology, Paris, 1978.*

a.



b.

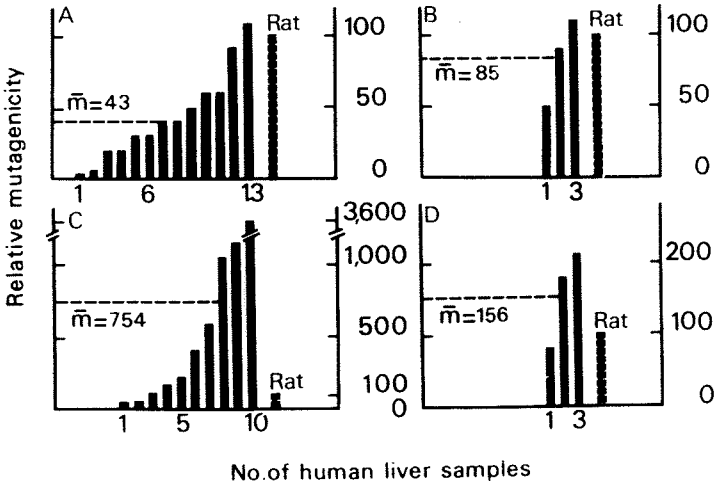


Fig. 12 Relative mutagenicities in *S. typhimurium* of halo-olefins (a) and *N*-nitrosamines (b), as mediated by human liver fractions. Mutagenicity of *N*-nitrosamines was measured in plate incorporation assays and that of halo-olefins by exposure to gaseous mixture in air, in the presence of liver fractions from different human subjects (surgical specimens) or from untreated mice or rodents. Mutagenicity in the presence of rodent liver is given as 100%

a: A = 1,4-dichlorobutene-2; B = 2-chlorobutadiene-1,3; C = vinylidene chloride; D = vinyl bromide; E = vinyl chloride

b: A = *N*-nitrosomorpholine; B = *N*-nitrosopyrrolidine; C = 1-methyl-4-nitrosopiperidine; D = nitrosopiperazine

applicable to epithelial cells. This problem is of considerable importance, since most human tumours are of epithelial origin[46].

As a continuation of studies aimed at differentiating normal epithelial cells from cells neoplastically transformed *in vitro*[47], a positive correlation has been observed between the presence of γ-glutamyl transpeptidase and the tumorigenicity of cultured liver cells[48]. This enzyme has been shown to increase during hepatocarcinogenesis *in vivo* and to be present in transplacental hepatoma[49].

A collagenase-perfusion technique[50] has been used for mass culture of rat hepatocytes in primary culture; these may carry over some differentiated functions, including drug-metabolism enzymes, into cultures and thus seem to be useful for the study of chemical transformation and mutagenesis. Phase-contrast pictures of isolated hepatocytes are shown in Figure 13. Single hepatocytes are spread on the surface of Petri dishes for eight hours; they then form agglutinated cell sheets in 48 hours. These cells can grow no further and are replaced by another type of epithelial cell, which resembles that of established lines from rat livers, e.g., IAR-20 (4 and 7 days in Fig. 12).

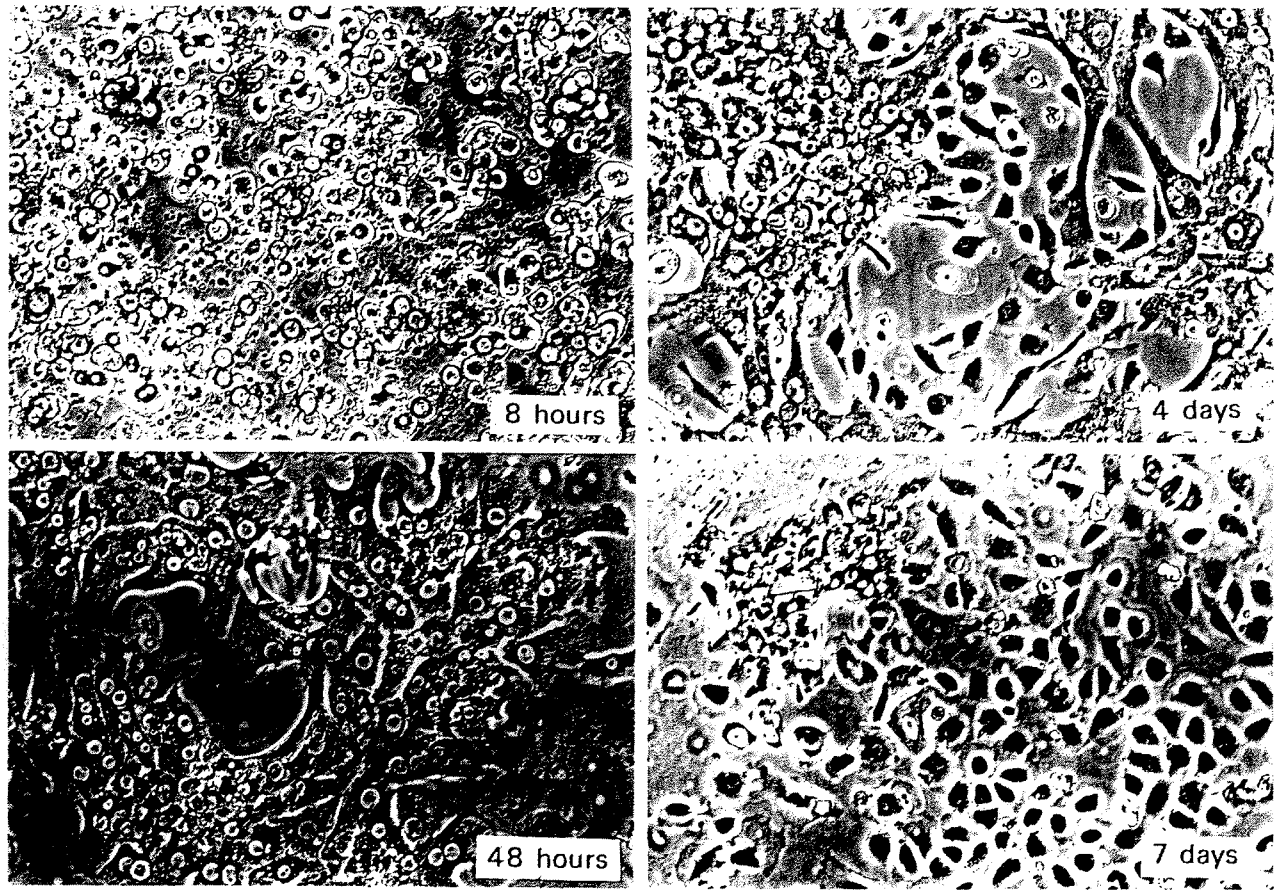


Fig. 13 Phase-contrast micrographs of rat hepatocytes in primary culture

[46] Clemmesen, J. (1964) *Statistical Studies in Malignant Neoplasms*, Munksgaard, Copenhagen.

[47] Montesano, R., Drevon, C., Kuroki, T., Saint Vincent, L., Handelman, S., Sanford, K. K., DeFeo, D. & Weinstein, I. B. (1977) *J. natl Cancer Inst.*, **59**, 1651–1658.

[48] Huberman, E., Montesano, R., Drevon, C., Kuroki, T., Saint Vincent, L., Pugh, T. D. & Goldfarb, S. (1978) *Cancer Res.* (in press).

[49] Fiala, S., Fiala, A. E. & Dixon, B. (1972) *J. natl Cancer Inst.*, **48**, 1393–1401.

[50] Laishes, B. A. & Williams, G. M. (1976) *In Vitro*, **12**, 521–532.

These IAR liver cells are known to possess metabolic competence and were used for cell-mediated mutagenesis, in which V79 Chinese hamster cells were co-cultured with X-irradiated liver cells and treated with the chemicals to be tested. Benzo(α)pyrene and its derivative were found to produce mutations under these conditions, but no mutagenicity was induced by *N*-nitrosodimethylamine. Hepatocytes isolated by the collagenase-perfusion technique are being investigated for use in detecting the mutagenicity of a wide range of chemicals.

Studies on the presence and behaviour of a surface glycoprotein, termed LETS (large external transformation-sensitive), and other surface proteins in epithelial liver cells, as compared with mesenchymal cells, are underway. The aim of these studies is to examine the changes in these surface proteins in relation to the differentiation and tumorigenicity of the cells after various times in culture.

(*b*) *Requirement of proximate or direct contact between target cells and metabolic activation for induction of mutagenesis*[51] (Dr T. Kuroki, Miss C. Drevon)

Experiments were designed to investigate whether direct (or proximate) contact is required between target cell and the membranes of the cells or microsomal particles that are carrying carcinogen-metabolizing enzymes to produce cell- and microsome-mediated mutagenesis in mammalian cells. When a V79 Chinese hamster cell monolayer was separated by 1 mm from a metabolically competent feeder layer or microsome suspension, no mutagenicity, as determined by 8-azaguanine- and ouabain-resistance, was induced by 7,8-dihydroxy-7,8-dihydrobenzo(α)pyrene in the cell-mediated assay or by *N*-nitrosodimethylamine in the microsome-mediated assay. Dose-related mutations were induced by conventional assay systems in which V79 cells were allowed to remain directly in contact with the metabolic activation system. These results, together with other supplementary evidence, indicate that such contact is necessary. This may also hold true for mutagenesis assays using microbial systems.

Two mechanisms may explain why such contact is required. One is the chemical instability of the ultimate reactive metabolite formed: unstable intermediates may decompose in aqueous media before reaching the DNA of the target cells, unless the distance of migration is reduced to a minimum. Secondly, when chemicals and their metabolites have lipophilic properties, they could reach the target cells by transfer through the lipid matrix of the membrane, and such a lipophilic environment may eventually contribute to a prolonged half-life.

The requirement of such contact has not previously been considered, and this may have led to the misinterpreting of some results, especially negative ones, in mutagenesis. This study will help further improve mutagenesis systems.

(*c*) *Comparative mutagenicity of benzo(a)pyrene and 7,8-dihydroxy-7,8-dihydrobenzo-(a)pyrene in microsome- and cell-mediated mutagenesis in V79 Chinese hamster cells* (Dr T. Kuroki, Dr R. Montesano, Miss C. Drevon, in collaboration with Dr J. K. Selkirk, Oak Ridge National Laboratory, Oak Ridge, TN, USA)

The known mutagenicities of benzo(*a*)pyrene and of its proximate form, 7,8-dihydroxy-7,8-dihydrobenzo(*a*)pyrene, were compared in cell- and microsome-mediated mutagenesis of V79 Chinese hamster cells, in which feeder layers of rats fibroblasts and liver S15 fraction from

[51] Kuroki, T. & Drevon, C. (1978) *Nature*, **271**, 368–370.

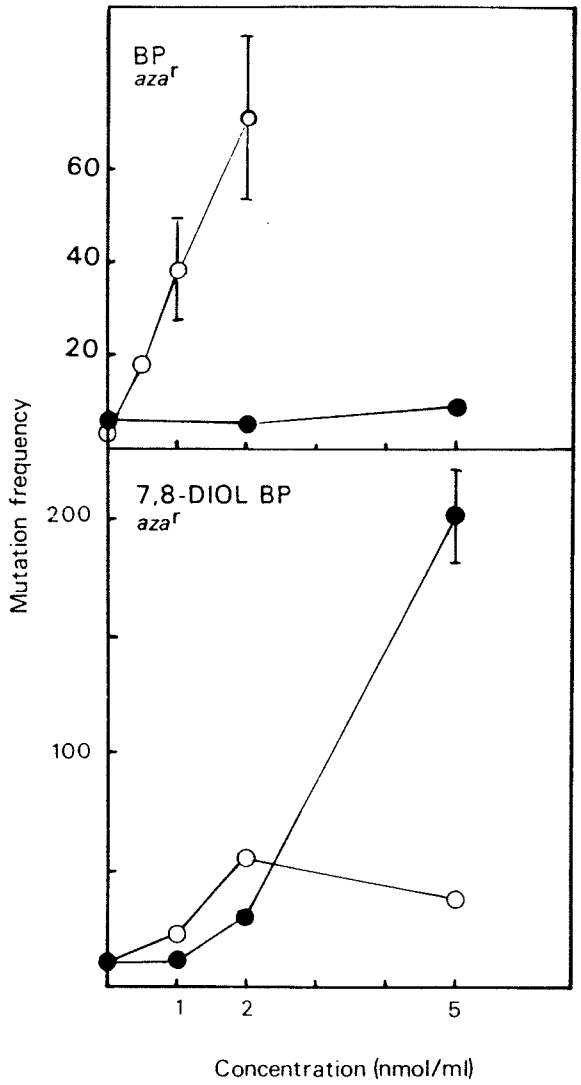


Fig. 14 Comparative mutagenicities of benzo(*a*)pyrene and 7,8-dihydroxy-7,8-dihydrobenzo(*a*)pyrene in microsome- and cell-mediated mutagenesis in V79 Chinese hamster cells

methylcholanthrene-pretreated rats at optimum concentrations were used, respectively. As shown in Figure 14, benzo(*a*)pyrene was a relatively potent mutagen in cell-mediated assays but was only slightly mutagenic in the microsome-mediated assay. 7,8-Dihydroxy-7,8-dihydrobenzo-(*a*)pyrene was a potent mutagen to an almost equal extent in both assay systems.

These results suggest that simple epoxides, e.g., K-region epoxide from benzo(*a*)pyrene and vicinal diol epoxide from 7,8-dihydroxy-7,8-dihydrobenzo(*a*)pyrene, may act as an ultimate form in microsome-mediated assays, while formation of 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetra-hydrobenzo(*a*)pyrene may be a main pathway in cell-mediated assays. These results, together with observations on patterns of metabolism in high-pressure liquid chromatography and those of binding to DNA in LH-20 column chromatography, lead to the hypothesis that microsome-mediated systems may not accurately reflect the metabolic pathway which occurs in intact cells, at least in the case of polycyclic aromatic hydrocarbons.

(*d*) *Microsome-mediated mutagenicity of polycyclic aromatic hydrocarbons and aflatoxin B_1 in V79 Chinese hamster cells* (Dr T. Kuroki, Mr C. Malaveille, Miss C. Drevon, in collaboration with Dr J. K. Selkirk, Oak Ridge National Laboratory, Oak Ridge, TN, USA)

We have previously reported microsome-mediated mutagenesis of various nitrosamines[52, 53] and of vinyl chloride[54] in V79 Chinese hamster cells. The assay procedure was standardized, using *N*-nitrosodimethylamine as a model compound: V79 cells in monolayer were treated with test compounds in a reaction mixture containing liver postmitochondrial fraction (S15) from rats at a concentration of 30 % (v/v) and cofactors; they were then replaced for determination of induced cytotoxicity and mutagenicity in terms of 8-azaguanine- and/or ouabain-resistance. These conditions were found to be inapplicable to the detection of the known mutagenicity of polycyclic aromatic hydrocarbons and aflatoxin B_1. After several trials, a breakthrough was achieved simply by reducing the amount of S15 fraction in the reaction mixture from 30 % to 1–2 %.

As seen in Figure 15, a sharp peak of mutagenicity was found with lower concentrations (1–5 %) of the S15 fraction, when cells were treated with benzo(*a*)pyrene, 7-8-dihydrobenzo-(*a*)pyrene and aflatoxin B_1: little or no mutagenic response was induced at higher concentrations of more than 10 %. In contrast with these lipophilic compounds, the mutagenicity of *N*-nitrosodimethylamine, which is hydrophilic, increased with increasing doses of S15 fraction in the reaction mixture. This also held true in liquid incubation assays in *Salmonella typhimurium*. This phenomenon, which does not appear to have been described before, can be explained by the fact that the compounds may be trapped or absorbed by free microsomes: with higher concentrations of S15 fraction, a large excess of free microsomes may absorb or trap chemicals by their high lipophilicity and thus lead to a reduction of the distribution of chemicals to bound microsomes. This study provides further evidence of the requirement of direct contact between target cells and microsomes[55].

(*e*) *Comparative mutagenicity of some* N- *and* O-*acyl derivatives of* N-*hydroxy-2-aminofluorene in V79 Chinese hamster cells*[56] (Dr T. Kuroki, Dr H. Bartsch, in collaboration with Professor E. C. Miller and Professor J. A. Miller, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, USA)

The mutagenicities of four *N*- and *O*-acyl derivatives of *N*-hydroxy-2-aminofluorene (acyl: acetyl or myristoyl residue) were examined in V79 Chinese hamster cells in the absence of a metabolic activation system. *N*-Myristoyloxy-*N*-acetyl-2-aminofluorene (*N*-Myo-AAF) was toxic and weakly mutagenic, inducing 8-azaguanine-resistant mutants in V79 Chinese hamster cells in a concentration-dependent fashion; while *N*-acetoxy-*N*-myristoyl-2-aminofluorene (*N*-AcO-MyAF) and *N*-myristoyloxy-*N*-myristoyl-2-aminofluorene (*N*-MyO-MyAF) were neither cytotoxic nor mutagenic. Under the same conditions, *N*-acetoxy-*N*-acetyl-2-aminofluorene (*N*-AcO-AAF) was highly toxic and mutagenic.

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[52] Kuroki, T., Drevon, C. & Montesano, R. (1977) *Cancer Res.*, **37**, 1044–1050.

[53] Drevon, C., Kuroki, T. & Montesano, R. (1977) In: Scott, D., Bridges, B. A. & Sobels, F. H., eds, *Progress in Genetic Toxicology*, Amsterdam, Elsevier/North Holland Biomedical Press, pp. 207–213.

[54] Drevon, C. & Kuroki, T. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells (submitted for publication).

[55] Kuroki, T. & Drevon, C. (1978) *Nature*, **271**, 368–370.

[56] Kuroki, T. & Bartsch, H. Mutagenicity of some *N*- and *O*-acyl derivatives of *N*-hydroxy-2-aminofluorene in V79 Chinese hamster cells (submitted for publication).

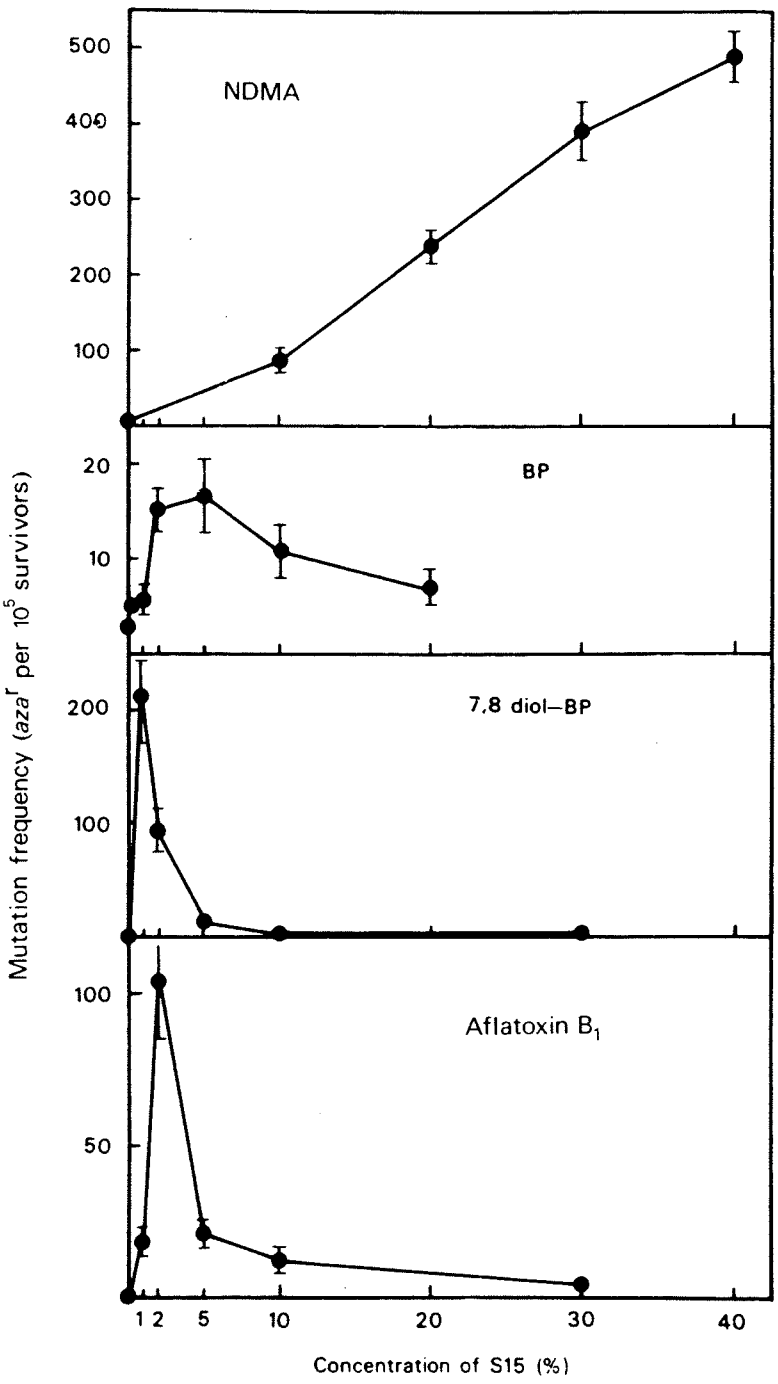

Fig. 15 Microsome-mediated mutagenicity of polycyclic aromatic hydrocarbons and aflatoxin B_1 in V79 Chinese hamster cells. NDMA = *N*-nitrosodimethylamine; BP = benzo(*a*)pyrene; 7,8-diol-BP = 7,8-dihydrobenzo(*a*)pyrene; aza^r = 8-azaguanine resistance; S15 = liver post-mitochondrial fraction

In Table 34, the carcinogenicity, electrophilicity and mutagenicity in *Salmonella typhimurium* strains TA98 and TA1538 and V79 Chinese hamster cells, and DNA repair induction activity of the four hydroxamic esters are compared qualitatively. The data show a general, qualitative correspondence between the induction of unscheduled DNA synthesis, the electrophilicity and the carcinogenicity of these esters. However, correlations of these activities with mutagenicity were

poor in view of the lack of mutagenicity of *N*-AcO-MyAF and *N*-MyO-MyAF in V79 Chinese hamster cells and of *N*-MyO-AAF and *N*-MyO-MyAF in *Salmonella typhimurium*. Furthermore, there was no good quantitative correlation between the carcinogenic activity of these esters and their effects *in vitro*: although *N*-AcO-AAF was the least active carcinogen, it was the most active in assays for electrophilicity, mutagenicity in V79 Chinese hamster cells and induction of DNA repair synthesis. In view of these false-negative results (carcinogenic chemicals that are not detected as mutagens) obtained in two mutagenic assays, the need for multiple short-term tests in the prediction of potential carcinogenic activity of chemicals is further stressed.

Table 34. Comparative carcinogenicity, electrophilicity and mutagenicity in *Salmonella typhimurium* and in V79 Chinese hamster cells, and DNA repair induction activity of four hydroxamic esters[a]

Ester	Carcinogenic in rats	Electrophilic to methionine	Mutagenic in		Unscheduled DNA synthesis in human fibroblasts
			S. typhimurium	V79	
N-AcO-AAF	+	+	+	+	+
N-AcO-MyAF	+	+	+	−	+
N-MyO-AAF	+	+	−	+	+
N-MyO-MyAF	+	+	−	−	+

[a] Data on carcinogenicity, electrophilicity and mutagenicity in *S. typhimurium* are from Bartsch, H., Malaveille, C., Stich, H.F., Miller, E.C. & Miller, J.A. (1977) *Cancer Res.*, **37**, 1461.

(*f*) *Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells*[57, 58] (Dr T. Kuroki, Dr H. Bartsch, Mr C. Malaveille, Miss C. Drevon)

The mutagenicities of vinyl chloride, vinylidene chloride (1,1-dichloroethylene) and chloroprene (2-chloro-1,3-butadiene) were tested in V79 Chinese hamster cells in the presence of a 15 000 x *g* liver supernatant from phenobarbitone-pretreated rats and mice. Mutations in two genetic loci, in terms of 8-azaguanine- and ouabain-resistance, were induced in a dose-related fashion by exposure to vapour of vinyl chloride in the presence of liver supernatant from phenobarbitone-pretreated rats. Vapour of vinylidene chloride and chloroprene induced a dose-related toxicity in the presence of liver supernatant from phenobarbitone-pretreated rats, but these two compounds were not mutagenic in V79 Chinese hamster cells. The results confirm previous observations on the mutagenicity of vinyl chloride in bacteria, yeasts and insects. Our failure to detect the known mutagenicity of vinylidene chloride and chloroprene is probably due to insufficient formation of mutagenic metabolites, which might be different from toxic metabolite(s), or to cytotoxicity, or to lack of specificity towards target genetic loci.

[57] Drevon, C., Kuroki, T. & Montesano, R. (1977) In: Scott, D., Bridges, B. A. & Sobels, F. H., eds, *Progress in Genetic Toxicology*, Amsterdam, Elsevier/North Holland Biomedical Press, pp. 207–213.

[58] Drevon, C. & Kuroki, T. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells (submitted for publication).

(*g*) *Inhibition by protease inhibitors of chemical transformation in C3H 10T ½ cells but not of mutagenesis in V79 Chinese hamster cells*[59] (Dr T. Kuroki, Miss C. Drevon, in collaboration with Dr T. Matsushima, Institute of Medical Science, University of Tokyo, Tokyo)

Five protease inhibitors (antipain, chymostatin, elastatinal, leupeptin and pepstatin) isolated from *Actinomycetes* were investigated with regard to their effects on chemical transformation in C3H 10T½ cells and on mutagenesis in V79 Chinese hamster cells. These inhibitors blocked methylcholanthrene-induced transformation in C3H 10T½ cells when added at a non-toxic dose (50 μg/ml) throughout the six weeks' course of transformation or from one week after carcinogen treatment. The simultaneous addition of these inhibitors for 48 hours with the carcinogen treatment did not cause inhibition of transformation. These protease inhibitors were not lethal to C3H 10T½ cells or to their transformed derivatives but reduced saturation density of the transformed cells and suppressed their overgrowth. This suppression was reversible. Marked heterogeneity was observed among the transformed cell lines in terms of sensitivity towards protease inhibitors, suggesting that proteases involved in transformation may not be a single species.

Mutations, as determined by 8-azaguanine- and/or ouabain-resistance, were induced in V79 Chinese hamster cells by both direct mutagens (*N*-methyl-*N*'-nitro-*N*-nitrosoguanidine and ultra-violet irradiation) and indirect mutagens (methylcholanthrene). The proteases were added at a concentration of 50 μg/ml during the treatment and the expression period. Little or no effect on mutation frequency was observed with comparable doses, with the exception of pepstatin, which reduced 8-azaguanine-resistance but not ouabain-resistance induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine.

Carcinogenesis appears to be a multistep process, the initial stages of which might overlap with chemical mutagenesis, e.g., metabolic activation, binding to macromolecules, error-free and error-prone repair of damaged DNA and fixation. Protease inhibitors seem to act more intensively during the later stages, perhaps in the promotion step rather than in the initiation step.

(*h*) *Human embryo fibroblasts*
First Institute of Pathology, Semmelweis Medical University, Budapest
Principal investigator: Professor K. Lapis

Human embryo fibroblasts have been established in culture and treated with methylcholanthrene and adriamycin. These cultures have been followed up to the 20th passage: no morphological or biological changes were detected in comparison with untreated cultured cells.

3.3 *Detection of potential chemical carcinogens in short-term tests*

(*a*) *Screening for adverse biological effects of an antischistosomal drug, Praziquantel* (Dr H. Bartsch, Dr T. Kuroki, Mr C. Malaveille, in collaboration with Dr N. Loprieno, Genetics Laboratory, University of Pisa, Pisa, Italy; Dr A. Abbondandolo, Laboratory

[59] Kuroki, T. & Drevon, C. Inhibition by protease inhibitors of chemical transformation in C3H 10T½ cells, but not mutagenesis in V79 Chinese hamster cells (submitted for publication).

for Mutagenicity and Differentiation, National Council for Research (CNR), Pisa, Italy; Dr E. Vogel, Department of Radiation Genetics and Chemical Mutagenesis, State University of Leiden, Leiden, The Netherlands; and Dr A. Davis, Unit of Schistosomiasis and other Helminthic Infections, Division of Malaria and other Parasitic Diseases, WHO Headquarters, Geneva, Switzerland)

Praziquantel (EMBAY 8440), a new, effective antischistosomal drug, was tested in various short-term assays which have shown a predictive value for the detection of potential carcinogens[60]. Using indicator organisms such as *Salmonella typhimurium* strains, *S. pombe, S. cerevisiae,* cultured V79 Chinese hamster cells or human heteroploid cells and *Drosophila melanogaster,* the induction of reverse and forward mutations, mitotic gene conversions, X-linked recessive lethals, sister chromatid exchanges and unscheduled repair synthesis were scored after treatment with Praziquantel; rodent liver microsomes, cell- and host-mediated assays were performed. Hycanthone, another schistosomicide, was included as a positive control. The absence of mutagenic activity of Praziquantel, which was uniformly obtained, further confirms the proposal that anti-schistosomal effectiveness is not necessarily related to the mutagenic activity of a drug. Although confidence is increased when similar results are obtained in a battery of short-term tests, the absence of any notable mutagenic effects of Praziquantel in the above-mentioned tests cannot be taken as proof that Praziquantel has no carcinogenic activity, and long-term carcinogenicity assays in rodents are at present underway.

(*b*) *Mutagenicity of environmental mixtures* (Mr C. Malaveille, Dr H. Bartsch, Mrs G. Brun, Mrs A. Hautefeuille, in collaboration with Dr N. Day, Unit of Biostatistics, IARC and Dr K. Szendrei, Medical University, Szeged, Hungary)

To study possible etiological factors involved in cancer of the œsophagus in areas of north-east Iran, crude opium and opium pyrolysates, which are eaten in considerable quantities, were investigated for their mutagenic activity[61]. Six samples of *sukhteh* (residues formed in the interior of opium smokers' pipes), collected from villages in north-east Iran, and six samples of crude opium from Turkey, Iran and Afghanistan, provided by the French Ministry of Health, were tested in the *Salmonella*/microsome mutagenicity test. Except in one case, no activity was found in the crude opium extracts, but the *sukhteh* samples gave consistently positive results (about 10–150 revertants per mg of dry starting material measured as dichloromethane extract) in TA98 strain, requiring the presence of a rat liver microsomal preparation for activity. One mutagenic *sukhteh* sample was fractionated by differential solvent extraction: more than 90 % of the mutagenic activity was located in the benzene fraction, revealing a specific mutagenicity of 1 300 revertants per mg of extract. The results suggest that the mutagenic principles may belong to a class of heterocyclic or polycyclic aromatic hydrocarbons.

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[60] Bartsch, H., Kuroki, T., Malaveille, C., Loprieno, N., Burale, R., Abbondandolo, A., Bonatti, S., Rainaldi, G., Vogel, E. & Davis, A. (1978) *Mutat. Res.* (in press).

[61] Hewer, T., Rose, E., Ghadirian, P., Malaveille, C., Bartsch, H. & Day, N. Ingested mutagens from opium and tobacco pyrolysis products and cancer of the œsophagus (submitted for publication).

(*c*) *Unscheduled DNA-synthesis as a short-term test of the detection of potential carcinogens*
(Mr A. Barbin, Miss C. Bordet, Mrs L. Saint-Vincent, Mr C. Malaveille, Dr H. Bartsch)

The measurement of DNA repair as unscheduled DNA synthesis in hepatocyte primary cultures isolated by collagenase perfusion of rat liver is being explored as a potential screen for carcinogens[62]. Such cultures have an important advantage: the possibility of activation in intact liver cells in the absence of replicative DNA synthesis, which normally complicates measurement of unscheduled DNA synthesis. *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine and derivatives of 2-acetylaminofluorene were used to optimize the system. Determination of sulphotransferase, a marker enzyme known to be involved in the metabolic activation of aromatic amines in rat liver was determined by a micro-assay; 24 hours after its isolation, the enzyme activity in attached cells was 45 % of that found in freshly isolated rat liver cytosol. These findings emphasize the suitability of this screening system for the assay of aromatic amines and amides. This method will be used as a routine screen in parallel with other test systems, but also as a tool to study mechanisms of the organ specificity of certain carcinogens.

For this purpose, an *in vivo* and *in vitro* system is being explored which involves the isolation of organs from carcinogen-treated animals, the incubation of tissue preparations in the presence of H^3-TdR and autoradiography. This system will be used to investigate whether the site of formation of metabolites which can react with DNA in the body coincides with the site(s) where the carcinogen induces tumours in experimental animals. *N*-Nitrosodimethyl- and *N*-nitrosodiethylamine will be tested in rats and hamsters, since these nitrosamines display organ-specific carcinogenic activity in the liver and the respiratory tract of these animal species, respectively.

(*d*) In vitro *biochemical assay for somatic mutagenesis*
Molecular Biology Department, Free University of Brussels
Principal investigators: Professor M. Errera, Dr M. Radman

The purpose of this study is to examine the mutagenic/carcinogenic potential of various chemical carcinogens in mammalian cells. In particular, the effect of promotors during mutation expression will be studied using mammalian cells.

(*e*) *Interaction between asbestos and chromosomal proteins*
Experimental Oncology Department, University of Genoa, Italy
Principal investigators: Dr L. Zardi, Professor L. Santi

Binding of asbestos incubated with chromosomal proteins from different human tissues is being studied using different pH levels, temperatures, ionic strengths and protein concentrations.

3.4 *Research training and visiting fellows*

Dr K. Toth, from the Research Institute of Oncopathology, Budapest, received training in the use of the *Salmonella*/microsome mutagenicity test system during a two-week period with an International Cancer Research Technology Transfer (ICRETT) award.

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[62] Williams, G. M. (1977) *Cancer Lett.*, **1**, 231–236.

Dr G. Margison from the Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK, carried out laboratory studies in the Unit for three weeks with an ICRETT award.

Dr J. Selkirk from the Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA, collaborated with the Unit for three weeks with an ICRETT award.

Dr A. J. Likhachev from the Professor N. N. Petrov Research Institute of Oncology, Leningrad, USSR, spent one month in the Unit within the collaborative programme between the two institutions.

Mrs B. Tudek from the Department of Biochemistry, Warsaw Medical School, Warsaw, received research training in mutagenicity testing in the Unit for four months. Subsequently, she was involved in setting up a method to detect mutagenic compounds in the urine of animals treated with carcinogens. The final aim of this study is to develop a technique applicable to the monitoring of exposure of human subjects to carcinogens/mutagens in the environment.

Dr G. Bannikov from the Cancer Research Centre, USSR Academy of Medical Sciences, Moscow, joined the Unit for one year as an IARC Research Training Fellow to participate in the study of DNA repair and metabolism of carcinogens and surface proteins in epithelial cells.

3.5 *The safe handling of chemical carcinogens in the laboratory*

The IARC has frequently been asked by various national laboratories to give advice on the safety precautions to be taken when handling chemical carcinogens. Consequently, guidelines have been prepared and discussed by an international group of scientists, who met in Lyon from 19–21 June 1978, and these will eventually be published.

3.6 *Workshops*

(*a*) *Workshop on basic requirements for carrying out long-term and short-term carcinogenicity testing*

Following recommendations from various governments and national and international organizations, the Agency is preparing to draft basic requirements for carrying out long-term and short-term carcinogenicity testing with the Medical School, Hanover, Federal Republic of Germany, and in collaboration with the Commission of the European Communities, Brussels. A Workshop will be convened from 4–9 June 1979 in Hanover, Federal Republic of Germany. An organizing committee met in May 1978 in Hanover to draft an agenda and to select participants for the June 1979 meeting.

(*b*) *Workshop on recent findings in chemical carcinogenesis*

Preceding the Workshop described above (3.6 *a*), an introductory session will be held to discuss recent advances in chemical carcinogenesis, in particular, those that can be related to carcinogenicity testing. This workshop is a follow-up to the meeting in Brussels in 1975[63].

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[63] Montesano, R., Bartsch, H. & Tomatis, L., eds (1976) *Screening Tests in Chemical Carcinogenesis*, Lyon *(IARC Scientific Publications No. 12)*.

(*c*) *Workshop on* in vitro *mutagenicity testing*

As the result of a discussion meeting held in March 1977 in Neuherberg, Munich, Federal Republic of Germany, a protocol has been published[64] which defines the fundamental criteria for carrying out bacterial mutagenicity tests *in vitro*.

4. PRENATAL CARCINOGENESIS

4.1 *Experimental studies*

(*a*) An experiment has been initiated to confirm the results of a previous experiment, which indicated the persistence of an increased cancer risk in subsequent generations of BD-VI rats treated with *N*-nitrosoethylurea during pregnancy (Dr A. Likhachev, Dr V. Ponomarkov).

(*b*) *School of Medicine, Hanover, Federal Republic of Germany*
Principal investigator: Professor U. Mohr

The findings following administration of 7,12-dimethylbenzanthracene to pregnant C57BL mice on three subsequent generations are being examined, and the data are being prepared for publication.

(*c*) *Cancer Research Centre, Academy of Medical Sciences of the USSR, Moscow*
Principal investigator: Dr V. S. Turusov

A study of the effect of administration of *N*-nitrosomethylurea to pregnant rats on four subsequent generations is in progress. Preliminary results show a high incidence of tumours in the first generation of descendants and a slight increase in the incidence of tumours in subsequent generations.

(*d*) *N. N. Petrov Research Institute of Oncology, Leningrad, USSR*
Principal investigator: Professor N. P. Napalkov

An investigation has been initiated to examine the multi-generation effects of modifying factors in transplacental carcinogenesis. The following specific experiments are in progress: prenatal treatment of mice with different dose levels of known animal chemical carcinogens (dimethylbenzanthracene, benzo(*a*)pyrene, *N*-nitroso-*N*-ethylurea), supplemented by a postnatal application of a co-carcinogen, TPA (12-*O*-tetradecanoyl-phorbol-13-acetate); investigation of the influence of hyperthyroid, euthyroid and hypothyroid status on the development of transplacentally-induced tumours; and a study of the effect of accelerated ageing on the development of transplacental carcinogenesis.

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[64] Mattern, I. E. & Greim, H. (1978) *Mutat. Res.*, **53**, 369–378.

5. UNIT OF RESEARCH TRAINING AND LIAISON

Dr W. DAVIS (Chief)

1. INTRODUCTION

The research training fellowships programme has continued this year, although it has not yet been possible to reinstate the Travel Fellowships programme. Three courses have been organized, and three titles have been added to the *IARC Scientific Publications* series.

A second meeting organized jointly with the French National Institute of Health and Medical Research (INSERM) took place in Lyon, December 1977.

2. THE FELLOWSHIPS SELECTION COMMITTEE

The Fellowships Selection Committee met in Lyon from 27–28 April 1978 to review current applications for Research Training Fellowships. The upward trend has continued this year in numbers of applications in the priority fields accorded by the Agency.

The members of the Committee were:

Professor M. Bagshaw, Department of Radiobiology, Stanford University, Stanford, CA, USA *(Radiobiology)*; also Chairman of the Commission on Fellowships and Personnel Exchange of the UICC

Doctor R. Kroes, Central Institute for Nutrition and Food Research, Zeist, The Netherlands *(Chemical Carcinogenesis)*

Professor N. P. Napalkov, Director, N. N. Petrov Research Institute of Oncology, Leningrad, USSR *(Chemical Carcinogenesis)*

Professor N. F. Stanley, Department of Microbiology, University of Western Australia, Perth, Australia *(Microbiology)*

Professor H. Sugano, Director, Cancer Institute (Japanese Foundation for Cancer Research), Tokyo *(Experimental Pathology)*

The committee were very pleased to welcome Dr R. Kroes, a new member, who was himself an IARC Research Training Fellow 1970–1971.

Dr B. G. Mansourian, Office of Research Promotion and Development, WHO, Geneva, was present as an observer.

This meeting was the last at which Professors Napalkov and Stanley would participate. The warm appreciation was recorded of the contribution that they had made to the Fellowships programme of the Agency.

3. RESEARCH TRAINING FELLOWSHIPS

Of the 81 applications received, eight were not processed for various reasons, leaving 73 to be reviewed by the Fellowships Selection Committee. Sufficient funds were available to recommend the award of fourteen fellowships, and the distribution by scientific discipline is given in Table 35.

The Committee was satisfied to see an increase in the number of high quality applications that fell within the priority fields of epidemiology, biostatistics and environmental carcinogenesis, but, at the same time, they regretted that the limitation of funds meant that some very high quality applications that were estimated to be in the priority fields could not be accepted as well.

4. CORVISSIANO FELLOWSHIPS

Dr Francesca Repetto, of the Department of Health of the Lombardy Region, Italy, has been working at the Agency as a Corvissiano Fellow under the direction of Dr R. Saracci in the Unit of Epidemiology.

5. ISABELLE DECAZES DE NOÜE PRIZE

The Isabelle Decazes de Noüe Foundation has given funds to provide an annual prize to former Research Training Fellows. The prize-winner would be able to obtain equipment and laboratory reagents to enable him to continue his research programme in his home laboratory.

On the advice of the Fellowships Selection Committee, three prizes, valued at US $ 3 000 each, have been awarded to:

Dr I. Hirsch, Institute of Sera and Vaccines, Prague

Dr T. Nomura, Institute for Cancer Research, Osaka, Japan

Dr S. Riazuddin, Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan.

6. SPECIALIZED COURSES

6.1 *Epidemiology of cancer*

Thirty-two participants followed the two-week course on 'Epidemiology of Chronic Diseases with Special Emphasis on Cancer', which took place in Karachi, Pakistan from 22 October–3 November 1977 (Fig. 16). They included representatives from Egypt, Iran, Iraq, Kuwait, Saudi Arabia and Sudan, whose attendance was supported by the WHO Regional Office for the Eastern Mediterranean (EMRO), and doctors and statisticians from all regions of Pakistan. The Agency is extremely grateful to Professor N. A. Jafarey, head of the Department of Pathology at the Jinnah Postgraduate Medical Centre in Karachi, for the excellent local arrangements, and to Dr N. Racoveanu, Regional Adviser on Radiation Health and Cancer of EMRO, for his collaboration in the organization of this course.

Table 35. Distribution of Research Training Fellowships by scientific discipline, 1978

Scientific discipline	No. of fellowships
Biostatistics	1
Chemical carcinogenesis	2
Epidemiology	4
Genetics/Experimental carcinogenesis	1
Haematology	1
Immunology	1
Physiology	1
Virology	3

The overseas faculty consisted of Professor I. Kessler, Department of Epidemiology, The Johns Hopkins University, Baltimore, MD, USA, Dr H. Tunstall-Pedoe, Department of Epidemiology, St Mary's Hospital, London, together with Dr C. S. Muir, Dr R. MacLennan and Dr W. Davis from the Agency. Contributions to the teaching programmes were also made by Dr J. A. Hashmi, Director of the Pakistan Medical Research Council, and Mr S. M. Ishaq, Director of the Statistics Division, Government of Pakistan, Karachi.

The course was considered to be highly successful, particularly from the point of view of the orientation of the programme, and it is hoped that the contacts established during this course between the Agency, the overseas faculty and the participants will continue to be mutually beneficial.

Fig. 16 Pathologists and clinicians from Pakistan, Sudan and Kuwait during the course on the epidemiology of chronic diseases, with special emphasis on cancer, held in Karachi, October 1977

Professor P. Cole (Department of Epidemiology, Harvard University, Cambridge, MA, USA), who spent the year 1977–78 at the Agency as consultant in epidemiology, also acted as the coordinator of a course on cancer epidemiology held in Lyon from 31 July–11 August 1978.

The first regional epidemiology course to be held in Australia will take place from 6–17 November 1978 at the School of Public Health and Tropical Medicine, University of Sydney.

Professor C. Thilly, Director of the School of Public Health of the Free University of Brussels, has very kindly accepted to collaborate in the organization of a course on cancer epidemiology (in French) to be held in Brussels from 5–16 June, 1979.

6.2 *Chemical carcinogenesis*

Fifty-three participants from sixteen countries attended the short course on 'Aspects of Chemical Carcinogenesis'—the first of its type to be organized by the Agency—from 14–19 November 1977.

Professors Elizabeth and James Miller (McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, USA) led the teaching faculty, assisted by Professor M. F. Rajewsky (Institute for Cell Biology, University of Essen, Federal Republic of Germany), Professor L. W. Wattenberg (Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA), Dr R. D. Bulbrook (Department of Clinical Endocrinology, Imperial Cancer Research Fund Laboratories, London) and Professor L. Fiore-Donati (Director, Institute of Anatomy and Pathological Histology, Verona, Italy). The scientific staff of the Unit of Chemical Carcinogenesis were closely involved in the programme planning and in the teaching faculty.

6.3 *Immunovirology of cancer*

The 'Third Postgraduate Course on Immunovirology of Cancer' was held in Lyon from 10–21 April 1978, with 30 participants from 20 countries.

As in the two previous courses of this type, Professor N. F. Stanley, University of Western Australia, was the coordinator, supported by Dr D. V. Ablashi (National Cancer Institute, USA), Dr A. C. Allison (Clinical Research Centre, Harrow, Middlesex, UK), Professor A. S. Evans (Yale University School of Medicine, New Haven, CT, USA), Dr J.-P. Lamelin (Alexis Carrel Medical Faculty, Lyon University, France), Professor C. A. Mims (Guy's Hospital Medical School, London), Professor N. A. Mitchison (University College, London), Dr J.-P. Revillard (Edouard Herriot Hospital, Lyon, France), Dr Natalie Teich (Imperial Cancer Research Fund Laboratories, London) and Dr G. Lenoir of the Unit of Biological Carcinogenesis. Special lectures were given by Professor M. A. Epstein (University of Bristol, UK), Dr D. Braun (Basel Institute for Immunology) and Sir Michael Woodruff (Medical Research Council Clinical and Population Cytogenetics Unit, Edinburgh, UK).

The manual of techniques in immunology and virology for cancer research workers, edited by Drs Lamelin and Lenoir, was updated and revised for distribution to the participants. Practical demonstrations were given both at the Agency and at the Edouard Herriot Hospital, thanks to the cooperation of Professor J. Traeger and Dr J.-P. Revillard.

This was the last time that Professor Stanley will be able to accept the responsibility of coordinating the programme of the immunovirology course, because of his increasing commitments in his home university. The Agency would like to express its gratitude and appreciation to Professor Stanley for his contribution to its education programme.

6.4 *Use of nonhuman primates in cancer research*

A planning meeting was held in Sukhumi, Abkhazian SSR, on 4 March 1978, to discuss the proposed course on the utilization of nonhuman primates in cancer research, which will take place there in May 1980.

A provisional programme has been drawn up in collaboration with Academician B. A. Lapin, Director of the Institute of Experimental Pathology and Therapy in Sukhumi.

7. PUBLICATIONS

In the *IARC Scientific Publications* series, the following four books have appeared: *Directory of On-Going Research in Cancer Epidemiology, 1977* (joint publication with the German Cancer Research Centre); *Environmental Carcinogens – Selected Methods of Analysis,* Vol. I: *Nitrosamines; Environmental Aspects of N-Nitroso Compounds; Nasopharyngeal Carcinoma: Etiology and Control.* Six more are in press: *Cancer Registration and its Techniques; Environmental Carcinogens – Selected Methods of Analysis,* Vol. II: *Vinyl Chloride; Pathology of Tumours in Laboratory Animals,* Vol. 2: *The Mouse; Oncogenesis and Herpesviruses III; Carcinogenic Risks – Strategies for Intervention* (joint publication with the French National Institute of Health and Medical Research); and *Directory of On-Going Research in Cancer Epidemiology, 1978* (joint publication with the German Cancer Research Centre). The list of publications in the series is given in Table 36.

Table 37 shows the up-to-date figures for the distribution and sales of the scientific publications and monographs.

8. SYMPOSIA

More than 200 participants took part in the symposium, organized jointly with the French National Institute for Health and Medical Research (INSERM) on carcinogenic risks—strategies for intervention that was held at the Agency, 30 November–2 December 1977. The symposium was opened by Professor P. Denoix, Director-General of Health in France, representing Madame Simone Veil, Minister of Health, and was presided over by Dr H. Voigtländer, Chairman of the Governing Council of the Agency.

The symposium brought together scientists and epidemiologists involved in chemical carcinogenesis studies, on the one hand, and public health administrators, lawyers, trade unionists and industrial managers involved in decision-making in the field of environmental carcinogenesis, on the other. It was hoped that discussions between these two broad groups would lead to a

Table 36. List of *IARC Scientific Publications*

No.	Title	Year of publication
1	*Liver Cancer*	1971
2	*Oncogenesis and Herpesviruses*	1972
3	*N-Nitroso Compounds — Analysis and Formation*	1972
4	*Transplacental Carcinogenesis*	1973
5	*Pathology of Tumours in Laboratory Animals,* Vol. 1: *The Rat,* Part 1	1973
6	*Pathology of Tumours in Laboratory Animals,* Vol. 1: *The Rat,* Part 2	1976
7	*Host-Environment Interactions in the Etiology of Cancer in Man*	1973
8	*Biological Effects of Asbestos*	1973
9	*N-Nitroso Compounds in the Environment*	1974
10	*Chemical Carcinogenesis Essays*	1974
11	*Oncogenesis and Herpesviruses II,* Parts 1 and 2	1975
12	*Screening Tests in Chemical Carcinogenesis*	1976
13	*Environmental Pollution and Carcinogenic Risks*	1976[a]
14	*Environmental N-Nitroso Compounds — Analysis and Formation*	1976
15	*Cancer Incidence in Five Continents,* Vol. III	1976
16	*Air Pollution and Cancer in Man*	1977
17	*Directory of On-Going Research in Cancer Epidemiology, 1977*	1977[b]
18	*Environmental Carcinogens — Selected Methods of Analysis,* Vol. I: *Nitrosamines*	1978
19	*Environmental Aspects of N-Nitroso Compounds*	1978
20	*Nasopharyngeal Carcinoma: Etiology and Control*	1978
21	*Cancer Registration and its Techniques*	1978[c]
22	*Environmental Carcinogens — Selected Methods of Analysis,* Vol. II: *Vinyl Chloride*	1978[c]
23	*Pathology of Tumours in Laboratory Animals,* Vol. 2: *The Mouse*	1978[c]
24	*Oncogenesis and Herpesviruses III*	1978[c]
25	*Carcinogenic Risks — Strategies for Intervention*	1978[a, c]
26	*Directory of On-Going Research in Cancer Epidemiology, 1978*	1978[b, c]
	Pathology of Tumours in Laboratory Animals, Vol. 3: *The Hamster*	1979[d]

[a] joint publication with INSERM
[b] joint publication with DKFZ
[c] in press
[d] in preparation

consensus aimed at providing guidelines for future decision-making, but in fact the gap between the two groups remained. Scientists were only prepared to provide data based on sound experimentation. If the available data were not sufficient for the decision-maker to take a clear position, the scientists did not consider that it was their role to assist with 'educated guesses'. Clearly much more research was needed before scientists could confidently extrapolate risk assessments for man from laboratory results of chemical carcinogenicity testing.

9. MEDLINE AND CANCERLINE

A terminal has now been installed at the Agency to give the staff on-line access to the computerized files of the National Library of Medicine (Bethesda, MD, USA).

The availability of automatic bibliographic searching will be of considerable assistance, especially to the clearing-house for on-going research in cancer epidemiology and to the staff

Table 37. Distribution of *IARC Scientific Publications* and *Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*

	Official distribution	Sales
Scientific Publications		
No. 1	693	831
2	800	1362
3	955	894
4	925	855
5	1035	1210
6	894	907
7	1030	721
8	1025	963
9	984	868
10	1006	1045
11 — Part 1	1087	599
11 — Part 2	1088	610
12	1182	977
13	909	773
14	954	621
15	888	908
16	989	667
17	1030	570
Monograph Series		
No. 1	2613	2074
2	1858	1881
3	1924	1825
4	1683	1635
5	1913	1447
6	1694	1487
7	2008	1358
8	1900	1159
9	1902	1117
10	1933	1349
11	2064	890
12	1961	1163
13	1900	996
14	2042	1335
15	1982	778
16	1943	601

involved in the preparation of the monographs on the evaluation of the carcinogenic risk of chemicals to humans.

The installation and use of the terminal is supported by contracts with the National Cancer Institute (Bethesda, MD, USA).

10. COORDINATING COMMITTEE FOR HUMAN TUMOUR INVESTIGATIONS

A preparatory meeting has been held in Athens for the Eighth International Symposium on the Biological Characterization of Human Tumours, which will take place there in May 1979.

6. INTERDISCIPLINARY PROGRAMME AND INTERNATIONAL LIAISON UNIT

Dr C. A. LINSELL (Chief)

1. INTRODUCTION

Liaison with the Regional Offices of WHO has been expanded, as medical research within the Organization has become increasingly a regional and national responsibility. A meeting of representatives from fourteen countries was held in Lyon in March 1978 to examine the impact of cancer research on, and the transfer of technology to, developing countries. Priority areas for cancer research in developing countries were identified, and it was agreed that the additional expertise provided by such research was welcomed in those countries. The complex problems of transferring technology and the effect of cancer legislation in developed countries on those in the Third World were seen as national responsibilities, and, although the Agency would make information available wherever possible, it was not considered that the Agency should advise specifically on regulatory action. It has been decided to establish a permanent committee of consultants to advise on the expansion of the Agency's programmes with the Regional Offices of WHO, and the Agency's Governing Council has provided additional funds for these activities. The Governing Council emphasized, however, that the Agency was concerned only with scientific programmes directed towards the solution of the cancer problem, and that these and the information they generated were for the benefit of all countries, whether Participating States of the Agency or not.

The identification of markers for some types of hepatitis has stimulated worldwide research on chronic liver diseases. The mycotoxins, and in particular the aflatoxins, are now seen as a global hazard, and UNEP, together with WHO, FAO and the Agency, sponsored a recent meeting in Nairobi which was attended by representatives from over 50 countries to consider appropriate national action. Although the Agency's field studies on evaluation of the aflatoxins as causal agents of liver cancer have become more complex following the research on hepatitis, they provide an increasingly important link in the strategy for the understanding and prevention of these two human hazards. Chronic liver disease, including liver cancer, has been identified as a research priority in the eastern Mediterranean, the south-east Asian and the western Pacific regions of WHO, and the Agency is actively involved in the establishment of an inter-regional programme.

An inter-regional programme on gastric cancer has been proposed in collaboration with the International Study Group on Gastric Cancer, directed by Professor Crespi of the Regina Elena Insitute, Rome. Feasibility studies covering the Latin American component of this programme are being carried out in conjunction with the Regional Offices for the Americas of WHO.

The Agency jointly sponsored the Third Asian Cancer Congress in Manila which was attended by over 500 Asian scientists.

The Unit has assumed responsibility for the coordination of field studies on œsophageal cancer, which involve programmes in the Units of Epidemiology and Biostatistics, Chemical Carcinogenesis and Environmental Carcinogens.

2. IMMUNOLOGY (Dr P. Sizaret)

2.1 *Meeting on tumour-associated antigens*

A meeting was convened to assess the current status of tumour-associated antigens and the role that the Agency should play in the international standardization of these antigens. The participants were: Dr R. Baldwin (UK), Dr I. Batty (Secretary, International Union of Immunological Societies), Dr H. Bétuel (France), Dr P. Burtin (France), Dr J. F. Doré (France), Dr A. Goussev (WHO), Dr J. C. Hendrick (Belgium), Dr F. G. Lehmann (Federal Republic of Germany), Dr A. Levin (IARC), Dr J. P. Mach (Switzerland), Dr R. Masseyeff (France), Dr F. Martin (France), Dr K. R. McIntire (USA), Dr R. Ritts (Chairman, International Union of Immunological Societies), Professor Y. S. Tatarinov (USSR) and Dr P. F. Zangerle (Belgium).

(*a*) *Cell-mediated immunity*

The meeting concluded that tests for tumour-associated immune reactions require standardization and further evaluation as to specificity and technique. It was advised that workshops should be established to compare tests for cell-mediated immunity in relation to the following cancers: melanoma, osteogenic sarcoma, carcinoma of lung, colon, rectum and breast.

(*b*) *Humoral immunity*

Although tests for humoral immunity in Burkitt's lymphoma and nasopharyngeal carcinoma are promising, the establishment of acceptable tumour cell lines for other solid tumours is difficult. Antigens such as the carcinoembryonic antigen using xenogenic antisera, although not tumour-specific, are of possible prognostic value.

(*c*) *Tumour markers other than those detected by immune methods*

It was doubted whether tumour markers such as isoenzymes, ectopic hormones and fetal products are suitable for diagnostic purposes at the present time.

2.2 *Workshops on carcinoembryonic proteins*

Workshops were held, with the assistance of the Agency, at the Fifth Meeting of the International Research Group for Carcinoembryonic Proteins, which was organized by

Dr B. Nørgaard-Pedersen and Dr N. H. Axelsen. An antigen described as a 'leukaemia associated antigen' [1] was found in fact to be related antigenically to isoferritin. It was also established that the basic fetoprotein reported by Dr Y. Ishi [2] in the serum of patients with primary liver cancer was different from other markers such as the oncofetal antigen described by Fritsche & Mach [3]. A further workshop, consisting of eleven experts, considered the nomenclature and classification of twelve pregnancy-associated proteins, some of which have been reported to be of potential value in studies of human oncology.

2.3 *Immunogenetics: MZ alpha-one-antitrypsin phenotype and primary liver cancer*
(Dr C. Chapuis-Cellier, Lyon, in collaboration with Professor D. Trichopoulos, Athens)

Over the past few years, there have been conflicting reports about an association between primary liver carcinoma and MZ alpha-one-antitrypsin phenotype in man. Preliminary results of studies on Greek Caucasians (50 primary liver cancer patients and 100 matched controls) have shown no association. Since the association was originally reported in patients from Africa, a collaborative study has been established with the Uganda Cancer Institute in Kampala and with the Centre Hospitalier Universitaire d'Abidjan.

2.4 *Standardization of tumour-associated antigens*

(*a*) *Pregnancy-specific beta-one glycoprotein*

A pilot study, carried out in collaboration with Dr J. H. de Bruijn (Bilthoven, The Netherlands) and Dr H. Bohn (Marburg, Federal Republic of Germany) showed that the lyophilized reference material was unsatisfactory. A second study is underway with the National Institute for Biological Standards and Control of the UK and Dr L. Van Es of the Red Cross Blood Transfusion Service, Amsterdam. This will use two pools of sera from pregnant women, the lipoproteins of which have been removed either by the freon technique or by treatment by Aerosil.

(*b*) *α-Fetoprotein (AFP) studies*

The Agency continues to act as a reference laboratory for AFP. The Agency was represented at the meeting in Bethesda, MD, USA, on 18–19 May, to define criteria for manufacturers of AFP kits used in the USA for the screening of sera of pregnant women for neural tube defects. It was decided that two national reference materials should be prepared, one from amniotic fluid and the other from maternal serum, which in turn should be calibrated against the WHO AFP standard. It is considered that when either amniotic fluid or sera are examined, specific reference material should be used, since differences, possibly due to the interference of proteins other than AFP and to errors of dilutions, have been observed when a common reference material has been used. It was reported that the AFPs found in amniotic fluid have different affinities for Concanavalin A from those

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[1] Berg, K., Staven, P. Harris, R., Noer, G. & Molne, K. (1976) *Scand. J. Haematol.*, **17**, 388–394.
[2] Ishii, M. (1978) In: *Proceedings of the V Meeting of the International Research Group for Carcinoembryonic Proteins, Copenhagen, 1977* (in press).
[3] Fritsche, R. & Mach, J. P. (1975) *Nature*, **258**, 734–737.

produced by the fetal liver in man and animals. This confirms the observations made at the Agency[4] that AFP from patients with yolk-sac-derived, germ-cell tumours has lower Concanavalin-A binding affinity than AFP from primary liver cancer patients.

The activity of the WHO AFP standard was expressed originally in international units; an IARC collaborative study in 1974, involving nine laboratories, showed marked variations in readings of the standards in units. Recognizing that absolute measurements by weight are preferred and that techniques of purification have improved in recent years, a collaborative study by the Agency, involving twelve laboratories, is now underway to assess the relationship of the original international units to mass units.

2.5 *Biological banking for cell-mediated immunity studies* (Dr A. G. Levin, IARC Research Centre, London)

The collection continues of specimens from patients and families in East Africa, together with the computer storage of clinical information; however, the main effort is now directed towards the exploitation of this material.

Specimens of cryopreserved lymphocytes, serum and/or tumour tissue have been distributed to 43 investigators at research centres in France, India, Japan, Kenya, Singapore, Sweden, Switzerland, UK, USA and USSR. Extensive clinical data always accompanies the issue of banked specimens, as this is essential for the interpretation of the results of cell-mediated immunity (CMI) tests, particularly on material from tropical countries.

Specimens from 20 of each of the following clinical groups were selected for preliminary studies: (i) untreated Burkitt's lymphoma (BL) patients, (ii) BL patients in long-term remission, (iii) untreated nasopharyngeal cancer (NPC) patients, (iv) NPC patients in remission, and (v) age- and sex-matched controls from the same geographical location and of similar socio-economic status.

(*a*) *Stimulation of cryopreserved lymphocytes with lymphoblastoid cell lines* (in collaboration with Dr S. Knight, Division of Surgical Sciences, Clinical Research Centre, London, and Dr C. M. Steel, Medical Research Council Population and Cytogenetics Unit, Edinburgh, UK)

The test systems employed were developed by Knight & Farrant[5] and showed that the biological phenomenon measured was the same whether fresh or preserved cells were used, and that tests were valid using the limited number of cells which are available from banked specimens. Baseline studies have therefore been established which will allow the disease categories of the pilot study to be evaluated.

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[4] Dambuyant, C., Sizaret, P., Martel, N., Bordes, M. & Bourgeaux, C. (1978) In: *Proceedings of the V Meeting of the International Research Group for Carcinoembryonic Proteins, Copenhagen, 1977* (in press).

[5] Knight, S. C. & Farrant, J. (1978) *J. Imm. Methods*, **22**, 63–71.

(*b*) *Reaction of cryopreserved lymphocytes with tissue-typing antisera and sera from parous women in a BL endemic area* (in collaboration with Mr P. Hall and Dr S. Knight, Division of Surgical Sciences, Clinical Research Centre, London; Dr C. Entwistle, National Tissue Typing Reference Laboratory, Bristol, UK; Dr C. M. Steel, Medical Research Council Population and Cytogenetics Unit, Edinburgh, UK; and Professor W. Bodmer, Department of Biochemistry, Oxford University, UK)

Cryopreserved lymphocytes from 60 individuals in the pilot study were reacted against a panel of Caucasian tissue-typing antisera from the National Tissue Typing Reference Laboratory, Bristol, UK; African antisera from Dr E. Wolf of the Transplantation Unit, London Hospital; Sin 2 antisera provided by the WHO Immunology Research Laboratory, Singapore; and 90 sera from parous women in the Shirati area of Tanzania. Analysis of the study at present aims only to define the antigenic frequencies of this population, and no attempt is made to relate these to disease.

(*c*) *Presence and nature of immune complexes* (Dr P.-H. Lambert, WHO Laboratory, Cantonal Hospital, Geneva, Switzerland)

Two techniques have been used for the study of immune complexes in 54 East African subjects and compared with 23 Swiss blood donors. Many of the African subjects have high levels of detectable immune complexes (Fig. 17). The relationship of these to disease processes is currently being investigated.

(*d*) *Comparative studies on malignant melanoma patients in East Africa and the USA* (Dr S. Golub, Department of Surgery, University of California Los Angeles Medical School, USA)

Sera from banks in the United States and from East Africa were examined for the oncofetal antigens which have been associated with melanoma[6]. Initial studies involve the 'OFA' antigen present in the human fetal brain and in many melanoma patients[7]. Table 38 gives results of comparative studies using an immune adherence test (Dr R. Irie, Department of Surgery, University of California Los Angeles Medical School, USA).

Table 38. Comparative study of levels of oncofetal antigens in sera from melanoma patients in the United States and from East African melanoma patients and controls, using an immune adherence test

Source of serum samples	No. of patients with antibody titre (% total)	Average titre in immune adherence test (IA50)
African melanoma patients	23/31 (74.2%)	18.3
African control donors	9/17 (52.9%)	14.2
American melanoma patients	25/76 (32.9%)	6.8

[6] Irie, R., Irie, K. & Morton, D. (1976) *Cancer Res.*, **36**, 3510–3517.
[7] Irie, K., Irie, R. & Morton, D. (1978) *Cancer Res.* (in press).

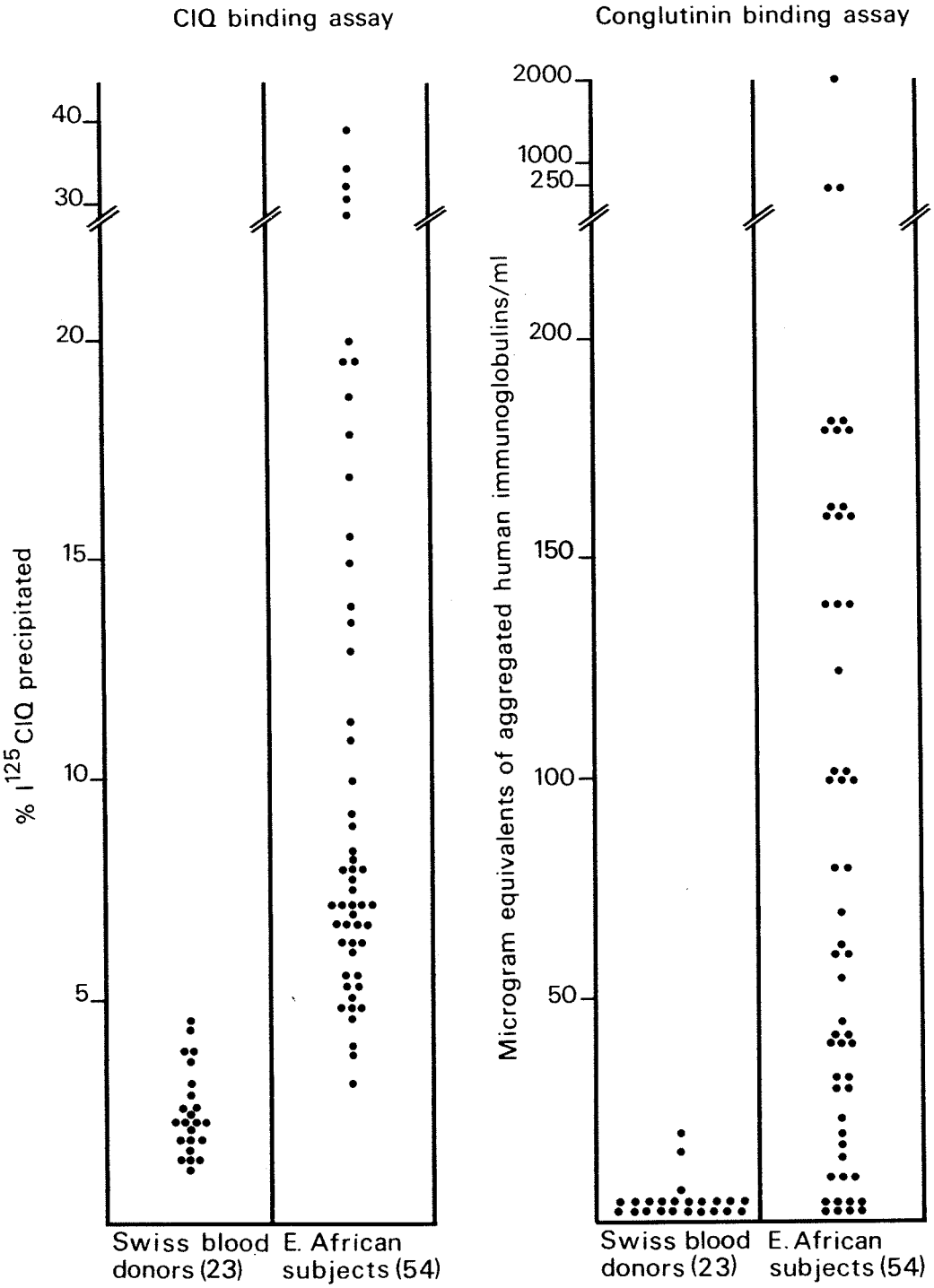

Fig. 17 Immune complexes in blood from 54 African subjects and from 23 Swiss donors, as determined by two techniques: C1Q assay and the conglutinin binding assay

2.6 *Immunological and immunogenetic studies on breast cancer in Bombay* (Dr D. J. Jussawalla, Director, and Dr J. S. Nadkarni and Dr S. G. Gangal, Biology Division, Cancer Research Institute, Tata Memorial Centre, Bombay, India)

(*a*) Pre-operative specimens which had been stored for more than three years, that had been obtained from 24 breast cancer patients and six patients with benign breast lesions, were studied

with respect to T and B cell surface markers and response to PHA stimulation. After prolonged cryopreservation it was found that viability, as measured by a dye exclusion test and recovery of frozen and thawed cells, was good. The percentage of T and B cells and PHA indices were not significantly affected when compared with fresh specimens taken at the time of cell preservation.

(*b*) Twenty-two breast cancer patients were further studied for T and B cell percentages and PHA responses preoperatively and at approximately three-monthly intervals postoperatively for a period of 6 to 30 months. These studies were undertaken on cryopreserved lymphocytes, and, as far as possible, the tests on samples from one patient were carried out simultaneously. In patients with no lymph node involvement all three parameters, T and B cell percentages and PHA response, were intact, but patients with node involvement or metastases showed lower T cell and higher B cell levels. After chemotherapy, T cell percentages were reduced, whatever the clinical stage of patient. The PHA responses did not appear to vary with the progress of the disease. Patients with benign lesions were followed for 15 months after operation and at no time did they show any change in these parameters. The studies continue.

(*c*) The study to investigate distinctive immunogenetic specificities of Parsee breast cancer patients and their families continues. Cryopreserved lymphocytes are also used in this project. Tissue typing techniques are being established at the Tata Memorial Centre.

2.7 *Studies in East Africa* (Professor A. Wasunna, Head, Nairobi Research Centre ; Dr J. Onyango, Radiation Therapy Department, Mr S. Singh and Mr I. Bal, Department of Head and Neck Surgery, Dr S. Ojuwang, Department of Gynaecology, Professor A. Kungu and Dr D. Gatei, Department of Pathology, and Dr R. Wambwa, Department of Surgery, Kenyatta National Hospital, Nairobi)

More than 100 cancer patients are under active follow-up, and 36 were seen during 1978 and blood specimens banked. Studies were made of the relationships of differential white cell counts and T-cell rosettes on these specimens (see p. 133).

2.8 *Shirati Mission Hospital* (Dr G. Brubaker)

An extension of the studies underway at the Shirati Mission Hospital, Tanzania, has been established with funds from the United Cancer Council of Rochester, New York, USA. The surveillance of families will be intensified, and the collection will be extended of material from such families and from parous women, to enable further HLA and associated antibodies to be tested.

3. PRENATAL EVENTS AND CHILDHOOD CANCER (Dr N. Muñoz, Dr L. Tomatis, Dr N. E. Day, in collaboration with Dr N. Wald, Department of the Regius Professor of

Medicine, Radcliffe Infirmary, Oxford, UK; Dr J. F. Bithel, Childhood Cancer Research Group, University of Oxford, Oxford, UK; and Dr A. Pacsa, Institute of Microbiology, University Medical School, Pécs, Hungary)

This programme uses material from established prospective studies to assess the role of prenatal events on the incidence of congenital malformations. The Oxford study was started in 1972; by December 1977 a cohort of 18 000 had been assembled. The pregnancy records in this study contain information on illnesses during pregnancy and on exposure to drugs and chemicals; two or more antenatal serum samples and one postnatal sample were collected for each woman admitted to the study. The Hungarian study dates from 1975 and now consists of the records of 12 500 pregnant women. In this study only antenatal specimens will be available, in addition to the pregnancy record. The children born to women from both these studies are being followed to identify those with congenital malformations or cancer. The occurrence of these diseases will be correlated with specific intrauterine exposures recorded in the pregnancy records, and the serum specimens and controls will be used appropriately.

4. LIVER CANCER

4.1 *Aflatoxins studies*

The Agency has collaborated with the Environmental Health Division of WHO in the production of a health criteria document on the mycotoxins: the evaluations in these technical reviews of health hazards are intended to assist governments in the elaboration of national health policy. In July, UNEP sponsored an interagency meeting to evaluate the results of the Nairobi WHO/FAO/IARC/UNEP meeting on the mycotoxins; a joint global strategy was sought to reduce the hazard to man and animals from aflatoxin contamination of foodstuffs. The Agency's intervention study in Swaziland to improve harvest and storage practices and to assess the effects on human health, specifically on the incidence of liver cancer, is one of the components of this interagency activity; and it is receiving a high priority in the programmes of all the organizations concerned.

4.2 *Cohort study on hepatitis B virus and liver cancer* (Professor Phoon Wai On, Department of Social Medicine and Public Health, University of Singapore, Singapore)

Four hundred subjects have been admitted to this study, which seeks to determine the risk of developing liver cancer among chronic carriers of hepatitis B. In addition to identification of hepatitis carriers, detailed clinical and laboratory protocols are prepared. The cancer components of this study will necessarily require a prolonged follow-up, but other medical and social parameters can be evaluated during the progress of the project (see p. 70).

4.3 *Experimental studies*

The collaboration continues between the gastroenterology departments of the All-India Institute of Medical Sciences, New Delhi and of Athens University, Athens, and the WHO Reference Laboratory for Viral Hepatitis, London School of Hygiene and Tropical Medicine, London, to study *in vitro* the effects of hepatitis virus and chemical carcinogens.

An IARC research training fellowship was awarded to Dr P. Das (New Delhi) to gain experience in tissue culture, tenable at the London School of Hygiene and Tropical Medicine. Techniques to standardize the growth of fetal liver cells have been established[8]. A tissue culture laboratory has been set up at the All-India Institute of Medical Sciences, New Delhi and equipped by the Agency, so that these studies can be continued on Dr Das' return to India.

4.4 *Hepatitis B markers in liver cancer*

(*a*) *Serological study* (Professor D. Trichopoulos, Department of Hygiene and Epidemiology, University of Athens Medical School, Athens; Dr E. Tabor, Bureau of Biologics, Food and Drug Administration, Bethesda, MD, USA; and Dr P. Sizaret, IARC)

The prevalence of serological markers of recent or past hepatitis B virus (HBV) infection was investigated in 80 patients with primary liver (PLC), 160 age- and sex-matched hospital controls and 40 patients with metastatic liver cancer (MLC); the relative risk for PLC associated with the various patterns of serological markers was calculated. All of the subjects studied were Caucasians of Greek nationality and permanent residence. Subjects were tested for serum AFP, hepatitis B surface antigen (HBsAg) and its antibody (anti-HBs), antibody to hepatitis B core antigen (anti-HBc) and hepatitis Be antigen (HBeAg) and its antibody (anti-HBe). Active HBV infection, as indicated by positive tests for HBsAg (with or without anti-HBc or anti HBs) or anti-HBc (without anti-HBs), was associated with PLC (relative risk 10.4; $P < 10^{-9}$) but not with MLC (relative risk 1.2; $P < 0.5$) (see Table 39).

Table 39. Hepatitis B serology in patients with primary and metastatic liver cancer and in control patients

HBV serological pattern	Primary liver cancer			Metastatic liver cancer			Control	
	No.	%	RR	No.	%	RR	No.	%
Active infection[a]	39	49	10.4	3	8	1.2	16	10
Anti-HBc \ Anti-HBs /	17	21	1.9	18	45	2.3	40	25
Anti-HBs only	8	10		11	27		38	24
			} 1.0			} 1.0		
Negative for all markers	16	20		8	20		66	41
TOTAL	80	100		40	100		160	100

[a] Active infection is indicated by the presence of HBsAg (with or without anti-HBc or anti-HBs) or anti-HBc (without anti-HBs)

HBV – hepatitis B virus; HBc – hepatitis B core antigen; HBs – hepatitis B surface antigen

[8] Tsiquaye, K. N., Das, P. K. & Zuckerman, A. J. (1978) *Br. J. exp. Pathol.* (in press).

People who lacked all markers and those positive only for anti-HBs had about the same low risk for PLC (relative risk 0.8: $P < 0.5$). Active infection was present more frequently in PLC patients with coexisting cirrhosis than in those without cirrhosis and more frequently in PLC patients with high serum AFP levels than in those with normal levels.

(*b*) *Studies in fixed liver tissue* (Dr N. Muñoz, in collaboration with Dr N. C. Nayak, All-India Institute of Medical Sciences, New Delhi; Dr A.-M. Mandard, François Baclesse Regional Centre, Caen, France; and Dr C. Quenum, Dakar University, Senegal)

The objective of this collaborative study is to determine the frequency of HBsAg and anti-HBc in post-mortem liver material from patients with primary liver cancer, cirrhosis and other liver diseases from geographical areas where the risk for primary liver cancer has been demonstrated to vary. The HBsAg is being identified by the Shikata Orcein stain and the anti-HBc by immunospecific peroxidase staining.

Liver sections from 200 patients with primary liver cancer, 400 patients with cirrhosis and 120 miscellaneous liver diseases have been admitted to the study.

5. ŒSOPHAGEAL CANCER (Dr N. Muñoz)

5.1 *Collaborative study on precancerous lesions of the œsophagus* (in collaboration with Dr R. H. Castelleto and Dr R. Drut, National University of La Plata, Argentina; Dr A.-M. Mandard, François Baclesse Regional Centre, Caen, France; Dr C. R. Smart and Dr J. L. Lyon, University of Utah, Salt Lake City, Utah, USA).

Œsophagi have been collected at autopsies of patients dying from diseases other than cancer of the œsophagus: 40 from Argentina, 8 from France, 18 from Gombad, Iran and 65 from Teheran and 13 from the USA.

These specimens have been processed and examined by the pathologists participating in the study, using standard techniques. Slides from each case are being sent to the Agency for circulation among the pathologists for a blind histopathological evaluation using a standard protocol.

5.2 *Collaborative study on screening for œsophageal cancer in the high-risk area of Iran* (in collaboration with Professor M. Crespi and Dr A. Grassi, Regina Elena Institute, Rome; Dr A. Nadim and Dr B. Aramesh, Institute of Public Health Research, Teheran; and Dr A. Mojtabai and Dr C. Amiri, Taj Pahlavi Institute, Teheran)

A total of 510 apparently healthy outpatients from 15 to 70 years of age, presenting to a field medical team, were examined in three villages of the Turkoman area (Hottan, Khorand and Ghapan) during May 1978. Endoscopic examinations were carried out in 441 subjects, including aimed cytology and biopsy. Blind abrasive cytology with the Crespi brush was taken in 41 and with the Chinese balloon in 18 individuals. The most striking finding was the presence of mild to severe macroscopic lesions in 80 % of the individuals examined endoscopically. Grossly, these lesions

appear as white patches in a thin, congestive and fragile mucosa; the histology is being evaluated. Seven œsophageal cancers were detected, two asymptomatic and five symptomatic. Saliva specimens were collected from 240 individuals on whom endoscopic examinations had been performed, and levels of nitrites and possibly opium metabolites will be determined to correlate with the œsophageal lesions. Gastric juice and sera were also collected in 25 individuals on whom œsophageal and gastric biopsies had been performed. Levels of *N*-nitroso compounds will be determined in these specimens to correlate with the status of the gastric and œsophageal mucosas.

5.3 *Œsophageal parasites* (in collaboration with Dr P. Ghadirian, Babol Research Station, Iran and Mr J. F. Pelloquin, IARC)

(*a*) Gongylonema pulchrum

This nematode, site-specific for the œsophagus, was found more frequently in goats and sheep from the high-risk area than in those from the low-risk area. As this parasite may also infest the human œsophagus, serum antibodies to *G. pulchrum* were sought in sera from patients with cancer of the œsophagus from Gorgan, Iran and from control patients in the same high-risk area in Iran and from Lyon, France. Frozen sections of *G. pulchrum* were used as antigens, and those of *Ascaris, Bilharzia* and *Filaria* were used as control antigens. Using an indirect immunofluorescent test, antibodies to *G. pulchrum* were found in 7 of 65 patients with œsophageal cancer and in 3 of 111 control patients from Iran. The 86 French control sera were negative. Cross-reactions with *Ascaris* were observed in some sera positive for *G. pulchrum.* In addition to these inconclusive findings, no evidence of œsophageal parasites was observed during the endoscopic survey referred in section 5.2.

(*b*) Spirocerca lupi

A total of 51 œsophagi from dogs of the Turkoman (high-risk) area of Iran and 50 from dogs of Babol (intermediate-risk area) were examined. Fibrotic nodules containing multiple parasites identified as *Spirocerca lupi* were found in the lower half of the œsophagi of 22 dogs from the Turkoman area and 22 dogs from Babol. The histology is being evaluated.

7. IARC RESEARCH CENTRE, NAIROBI

Professor A. WASUNNA (Head)

1. EPIDEMIOLOGY OF ŒESOPHAGEAL CARCINOMA

1.1. *Current study*

The study of the epidemiology of carcinoma of the œsophagus in Kenya has continued as a collaborative project with the Department of Surgery and Pathology, University of Nairobi.

These data are being collected from all patients with œsophageal cancer in Kenyatta National Hospital, Nairobi, and in the provincial hospitals of Kisumu, western Kenya and Nyeri in central Kenya, where the disease appears to occur particularly frequently. A standard protocol suitable for computer analysis is being used in this study. In the last 12 months, 47 new cases of the disease have been thus documented at the Kenyatta National Hospital alone. The clinical follow-up data, at the Kenyatta National Hospital, now has 500 patients.

1.2. *Retrospective study*

In addition, a retrospective study of the clinical, radiological, histological and geographical aspects of this disease in Kenya has recently been completed and published[1].

It was found that this cancer was diagnosed more often in males than in females, with a ratio of 8:1 (Kenya Cancer Registry). The most common age in both males and females was 50–59 years. The regions of the œsophagus most commonly involved were the middle and lower thirds, in almost equal proportions. An unexplained tendency for the tumour to be poorly differentiated towards the lower third was noted. In addition, a review on the possible etiological factors was presented.

2. COLLECTION OF BLOOD SPECIMENS

The follow-up of over 100 patients suffering from a variety of tumours, whose blood specimens are already under cryopreservation, continued in collaboration with the Departments of Surgery, Head and Neck Surgery, Radiotherapy and Pathology of the University of Nairobi. Of these patients, 75 were contacted and clinically assessed, and further blood samples were taken (see page 124).

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[1] Gatei, D. G., Odhiambo, P. A., Orinda, D. A. O., Muruka, F. J. & Wasunna, A. (1978) *Cancer Res.*, **38**, 303–307.

3. IMMUNOLOGICAL RESPONSE IN CANCER PATIENTS

Quality control studies for the various relevant laboratory procedures have been continued, and tests were applied to assess the immunological response of patients with Kaposi's sarcoma at different stages of the disease, including the period of treatment. In this regard, 45 lymphocyte count and T-cell rosettes were performed during the year. Serial differential white-cell counts were performed in 24 patients with Kaposi's sarcoma.

4. EFFECT OF NUTRITIONAL STATUS (in collaboration with the staff of Wellcome Trust/WHO Research Laboratory, Nairobi)

Twenty-four experiments have been performed during the year, in the comparative study of the response to mitogens of lymphocytes and sera from well-nourished and poorly-nourished Kenyans.

5. BURKITT'S LYMPHOMA (in collaboration with Dr G. Brubaker, Shirati Hospital, Tanzania)

Surveillance of families of Burkitt's lymphoma patients has continued. Antisera from the Shirati area were received at three-monthly intervals. A panel of antisera for immunogenetic studies is now well established.

8. IARC RESEARCH CENTRE, SINGAPORE

Professor K. SHANMUGARATNAM (Head)

1. THE SINGAPORE CANCER REGISTRY (RA/67/009)

Principal investigator: Professor K. Shanmugaratnam
Supporting staff: 3

Comprehensive registration of all cancer cases in Singapore has been maintained since 1968. Morbidity data for each of the major dialect groups in Singapore for the second half of this period are being prepared and will be submitted for inclusion in *Cancer Incidence in Five Continents, Vol. IV*. The Registry has continued to provide epidemiological data for on-going research projects on cancers of the nasopharynx, liver, lung and breast.

2. IMMUNOGENETICS OF NASOPHARYNGEAL CARCINOMA

Principal investigator: Dr S. H. Chan
Supporting staff: 6

2.1. *Introduction*

During the year under review, the WHO Immunology Centre was involved in two HLA workshops—The Austral-Asian Regional Workshop, involving ten typing centres in Australia, New Zealand and Singapore, and the 7th International Histocompatibility Workshop. During the latter conference, the new Chinese locus B antigen, Sin 2, was given an official WHO number, BW46.

2.2 *HLA locus A and B typing in Chinese*

(*a*) *Newly-diagnosed nasopharyngeal carcinoma patients and long-term survivors*

Typing of newly-diagnosed and long-term surviving NPC patients is being continued; 120 NPC patients, including 93 that were newly diagnosed, were typed. The NPC registry now covers over 460 NPC patients.

Last year we reported[2] that, in addition to BW46 (Sin 2), B17 (BW17) was also associated with an increased risk for development of NPC. This hypothesis was tested in the additional 93 newly-diagnosed NPC patients: Table 40 shows the frequencies of A2, A11, B17 and BW46 and of joint occurrences of A2 BW46, AW19/Blank B17 in the 141 newly-diagnosed NPC patients from the first study (last year's report) and in the 93 NPC patients in the current second study, compared with 238 normal Chinese subjects. The similarities in the frequencies of these antigens in the two studies were remarkable. NPC patients again showed a higher frequency of HLA-A2 ($\chi^2 = 5.13$; one-sided $P < 0.012$) and a lower frequency of HLA-A11 ($\chi^2 = 9.33$; one-sided $P < 0.002$) than did normal subjects. HLA-BW46 showed a frequency of 34 % among the patients in the first study and of 36.6 % in the second study; the difference in the combined study in frequency of BW46 between patients and controls was significant ($\chi^2 = 8.78$; $P < 0.002$; relative risk (RR) = 1.84). As in the first study, B17 again showed a significantly higher frequency among patients than controls ($\chi^2 = 8.42$; $P < 0.002$; RR = 2.33); this provided confirmation that in Chinese B17 is associated with an increased risk for NPC. The second study confirmed that the association of A2 BW46 and AW19/Blank B17 with the development of NPC is stronger thant that of BW46 or B17 alone. The associations of BW46 with older and of B17 with younger patients were again observed in the second study, but were less marked.

(*b*) *HLA and prognosis*

Is was observed previously[3] that long-term survivors of NPC had lower frequencies of B17 and BW46 and a higher frequency of A2 without BW46 or B17 than did newly-diagnosed NPC patients. It was suggested that B17 and, to a lesser extent, BW46 were associated with poor survival, whereas A2 without B17 or BW46 was associated with a good prognosis. We have now followed up some of the newly-diagnosed NPC patients for more than five years and observed the HLA pattern in patients who died of the disease. Table 41 shows the frequency of B17 and BW46 and of A2 without B17 or BW46 in all newly-diagnosed patients, in patients who died within two years of diagnosis, in patients who died between two and five years and in long-term survivors. The high frequency of B17 in the newly-diagnosed patients (28.2 %) was also reflected in the patient subgroup that died within two years of diagnosis (29.6 %); the frequency of B17 in the other two subgroups of patients was not essentially different from that of controls. The high frequency of BW46 in the newly-diagnosed patients (35 %) was reflected in both subgroups of dead patients, although the subgroup that died between two and five years had the highest frequency; the long-term survivors had a BW46 frequency only slightly higher than normal people. The frequency of A2 without B17 or BW46 was lowest in patients who died within two years, higher in patients who died between two and five years and highest in long-term survivors. These results confirm our hypotheses that the presence of B17 and BW46 is a poor prognostic factor and that A2 without B17 or BW46 is associated with survival. The findings that the frequency of B17 is highest in those dead within two years and that BW46 is highest in those that died between two and five years are interesting; more data will be necessary to confirm these results.

2.3 *HLA locus A and B typing in Malays*

Malay NPC patients from Singapore continue to be HLA typed. So far, 26 have been typed and their HLA profiles compared with those of 106 normal Malays. Malay NPC patients had higher

[2] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 128.
[3] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 128.

Table 40. HLA antigens in Chinese nasopharyngeal carcinoma (NPC) patients: comparison of first and second studies

Antigen	NPC 1st study n = 141	NPC 2nd study n = 93	NPC total n = 234	Controls n = 238
A2	86 (61.0%) χ^2 = 2.33 P = 0.064[a] RR = 1.39	62 (66.7%) χ^2 = 5.13 P < 0.012[a] RR = 1.78	148 (63.2%) χ^2 = 5.15 RR = 1.53	126 (52.9%)
A11	57 (40.4%) χ^2 = 14.3 P = 0.004[b] RR = 0.44	39 (41.9%) χ^2 = 9.33 P < 0.002[a] RR = 0.47	96 (41.0%) χ^2 = 17.91 RR = 0.45	144 (60.5%)
B17	40 (28.4%) χ^2 = 11.18 P = 0.02[b] RR = 2.38	26 (28.0%) χ^2 = 8.42 P < 0.002[a] RR = 2.33	66 (28.2%) χ^2 = 13.69 RR = 2.36	34 (14.3%)
BW46	48 (34.0%) χ^2 = 5.80 P = 0.008[a] RR = 1.76	34 (36.6%) χ^2 = 6.59 P ≃ 0.005[a] RR = 1.96	82 (35.0%) χ^2 = 8.78 RR = 1.84	54 (22.7%)
A2 BW46	41 (29.1%) χ^2 = 7.33 P = 0.0034 RR = 1.97	30 (32.3%) χ^2 = 8.97 P < 0.002 RR = 2.29	71 (30.3%) χ^2 = 11.21 RR = 2.09	41 (17.2%)
AW19/B17	36 (25.5%) χ^2 = 13.8 P = 0.0002 RR = 2.80	23 (24.7%) χ^2 = 10.11 P ≃ 0.0005 RR = 2.6	59 (25.2%) χ^2 = 16.32 RR = 2.75	26 (10.9%)

[a] One-sided P value
[b] Two-sided P value

Table 41. HLA antigens in various subgroups of nasopharyngeal carcinoma patients (NPC) and controls

Subjects	B17	BW46	A2 without B17 or BW46
NPC newly-diagnosed	66/234 (28.2%)	82/234 (35.0%)	58/234 (24.8%)
NPC dead < 2 yr	21/71 (29.6%)	25/71 (35.2%)	17/71 (23.9%)
NPC dead 2-5 yr	4/28 (14.3%)	13/28 (46.4%)	8/28 (28.6%)
NPC alive > 5 yr	7/48 (14.6%)	13/48 (27.1%)	18/48 (37.5%)
Controls	34/238 (14.3%)	54/238 (22.7%)	73/238 (30.7%)

frequencies of HLA-B17 and B18 and lower frequencies of HLA-A10, B15 and BW35, when compared with normal controls: 8/26 (30.8%) NPC patients had B18 compared with 15/106 (14.2%) normal controls (χ^2 = 4.01; P < 0.05; RR = 2.7). However, this difference was not significant when corrected for the number of antigens typed.

(*a*) *Haplotype association*

The presence of HLA-B18 in NPC patients was most frequently associated with A9, giving a delta value of 0.079—a strong association. The delta value of A9/B18 in the normal population was 0.003, i.e., there was no association. The frequency of A9/B18 was higher in patients (7/26, 26.9%) than in controls (9/106, 8.5%; $\chi^2 = 6.66$; P = < 0.01; RR = 3.97).

The haplotype AW19/Blank, B17, which was found in Chinese NPC patients, was also higher in Malay NPC patients than in controls: the joint occurrence of AW19/Blank and B17 was observed in 6/26 (23.1%) Malay NPC patients, compared with 9/106 (8.5%) normal Malay controls ($\chi^2 = 4.41$; $P < 0.05$; RR = 3.23).

(*b*) *A locus blank*

It was reported previously[4] that Malay NPC patients had a significantly higher frequency of A locus blank than controls. This blank could be due to homozygosity of A locus antigens or to the presence of yet undetected locus A antigens. In an attempt to identify such antigens we have used 360 maternal sera from Malay subjects to screen Malay cells that possess the blank. So far, we have not identified any sera that type for the blank. The study was limited by the small numbers of Malay NPC patients in Singapore; a study of Malay NPC patients in collaboration with Mr Prasad, ENT Department, University of Malaya, Kuala Lumpur, was postponed until next year because of Mr Prasad's absence.

The other possibility is that the locus A blank is due to homozygosity. There were 15 locus A blanks among the 26 Malay NPC patients (58%); of these blanks, 7 (47%) were associated with A9. The expected number of A9 homozygotes and heterozygotes was calculated from the gene frequency of A9 in patients and controls and compared with the observed numbers (Table 42). In the normal population, the numbers were similar ($\chi^2 = 0.88$); however, in the patients there was a higher number of observed A9 homozygotes and a lower number of heterozygotes than expected ($\chi^2 = 6.15$; $P < 0.025$), suggesting that there is an excess of A9 homozygotes among patients. However, the blank could still represent missing antigens strongly associated with A9 in patients. Family studies should solve this question.

Table 42. A9 homozygotes and heterozygotes among Malay nasopharyngeal carcinoma (NPC) patients and controls

Subjects	A9/Blank	A9/X	X/X
Malay controls			
Expected	13	48	45
Observed	16	48	45
	$\chi^2 = 0.88$	not significant	
Malay NPC patients			
Expected	3	11	11
Observed	7	8	11
	$\chi^2 = 6.15$	$P < 0.025$	

[4] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 128.

2.4. *HLA locus A and B typing in Kadazans*

The crude incidence of NPC in Kadazans has been reported to be as high as that in Chinese. These patients are mostly quite young, of an age similar to that of Tunisian patients. In collaboration with Mr Kulkarni of Sabah General Hospital, Sabah, East Malaysia, we began (June 1978) HLA typing of NPC patients and controls. This pilot study is being done blind and the code broken only after completion of typing of 25 NPC patients and 25 age- and sex-matched controls. Histological specimen blocks and sera will be kept for future confirmation and analysis.

2.5. *Locus C typing*

Locus C typing with sera from the 7th International Histocompatibility Workshop has been started; so far we have typed 43 NPC patients and 24 control subjects. CW2, CW5 and CW6 occurred in low frequencies in Chinese. The joint occurrence of CW1/CW3 was observed more frequently among patients than among controls: in 21/43 (49 %) NPC patients compared with 7/24 (29 %) controls; and there was a strong association of CW1/CW3 with the A2 BW46 haplotype. This also suggests that a segment of chromosome is held together in strong linkage disequilibrium, the haplotype being A2 CW1/CW3 BW46.

2.6 *Locus DR (Ia) typing*

During the 7th International Histocompatibility Workshop conference it was felt that locus D typing by the mixed lymphocyte reaction (MLR) method, locus DR typing by serological methods and locus D typing by primed lymphocyte transformation (PLT) may all be detecting the same gene product.

The sera from this workshop were used to type 46 unrelated, newly-diagnosed Chinese NPC patients and 22 unrelated Chinese controls. DRW1, W5, W7 and W8 occurred in low frequencies or were absent in the Chinese population. DRW4 × 7 and DR locus blank showed a higher frequency and DRW4 a lower frequency among NPC patients than among controls: DRW4 × 7 was observed in 10/46 (21.7 %) NPC patients compared with 2/22 (9.1 %) controls ($P = 0.13$; RR = 2.78). DR locus blank showed a gene frequency of 60.1 % among patients compared with 38.6 % among controls, a situation reminiscent of pre-Sin 2 days. Interestingly, the reactivities of two local Ia sera, AH21 and AH214, filled in some of the DR locus blanks.

We reported previously that NPC patients had a higher frequency of reactivity to AH21, AH214 and AH54 than did normal subjects[5]. In a second study, AH21 reactivity was observed in 18/52 (35 %) NPC patients, compared with 2/22 (9 %) controls ($\chi^2 = 3.89$; one-sided $P = 0.025$; RR = 5.29). We also showed in one family that AH21 reactivity segregated within the family and was linked with the A10 BW46 haplotype. DR locus typing of NPC patients and controls is being continued, and further comparisons of DR locus antigens with antigens from other loci will be possible at a later date.

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[5] Chan, S. H. & Simons, M. J. (1977) *Ann. Acad. Med.*, **6**, 4.

We have initiated in Ia sera exchange programme with other laboratories; the response has been very good, so much so that we now have sufficient antisera for all the currently known antigens for 1 500 subjects.

3. RISK FACTORS FOR LUNG CANCER IN SINGAPORE CHINESE
Co-investigators: Dr. J. L. DaCosta and Dr. Y. K. Ng
Co-ordinating officer: Dr R. MacLennan

This study has been concluded and the results have been published[6].

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[6] MacLennan, R. DaCosta, J., Day, N. E., Law, C. H., Ng, Y. K. & Shanmugaratnam, K. (1977) *Int. J. Cancer,* **20,** 854–860.

9. IARC RESEARCH CENTRE TEHERAN

Dr B. ARAMESH (Head)
Mr P. GHADIRIAN (Director, Babol Research Station)
Dr J. KMET (IARC Consultant)
Dr G. STEIN, Centre for Disease Control, Atlanta, GA, USA (Consultant)
Professor T. HEWER, University of Bristol, UK (Consultant)
Mrs P. COOK-MOZARAFFI, Cancer Epidemiology and Clinical Trials Unit, Oxford, UK (Consultant)

Collaborating Institute:
Institute of Public Health Research, University of Teheran (Director, Dr A. Nadim)

1. CASPIAN CANCER REGISTRY

The work of the Caspian Cancer Registry has continued (RA/70/024), and data up to June 1977 have been sent to IARC. The Registry was visited by a WHO consultant in February 1978 at the request of the WHO Regional Office for the Eastern Mediterranean (EMRO). Periodical checks on the registration process are undertaken, but the computation of rates still awaits the detailed results of the 1976 census.

2. ŒSOPHAGEAL CANCER STUDIES (Dr N. E. Day)

The results of preliminary observations in zones of contrasting œsophageal cancer incidence have now been published [1], and analysis of a study of cases and controls in their households has now been completed [2].

2.1 *Case-control studies*

At a progress review meeting held in Iran in October 1976 of Iranian and IARC investigators and attended by representatives of the National Cancer Institute (USA), it was decided that the next step would comprise a further case-control study to examine the role of external carcinogens,

[1] Joint Iran-IARC Study Group (1977) *J. natl Cancer Inst.*, **59**, 1127–1138.
[2] International Agency for Research on Cancer (1977) *Annual Report, 1977*, Lyon, p. 135.

possibly derived from opium products, and of bread contaminants acting upon œsophageal mucosa perhaps rendered more susceptible by nutritional and genetic factor imbalance. To study these relationships, about 180 cases and their households will be compared with the same number of matched control households. Approximately 120 cases from the high-risk area districts of Gonbad and Gorgan will be selected, in addition to 60 cases from the lower risk area of Gilan. It is estimated that it will take two years to complete the study.

(*a*) *Nutritional status*

The nutritional status of the members of the case and control households will be studied through biochemical tests and comparisons of dietary intake. In a limited number of multiple-case families, HLA haplotypes will be studied to identify postulated disease susceptibility genes. Other aspects of the genetic profiles of cases, controls and their family members will be assessed by analysing red-cell enzymes and serum protein systems.

In relation to external carcinogens, urine samples will be collected from members of the case and control households to evaluate the presence of morphine metabolites, and a small number of urine samples from opium addicts will be tested for mutagenic activity (see p. 110). Further inquiries will be made into the wheat storage practices in the highest-risk regions, to identify potentially harmful contaminants, and the adventitious seeds identified in locally consumed wheat will be tested for mutagenic activity. Liver enzyme activities in members of the case and control households will be compared by studying the dynamics of antipyrine metabolism to ascertain whether there are differences in the ability to metabolize chemical components between case and control households.

(*b*) *Questionnaire*

The questionnaire and data collection forms were designed and translated from the original English to Persian and then retranslated to ensure the identity of both texts.

(*c*) *Pilot study*

A pilot study began in February 1977 in four villages. Based on this experience, forms and procedures were adapted, and the logistic plans completed and reviewed.

2.3 *Studies on opium habits in the low-risk region*

The study group of the Institute for Public Health Research, Teheran, organizing population laboratory research in a region of Gilan, an area which was also selected as a control for the high œsophageal cancer risk Turkoman region, has made detailed enquiries into opium habits in a population subsample of 3 300 people of all ages[3]. More than half the subjects interviewed, males and females over 60 years of age, have admitted to smoking and/or eating opium regularly. Identical patterns emerged after a similar study in the high-risk Guklan in Gonbad, a pure Turkoman high-risk region[4]. Thus, if opium products are factors in the causation of œsophageal cancer in the high-incidence areas of the Caspian, they are unlikely to act in isolation.

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[3] Alemi, A. A. & Naraghi, M. M. (1978) *Drug Alcohol Dependence*, **3**, 107–112.
[4] Dr Keyvan (personal communication).

2.4 *Studies of nitrites in saliva*

While previous studies had not shown significant differences in nitrosamine content of diet in high and low incidence areas, there were differences in nitrite ingestion, and the question of *in vivo* formation remained open. To assess the intake of nitrate from endogenous sources, in October 1977 and May 1978 the concentration of nitrites in saliva was studied in selected population groups in high-risk Turkoman villages and in low-risk Gilan. After initial results suggested a difference, the examination of large numbers of subjects failed to demonstrate significantly higher concentrations of nitrites among the Turkomans (see p. 47).

2.5 *Nutritional studies*

Further analyses of the field studies conducted in the autumn of 1976 and in the spring of 1977 have confirmed the original observation that riboflavin deficiency, as assessed by the clinical signs of an angular stomatitis, is frequent in children and pregnant and lactating women in both high and low œsophageal cancer incidence areas. The glutathione reductase estimations have shown that a biochemical deficiency is more widespread than the clinical signs would indicate. If involved in the etiology of this disease, the deficiency could, therefore, merely be facilitating the action of unknown carcinogen(s) or promoting other mechanisms involved in the cancerization of œsophageal mucosa. It is highly probable that nearly all those of low socio-economic levels suffer from riboflavin deficiency at some time in their lives. Test of humoral immunity failed to show differences between riboflavin-deficient and control subjects.

2.6 *Further studies of the ethnic distribution of œsophageal cancer*

It has been suggested that persons of Turkic or Kurdish origin are at greater risk for œsophageal cancer than those of Persian stock. Further enquiries have thus been made into the ethnic composition of the high-risk, non-Turkoman parts of southern Gonbad and southern Gorgan, which indicate a strong admixture of Turkish genetic elements, both past and present.

2.7 *Familial aggregation of cancer of the œsophagus in high-risk Turkomans*

Retrospective enquiry among 428 families of patients with cancer of the œsophagus who reported to the Registry during the last few years revealed multiple case families: over half of the families had more than one case. In 38 families there were 3 cases, in 14 families 4 cases, in 9 families 5 cases, in 2 families 6 cases, in one family 7 cases and in another 8 cases. The significance of this finding in a high-incidence area is being evaluated. Such families are being studied for HLA pattern.

2.8 *Virus and immunological studies* (Dr F. Modabber)

(*a*) *Herpesviruses*

In view of the Agency's interest in the possible carcinogenic role of viruses in human cancer, the possible association of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) with cancer of the œsophagus has been studied. Antiviral capsid antigen (VCA) of EBV was determined in 140 patients and 140 controls. No significant increase in the anti-VCA titre was observed in patients, although a higher percentage of patients had titres > 1:160 than did controls (26 % of patients compared with 13 % of controls). The anti-CMV titres showed no difference between patients and controls.

(*b*) *Tumour-associated antigens*

Tumour-associated antigens were sought using the direct immunofluorescence test. Accordingly, the fluorescein-conjugated gamma-globulin of one patient's serum, reacted with a number of fresh tumour cells, was tested with tumour cells grown in culture for various time periods. Sera of patients or normal controls were used as inhibitors of this reaction. The preliminary findings are that 70 % of patients' sera, in contrast to 40 % of normal sera, can inhibit the direct immunofluorescent test. This work is being continued.

(*c*) *Tumour-cell cultures*

Tumour cells are being grown in culture, and various conditions for cell growth and characteristics of cultured cells, such as morphology and division rate, are being studied[5]. The cells are also being studied by electron microscopy (in collaboration with Dr L. Williamson).

(*d*) *Immunogenetics*

To explore the possibility of an association between HLA profile and œsophageal cancer, 151 patients with histologically-confirmed œsophageal cancer were compared with 214 controls of similar ethnic background[6]. The initial higher frequency of HLA BW40 in cases did not persist when larger numbers were tested, and no significant differences were found. However, before the possibility of an association between HLA antigens and the disease can be overruled, families with multiple cases must be explored. Possible involvement of two sets of genes, including genetic loci not linked to HLA antigens, as well as limitations of genetic variations in family units, indicate that such studies are warranted.

2.9 *Pathological studies*

The proportion of cases with œsophageal cancer reported to the Caspian Registry, diagnosed histologically, has never been more than 15 %, and it has hitherto proved difficult to obtain

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[5] Sabari, S. & Mategh, R. (in preparation).

[6] Mohagheghpour, N. (1978) In: *Proceedings of the First International Symposium on HLA and Disease, Paris, 1976* (in press).

necropsy material to determine whether there were other œsophageal lesions in the Caspian area and their association with the cancer.

Examination of specimens of œsophagi from Turkomans dying in Gonbad and Teheran from causes other than œsophageal cancer have shown atrophic and dysplastic changes (in collaboration with Dr A. Cor, Gonbad, Dr K. Laden, Rasht and Professor A. Armin, University of Teheran). Combined with the findings from the early detection programme conducted in May 1978 (see section 2.10 below), studies of the natural history of the disease can now be considered to be on a sound basis.

2.10 *Early detection studies*

A pilot study of early detection screening was mounted in three high-risk Turkoman villages in May 1978 to assess the natural history of the disease in the high-incidence areas, to look for associated lesions and to ascertain the possible load on œsophagus cancer treatment facilities in Teheran, if mass screening was to be introduced. Endoscopy examination, which included aimed cytology and biopsy, was carried out on 441 of the 510 apparently healthy males and females aged 15 to 70 years presenting to the field medical team (Dr C. Amiri, Dr M. Crespi, Dr A. Grassi, Dr N. Muñoz). Blind abrasive cytology using the Crespi brush was carried out on 41 persons and with the Chinese balloon in 18 individuals. The most striking feature was the presence of mild to severe macroscopic lesions in 85% of individuals examined endoscopically. These lesions appeared as white patches in a thin congested and fragile mucosa. The histology is being evaluated in Teheran and Lyon and will be compared with the cytological findings being assessed in Rome and Teheran. Seven cases of cancer of the œsophagus were seen, two of them already reported to the Registry. Of the remaining five, three were symptomatic and two asymptomatic (see p. 130). Histological examination revealed a further five cases of cancer.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE SEVENTEENTH SESSION OF THE IARC GOVERNING COUNCIL 4–5 MAY 1978

Australia

Dr R. W. CUMMING
Assistant Director-General
International Health Branch
Department of Health
Canberra

Dr J. RAVENSCROFT
Director, Accounting Office
Australian Department of Finance
Geneva, Switzerland

Belgium

Professor S. HALTER
Secretary-General
Ministry of Public Health and the Family
Brussels

France

Professor E. J. AUJALEU
Honorary Director-General
National Institute of Health and Medical Research
Counsellor of State
Paris

Dr J. F. DUPLAN *(Rapporteur)*
Counsellor
National Institute of Health and Medical Research
Bordeaux

Mr J. F. STUYCK-TAILLANDIER
Ministry of Foreign Affairs
Paris

Federal Republic of Germany

Mr H. VOIGTLANDER *(Chairman)*
International Health Relations Section
Federal Ministry for Youth, Family Affairs and Health
Bonn

Italy

Professor R. VANNUGLI *(Vice-Chairman)*
Director, Bureau of International Relations
Ministry of Health
Rome

Professor L. SANTI
Director, Institute of Oncology, University of Genoa
Genoa

Japan

Dr A. TANAKA
Ministry of Health and Welfare
Tokyo

The Netherlands

Dr J. SPAANDER
Director-General
National Institute of Public Health
Bilthoven

Mr W. J. KAKABEEKE
Deputy Director International Affairs
Ministry of Health and Environmental Protection
Leidschendam

Union of Soviet Socialist Republics

Professor N. N. BLOKHIN
Director, Cancer Research Center
President, Academy of Medical Sciences of the USSR
Moscow

Professor V. P. DEMIDOV
Chief of Cancer Department
Ministry of Public Health of the USSR
Moscow

Dr Y. I. PUCHKOV
Chief, Department of International Scientific Relations
Cancer Research Center
Academy of Medical Sciences
Moscow

Dr M. N. SAVELIEV
Adviser-Deputy Chief, External Relations Board
Ministry of Public Health of the USSR
Moscow

United Kingdom

Dr R. C. NORTON
Senior Principal Medical Officer
Medical Research Council
London

Dr T. VICKERS
Deputy Chief Scientific Officer
Medical Research Council
London

Dr T. J. GREFFEN
Senior Principal Medical Officer
Department of Health and Social Security
London

United States of America

Professor A. C. UPTON
Director
National Cancer Institute
National Institutes of Health
Bethesda, Md.

Mr R. F. ANDREW
Director, Agency for Health and Drug Control
Department of State
Washington, D.C.

Dr G. T. O'CONOR
Associate Director for International Affairs
National Cancer Institute
National Institutes of Health
Bethesda, Md.

World Health Organization

Dr T. A. LAMBO
Deputy Director-General

Mr A. GROENENDIJK
Director, Division of Budget and Finance

Mr C. H. VIGNES
Director, Legal Division

Observers

Professor S. ECKHARDT
Outgoing Chairman of the IARC Scientific Council

Professor K. MUNK
Incoming Chairman of the IARC Scientific Council

Annex 2

MEMBERS OF THE SCIENTIFIC COUNCIL AT ITS FOURTEENTH SESSION, 21–23 FEBRUARY 1978

Professor P. BOGOVSKI
Director
Institute of Experimental and Clinical Medicine
Tallinn, Estonian SSR

Professor A. CAPUTO
Director
Regina Elena Institute for Cancer Research
Rome

Sir RICHARD DOLL
Regius Professor of Medicine, Oxford University
Radcliffe Infirmary
Oxford, UK

Professor S. ECKHARDT *(Chairman)*
Director
National Institute of Oncology
Budapest

Professor J. MILLER *(Rapporteur)*
Head, Experimental Pathology Unit
Walter and Eliza Hall Institute of Medical Research
Royal Melbourne Hospital PO
Melbourne, Australia

Professor K. MUNK *(Vice-Chairman)*
Director, Institute of Virology
German Cancer Research Centre
Heidelberg, Federal Republic of Germany

Professor E. SAXEN
III Department of Pathology
University of Helsinki
Helsinki

Professor M. TUBIANA
Head, Department of Radiation
Gustave-Roussy Institute
Villejuif, France

Professor T. G. VAN RIJSSEL
Pathology Laboratory, Faculty of Medicine
National University of Leiden
Leiden, The Netherlands

Annex 3

RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS JUNE 1977 – JUNE 1978

Support of IARC Research Centres

RA/68/002	University of Singapore (Contribution to the maintenance of an IARC Research Centre at the University of Singapore)
RA/75/020	University of Nairobi (Contribution to the maintenance of an IARC Research Centre at the University of Nairobi)

Reference centres/Serum banks

RA/73/029	Institute of Experimental Oncology, University of Genoa, Genoa, Italy (IARC Reference Centre for environmental carcinogenesis)
RA/73/033	Medical College, Hanover, Federal Republic of Germany (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/74/003	Institute for Documentation, Information and Statistics, German Cancer Research Centre, Heidelberg, Federal Republic of Germany (Clearing-house for on-going research in cancer epidemiology)
RA/75/014	National Institute of Hygiene, Budapest (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/76/019	Angel H. Roffo Oncological Institute, Buenos Aires (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/77/004	Cairo Cancer Institute, Cairo (Agreement for collection and extraction by dichloromethane of urinary samples from twenty patients with bilharzia and twenty patients with urinary bladder cancer)
RA/77/005	British Food Manufacturing Industries Research Association, Leatherhead, Surrey, UK (Extraction and examination of urine samples from twenty patients with bladder cancer and twenty paraplegic patients)

RA/78/002 School of Pharmacy, Catholic University of Louvain, Brussels
(Creation of an IARC Reference Centre for the *in vivo* monitoring of drug metabolizing enzymes)

RA/78/006 Laboratory of Genetics, University of Pisa, Pisa, Italy
(Creation of an IARC Reference Centre for environmental carcinogenesis)

Cancer registries/Incidence studies

RA/67/009 IARC Research Centre, University of Singapore
(Cancer registry at Singapore)

RA/70/024 Institute of Public Health Research, University of Teheran, Teheran
(Study on the incidence of cancer in the Caspian littoral of Iran)

RA/72/014 Department of Pathology, University of the West Indies, Kingston, Jamaica
(Partial support of the Jamaica Cancer Registry)

RA/73/016 International Association of Cancer Registries
(Provision of a secretariat and other supporting services)

RA/76/016 Medico-Social Research Board, Dublin
(Study of causes of death among Guinness brewery workers in Dublin)

RA/76/018 Birmingham Cancer Registry, Birmingham, UK
(Development and completion of a computer-based exercise based on a hypothetical occupational cancer risk)

RA/77/019 Medico-Social Research Board, Dublin
(Study of causes of death among Irish whiskey distillery workers)

RA/77/027 Institute of Hygiene, University of Aarhus, Aarhus, Denmark
(Study of diet, intestinal microecology and colon cancer in Denmark)

RA/77/028 National Institute of Health and Medical Research, Nutrition Department, Le Vésinet, France
(Study on the relationship between alcohol and ischaemic heart disease in Rouen)

RA/77/030 Finnish Cancer Registry, Helsinki
(Study of diet, intestinal microecology and colon cancer in Finland)

Œsophageal cancer studies

RA/75/015 National Institute of Health and Medical Research, Division of Medico-Social Research, Le Vésinet, France
(Study of cases of œsophageal cancer and their controls in the Calvados region of France)

RA/78/003 Institute of Public Health Research, University of Teheran, Teheran
(Joint Iran/IARC study of characteristics of selected population groups in areas of differing œsophageal cancer incidence in the Caspian littoral of Iran: nutritional, genetic and environmental studies in high- and low-risk areas)

Studies on cancers linked with herpesviruses

RA/70/013 Hong Kong Anti-Cancer Society, Hong Kong
(Studies on the relationship between herpes-type infection and nasopharyngeal carcinoma)

RA/70/017 Department of Pathology, University of Singapore
(Studies on the relationship between herpes-type infection and nasopharyngeal carcinoma)

RA/71/020 East African Virus Research Institute, Entebbe, Uganda
(Follow-up study on Burkitt's lymphoma and Epstein-Barr herpesvirus infection in the West Nile District of Uganda)

RA/72/030 Netherlands Cancer Institute, Amsterdam
(Collaborative studies on immunoserology of Burkitt's lymphoma and nasopharyngeal carcinoma)

RA/73/017 Sainte Marie-Thérèse Clinic, Lyon, France
(Study of the role of the herpesvirus type Epstein–Barr in the establishment of permanent cell lines from cord blood specimens)

RA/74/001 Association for the Development of Cancer Research, Primatology Laboratory, National Centre for Scientific Research, Villejuif, France
(Studies on the induction of lympho-epithelial tumours in the marmoset with Epstein–Barr virus)

RA/74/018 University of Hong Kong, Queen Mary Hospital Compound, Hong Kong
(Isolation and purification of Epstein–Barr virus-specific antigens)

RA/75/002 Ross Institute, London School of Hygiene and Tropical Medicine, London
(Malaria antibody testing to be carried out by the Institute on sera from Burkitt's lymphoma studies in the West Nile District of Uganda and the Mara Region of Tanzania)

RA/75/006 Lyon Blood Transfusion Centre, Plasma Desiccation Department, Histocompatibility Department, Beynost, Miribel, France
(HLA typing of blood from families with nasopharyngeal carcinoma in Tunisia)

RA/77/008 Shirati Mission Hospital, Musoma, Tanzania
(Studies on the effect of partial malaria suppression on incidence of Burkitt's lymphoma in North Mara)

RA/77/015 Department of General and Applied Biology, Claude Bernard University, Villeurbanne, France
(Characterization and purification of viral antigens for the development of serological tests)

Liver cancer studies

RA/76/012 Geneva Tumour Registry, Geneva, Switzerland
(Study of liver disease, including primary liver cancer, in the canton of Geneva)

RA/77/007 School of Pathology, Middlesex Hospital Medical School, London
(Estimation of hepatitis B antigen and antibody and other viral antibodies in serum specimens from East African cancer patients)

RA/77/018 Department of Social Medicine and Public Health, University of Singapore
(Cohort study on hepatitis B carriers and liver cancer)

RA/77/020 Department of Pathology, All-India Institute of Medical Sciences, New Delhi
(Experimental studies on hepatitis B and aflatoxin and a collaborative study on localization of hepatitis B antigens in fixed liver tissue)

Studies on chemical carcinogenesis

RA/70/002 Medical College, Hanover, Federal Republic of Germany
(Investigation of the effects of chemical carcinogens administered transplacentally on the fetal reproductive organs)

RA/70/003 Institute of Pathology, Medical University, Budapest
(Investigation of the effects of minute doses of chemical carcinogens on cells cultured *in vitro)*

RA/74/007 National Institute of Public Health, Bilthoven, The Netherlands
(Study on the potential carcinogenicity of maleic hydrazide)

RA/74/011 Ministry of Health, Institute of Experimental and Clinical Medicine, Tallinn, Estonian SSR
(Investigations on the combined carcinogenic action of asbestos dust and *N*-nitroso compounds in the hamster)

RA/76/017 Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow
(Investigation on the effect of prenatal exposure to a chemical on successive untreated generations)

RA/76/027 Institute for Experimental Toxicology and Chemotherapy, German Cancer Research Centre, Heidelberg, Federal Republic of Germany
(Study of elaboration of analytical methods for identification and quantification of *N*-nitroso compounds in various environmental media)

RA/77/022 N. N. Petrov Research Institute of Oncology, Leningrad, USSR
(Multi-generation studies of modifying factors in transplacental carcinogenesis)

RA/77/023 Institute for Experimental Toxicology and Chemotherapy, German Cancer Research Centre, Heidelberg, Federal Republic of Germany
(Study to find suitable methods for the preservation of human urines to be analysed for *N*-nitroso compounds)

RA/77/024 Institute of Oncology, Sofia
(Investigation on the combined action of several chemical carcinogens)

RA/77/025 Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow
(Investigation on the combined action of several chemical carcinogens)

RA/77/026 Central Institute for Cancer Research, Academy of Sciences of the German Democratic Republic, Berlin
(Investigation on the combined action of several chemical carcinogens)

RA/78/004 Laboratory of Biophysics and Radiobiology, Free University of Brussels, Rhode-Saint-Genèse, Belgium
(Investigation of an *in vitro* biochemical assay for somatic mutagenesis by chemical mutagens/carcinogens and the effects of promoters in chemical carcinogenesis)

RA/78/005 Department of Pharmacognosy, Medical School, University of Szeged, Szeged, Hungary
(Study to identify the mutagenic components of crude opium and opium dross)

Studies on carcinogens other than chemicals

RA/76/008 Joint European Medical Research Board, Liverpool, UK
(International epidemiological research programme to examine health effects, particularly as these concern cancer, of exposure to man-made mineral fibres in man)

RA/76/026 Institute of Oncology of the University of Genoa, Genoa, Italy
(Study on interaction between asbestos and chromosomal proteins from different human tissues)

RA/78/007 Medical Research Council of the United Kingdom, London
(Study of mineral fibres, natural and man-made, including asbestos erionite and others causing airborne pollution)

RA/78/011 Medical Research Council Pneumoconiosis Unit, Llandough Hospital, Penarth, UK
(Study of mesothelioma in Central Turkey)

RA/78/012 Department of Chest Diseases, Hacettepe University, Ankara
(Study of mesothelioma in Central Turkey)

Studies of various other cancer forms

RA/73/004 Department of Pathology, University of Iceland, Reykjavik
(Investigations on familiality of carcinoma of the breast)

RA/77/010 Department of Community Medicine, University of Hong Kong, Hong Kong
(Case-control study of lung cancer in Chinese in Hong Kong)

RA/77/013 Tata Memorial Centre, Parel, Bombay, India
(*In vitro* immunological studies on cancer patients in Bombay)

RA/77/016 Institute of Oncology and Radiobiology, Havana
(Study of lung cancer in Cuban women)

RA/78/013 Department of Clinical Genetics, University Hospital of Lund, Lund, Sweden
(Study on possibility of correlating karyotypes of cancer cells to specific etiological factors)

Support of meetings

RA/77/001 International Epidemiological Association, Johns Hopkins University, Baltimore, Md., USA
(Partial support of attendance costs of selected participants to a symposium and sessions relating to cancer at 8th International Scientific Meeting of IEA in Puerto Rico, 17–23 September 1977)

RA/77/011 Protein Laboratory, University of Copenhagen, Copenhagen
(Support of a workshop of the 5th Meeting of the International Research Group for Carcino-embryonic Proteins)

RA/77/014 Department of Microbiology, Milton S. Hershey Medical Center, Pennsylvania University, Hershey, Pa., USA
(Contribution to the Third International Symposium on Oncogenesis and Herpesviruses, Cambridge, Mass., USA, 25–30 July 1977)

RA/77/017 New England Center for Continuing Education, University of New Hampshire, Durham, N.H., USA
(Organization of 5th Meeting on Analysis and Formation of *N*-Nitroso Compounds, Durham, N.H., 22–26 August 1977)

RA/77/029 Cytology and Cancer Detection Centre, Geneva, Switzerland
(Partial support for a meeting on epidemiology of cancers of the larynx)

RA/78/001 Medical Clinic, Marburg/Lahn, Federal Republic of Germany
(Support of attendance costs of selected participants at the 6th Meeting of the International Research Group for Carcino-embryonic Proteins, Marburg, 17–21 September 1978)

RA/78/008 Zaragoza Tumour Registry, Zaragoza, Spain
(Support for the meeting of the Latin-Tongued Cancer Registries, 4–5 May 1978)

Annex 4

MEETINGS AND WORKSHOPS ORGANIZED BY IARC, 1977–78

Third international symposium on oncogenesis and herpesviruses	Cambridge, Mass., USA, 25–30 July 1977
Fifth meeting on the analysis and formation of *N*-nitroso compounds	Durham, N.H., USA 22–26 August 1977
Meeting on criteria for evaluating the carcinogenic risk of chemicals to man	Lyon, 3–7 October 1977
Working group meeting for the organization of an epidemiological study on laryngeal cancer	Lyon, 6–7 October 1977
Evaluation of the carcinogenic risk of chemicals to man: some *N*-nitroso compounds and polychlorinated biphenyls	Lyon, 10–15 October 1977
Course on the epidemiology of chronic diseases with special emphasis on cancer	Karachi, Pakistan, 22 October–3 November 1977
Course on aspects of chemical carcinogenesis	Lyon, 14–19 November 1977
Study of risk from man-made mineral fibres—protocol meeting	Lyon, 16–17 November 1977
Editorial board on manual of selected methods of analysis of environmental carcinogens	Lyon, 17–18 November 1977
International network for the continuing evaluation of environmental factors in human cancer: Group meeting I	Lyon, 23–25 November 1977
Meeting on the biological action of alcohol	Lyon, 28 November 1977
IARC/INSERM symposium on carcinogenic risks—strategies for intervention	Lyon, 30 November–2 December 1977
Workshop on analysis of case-control studies in epidemiology	Lyon, 12–15 December 1977
Joint IARC/EEC working group on dietary fibre and disease	Lyon, 19–21 December 1977
Joint NIEHS/IARC working group on coordination of epidemiological studies on the long-term hazards of chlorinated dibenzodioxins and chlorinated dibenzofurans	Lyon, 10–11 January 1978

Meeting of the advisory committee for the coordination of chemical studies on *N*-nitroso compounds	Lyon, 23–25 January 1978
Meeting of the editorial board for *Cancer Incidence in Five Continents*, Vol. 4	Lyon, 30–31 January 1978
Meeting on tumour immunology	Lyon, 2–3 February 1978
Evaluation of the carcinogenic risk of chemicals to man: some plastics and synthetic rubber compounds	Lyon, 7–13 February 1978
Working group meeting for the organization of an epidemiological study on laryngeal cancer	Turin, Italy, 23–25 February 1978
Workshop on the role of cancer research in developing countries	Lyon, 14–16 March 1978
Meeting on alcohol and cancer	Lyon, 30 March 1978
Third postgraduate course on immunovirology of cancer	Lyon, 10–21 April 1978
Study of risk from man-made mineral fibres: planning workshop	Copenhagen, 17–19 April 1978
Working group to evaluate the significance of carcinogenicity evidence for chemicals considered in the *Monographs*	Lyon, 24–26 April 1978
Alcohol and cancer: training seminar	Lyon, 22–31 May 1978
Organizing committee for working group to establish basic requirements for carrying out long-term and short-term carcinogenicity and related tests, to be held in Hanover 11–16 June 1979	Hanover, Federal Republic of Germany, 26 May 1978
Evaluation of the carcinogenic risk of chemicals to man: some halogenated hydrocarbons	Lyon, 6–13 June 1978
Meeting of editorial board of the manual on the safety of handling carcinogens in the laboratory	Lyon, 19–21 June 1978

Annex 5

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Annex 6

INTERNAL TECHNICAL REPORTS, 1977–78

IARC Internal Technical Report No.	
77/002	IARC monograph programme on the evaluation of the carcinogenic risk of chemicals to humans—preamble (Lyon, 3–7 October 1977)
78/001	Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans—report of a joint NIEHS/IARC working group meeting (Lyon, 10–11 January 1978)
78/002	Cancer incidence cumulatives rates. International comparison based on *Cancer Incidence in Five Continents,* Volumes I, II and III
78/003	Chemicals with sufficient evidence of carcinogenicity in experimental animals – *IARC Monographs* Volumes 1–17 (Lyon, 24–26 April 1978)

Annex 7

PAPERS PUBLISHED OR SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS

Barbin, A., Planche, G., Croisy, A., Malaveille, C. & Bartsch, H. (1977) *Detection of electrophilic metabolites of halogenated olefins with 4-(4-nitrobenzyl)pyridine (NBP) or with* Salmonella typhimurium. In: *Abstracts, Second International Conference on Environmental Mutagens, Edinburgh*

Bartsch, H., Kuroki, T., Malaveille, C., Loprieno, N., Barale, R., Abbondandolo, A., Bonatti, S., Rainaldi, G., Vogel, E. & Davis, A. (1978) Absence of mutagenicity of Praziquantel, a new, effective, antischistosomal drug, in bacteria, yeast, insects and mammalian cells. *Mutat. Res.* (in press)

Bartsch, H., Malaveille, C., Barbin, A. & Planche, G. Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced in rodent or human liver tissues; evidence for oxirane formation by P450-linked microsomal mono-oxygenases (submitted for publication)

Bartsch, H., Margison, G. P., Malaveille, C., Camus, A. M., Brun, G. & Margison, J. M. (1977) Some aspects of metabolic activation of chemical carcinogens in relation to their organ specificity. *Arch. Toxicol.*, **39**, 51–63

Breslow, N. E., Chan, C. W., Dhom, G., Drury, R. A. B., Franks, L. M., Gellei, B., Lee, Y. S., Lundberg, S., Sparke, B., Sternby, N. H. & Tulinius, H. (1977) Latent carcinoma of prostate at autopsy in seven areas. *Int. J. Cancer*, **20**, 680–688

Breslow, N. E., Day, N. E., Sabai, C. & Halvorsen, K. T. (1978) Estimation of multiple relative risk functions in matched case-control studies. *Am. J. Epidemiol.* (in press)

Camus, A. M., Wiessler, M., Malaveille, C. & Bartsch, H. (1978) High mutagenicity of *N*-(α-acyloxy)alkyl-*N*-alkylnitrosamines in *S. typhimurium*: Model compounds for metabolically activated *N*,*N*-dialkylnitrosamines. *Mutat. Res.*, **49**, 187–194

Castegnaro, M. & Walker, E. A. (1978) Analyse des *N*-nitrosamines par spectrométrie de masse: étude des spectres de leurs dérivés d'oxydation. *Analusis* (in press)

Castegnaro, M. & Walker, E. A. (1978) *New data from collaborative studies on nitrosamines.* In: Walker, E. A., Castegnaro, M., Griciute, L. & Lyle, R. E., eds, *Environmental Aspects of* N-*Nitroso Compounds*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 19), pp. 53–62

Castegnaro, M., Eisenbrand, G., Ghadirian, P., Griciute, L., Keighobadi, G., Preussmann, R., Spiegelhalder, B. & Walker, E. A. (1978) *Preliminary results of saliva nitrite analyses in Iran.* In: *Proceedings of the 3rd International Symposium on Oncology, Teheran, 4–8 March 1978* (in press)

Castegnaro, M., Garren, L., Griciute, L., Pignatelli, B., Toussaint, G. & Walker, E. A. (1978) *Experience of the TEA detector in the analysis of nitrosamines in a wide range of environmental samples.* In: *Proceedings of the 1st Mediterranean Congress on Chemical Engineering, Barcelona, Spain, November 1978* (in press)

Chan, S. H., Goh, E. H., Khor, T. H., Chew, T. S., de-Thé, G. & Shanmugaratnam, K. (1978) *General immunological status of nasopharyngeal carcinoma patients in Singapore.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 495–501

Chan, S. H., Levine, P. H., de-Thé, G., Lavoué, M. F. & Goh, E. H. (1978) *Prognostic value of EBV serology in NPC.* In: *Proceedings of the 3rd Asian Cancer Conference*

Chan, S. H. & Simons, M. J. (1977) Immunogenetics of nasopharyngeal carcinoma. *Ann. Acad. Med.,* **6**, 4

Chan, S. H., Simons, M. J. & Day, N. E. (1978) *Immunogenetics and immunology of nasopharyngeal carcinoma.* In: *Proceedings of the 3rd Asian Cancer Conference*

Chan, W. C. & MacLennan, R. (1977) Lung cancer in Hong Kong Chinese: mortality and histological types, 1960–72. *Br. J. Cancer,* **35**, 226–231

Dambuyant, C., Sizaret, P. & Martel, N. (1978) *Immunochemical characteristics of concanavalin A reactive and non-reactive alpha-foetoprotein.* In: *Proceedings of the Meeting of the International Research Group for Carcinoembryonic Proteins, Copenhagen, August 1977* (in press)

Dambuyant, C., Sizaret, P., Martel, N., Bordes, M. & Bourgeaux, C. (1978) *Internactions of alpha-foetoprotein and other proteins with concanavalin A.* In: *Proceedings of the Meeting of the International Research Group for Carcinoembryonic Proteins, Copenhagen, August 1977* (in press)

Davis, W. & Harrap, K. R., eds (1978) *Advances in Tumour Prevention, Detection and Characterization, Vol. 4. Characterization and Treatment of Human Tumours,* Amsterdam, Excerpta Medica (*International Congress Series* No. 420)

Davis, W., & Rosenfeld, C., eds (1978) *Carcinogenic Risks—Strategies for Intervention,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 25) (in press)

Day, N. E. (1978) *High risk for cancer.* In: Nieburgs, H., ed., *Prevention and Detection of Cancer, Part II, Detection,* New York & Basel, Marcel Dekker, Inc. (in press)

Day, N. E., Muenz, L. & Tulinius, H. (1978) *Some aspects of familial breast cancer.* In: *Proceedings of the 8th International Symposium of the Gesellschaft zur Bekampfung der Krebskrankheiten Nordrhein-Westfalen, Dusseldorf, Federal Republic of Germany, June 1976* (in press)

Day, N. E. & Simons, M. J. (1976) Disease susceptibility genes—their identification by multiple case family studies. *Tissue Antigens,* **8**, 109–119

Desgranges, C. & de-Thé, G. (1977) Epstein-Barr virus induces viral nuclear antigen in nasopharyngeal epithelial cells. *Lancet,* **i**, 1286–1287

Desgranges, C. & de-Thé, G. (1977) *IgA and nasopharyngeal carcinoma.* In: de-Thé, G., Henle, W. & Rapp, F., eds, *Oncogenesis and Herpesviruses III,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 24) (in press)

Desgranges, C. & de-Thé, G. (1978) *Presence of Epstein-Barr virus specific IgA in saliva of nasopharyngeal carcinoma patients: their activity, origin and possible clinical value.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 459–469

Desgranges, C., Lavoué, M. F., Patet, J. & de-Thé, G. *In vitro* transforming activity of EBV. II. Comparison of M81 and B95-8 EBV strains (submitted for publication)

Desgranges, C., Li. J. Y. & de-Thé, G. (1977) EBV specific secretory IgA in saliva of NPC patients. Presence of secretory piece in epithelial malignant cells. *Int. J. Cancer*, **20**, 881–886

de-Thé, G. (1977) *Viruses as causes of some human tumours? Results and prospectives of the epidemiological approach.* In: Hiatt, H. H., Watson, J. D. & Winsten, J. A., eds, *The Origins of Human Cancer*, Cold Spring Harbor (*Cold Spring Harbor Cell Proliferation Series* Vol. 4), pp. 658–667

de-Thé, G. (1978) Epstein-Barr virus—is it timely to discuss a vaccine? *Biomedecine*, **28**, 15–17

de-Thé, G. (1978) *Epidemiological evidence implicating the Epstein-Barr virus in Burkitt's lymphoma and nasopharyngeal carcinoma etiology.* In: *Proceedings of the NATO International Advanced Study Institute on Anti-Viral Mechanisms for the Control of Neoplasia, Corfu*, New York, Plenum Press (in press)

de-Thé, G. (1978) *The Epstein-Barr virus—its impact in human diseases.* In: Melnick, J., ed., *Monographs in Virology*, Basel, Karger (in press)

de-Thé, G. (1978) *Review of the role of environmental factors in herpesvirus-associated tumours and a comparison of human diseases with other models.* In: de-Thé, G., Henle, W. & Rapp. F., eds, *Oncogenesis and Herpesviruses III*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 24) (in press)

de-Thé, G. (1978) *Demographic studies implicating the virus in the causation of Burkitt's lymphoma. Prospects for nasopharyngeal carcinoma.* In: Epstein, M. A. & Achong, B. G., eds, *The Epstein-Barr Virus*, Berlin, Springer-Verlag (in press)

de-Thé, G. (1978) *Events early in life and risk to develop Burkitt's lymphoma. Role of neonatal Epstein-Barr virus infection and heavy malaria burden.* In: *Proceedings of the Conference on Tumours of Early Life in Man and Animals, Perugia* (in press)

de-Thé, G., Geser, A., Day, N. E., Tukei, P. M., Munube, G., Williams, E. H., Beri, D. P., Smith, P. G., Dean, A., Bornkamm, G. W., Feorino, P. & Henle, W. (1978) Epidemiological evidence for the causal relationship between Epstein-Barr virus and Burkitt's lymphoma for Ugandan prospective study. *Nature*, **274**, 756–761

de-Thé, G., Henle, W. & Rapp, F., eds (1978) *Oncogenesis and Herpesviruses III*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 24) (in press)

de-Thé, G. & Ito, Y., eds (1978) *Nasopharyngeal Carcinoma: Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20)

de-Thé, G., Lavoué, M. F. & Muenz, L. (1978) *Differences in EBV-antibody titres of patients with nasopharyngeal carcinoma originating from high, intermediate and low incidence areas.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 471–481

de-Thé, G. & Lenoir, G. (1977) *Comparative diagnosis of Epstein-Barr virus related diseases: infectious mononucleosis, Burkitt's lymphoma and nasopharyngeal carcinoma.* In: Kurstak, E., ed., *Comparative Diagnosis of Viral Diseases*, New York, Academic Press, pp. 195–240.

Drevon, C. & Kuroki, T. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells (submitted for publication)

Drevon, C., Kuroki, T. & Montesano, R. (1977) *Microsome-mediated mutagenesis of a Chinese hamster cell line by various chemicals.* In: Scott, D., Bridges, B. A. & Sobels, F. H., eds, *Progress in Genetic Toxicology*, Amsterdam, Elsevier/North Holland Biomedical Press, pp. 207–213

Gatei, D. G., Odhiambo, P. A., Orinda, D. A. O., Muruka, F. J. & Wasunna, A. (1978) Retrospective study of carcinoma of the esophagus in Kenya. *Cancer Res.*, **38**, 303–307

Gerstner, H. B. & Huff, J. E. (1977) Clinical toxicology of mercury. *J. Toxicol. environ. Hlth*, **2**, 491–526

Gerstner, G. B. & Huff, J. E. (1977) Selected case histories and epidemiological examples of human mercury poisoning. *Clin. Toxicol.*, **11**, 131–150

Gerstner, H. B., Huff, J. E. & Ulrikson, G. U. (1977) Information analysis center concept: products, services, and pricing policies. *Am. Lab.*, **9**, 41–48

Geser, A., Charnay, N., Day, N. E., Ho, H. C. & de-Thé, G. (1978) *Environmental factors in the etiology of nasopharyngeal carcinoma: Report on a case-control study in Hong Kong.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 213–229

Giraldo, G., Beth, E., Henle, W., Henle, G., Miké, V., Safai, B., Huraux, J. M., McHardy, J. & de-Thé, G. Antibody patterns to herpesviruses in Kaposi's sarcome: II. Serological association of American Kaposi's sarcoma with cytomegalovirus (submitted for publication)

Glaser, R., Lenoir, G., Ferrone, S., Pellegrino, M. A. & de-Thé, G. (1977) Cell surface markers on epithelial-Burkitt hybrid cells superinfected with Epstein-Barr virus. *Cancer Res.*, **37**, 2291–2296

Goh, E. H., Chan, S. H. & Simons, M. J. (1978) *Effect of levamisole on cell-mediated immune responses in patients with nasopharyngeal carcinoma.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma —Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 503–510

Griciute, L. (1978) Cancérogènes industriels—la clef pour l'évaluation des cancérogènes de l'environnement. *Méd. Biol. Environ.* (in press)

Griciute, L. (1978) Les substances cancérogènes dans les aliments. *Bull. Cancer*, **65**, 53–58

Griciute, L. (1978) Measurement of chemical carcinogens in the human environment: the objectives and problems encountered. *Prog. biochem. Pharmacol.*, **14**, 57–69

Griciute, L. (1978) Méthodes de dépistage du pouvoir cancérogène des médicaments, des aliments et des cosmétiques. *Acta zool. pathol. Antverp.* (in press)

Hammons, A. S., Huff, J. E., Braunstein, H. M., Drury, J. S., Shriner, C. R., Lewis, E. B., Whitfield, B. L. & Towill, L. E. (1978) Reviews of the environmental effects of polluants: IV. Cadmium. ORNL/EIS-106 (EPA-600/1-78-026), Oak Ridge, Tenn., Oak Ridge National Laboratory

Hashemi, S., Dowlatshahi, K., Mohagheghpour, N., Day, N. E., Kmet, J., Takasugi, M. & Moddaber, F. Esophageal cancer studies in the Caspian littoral of Iran: introductive assessment of the HLA profile in patients and controls (submitted for publication)

Hewer, T., Rose, E., Ghadirian, P., Malaveille, C., Bartsch, H. & Day, N. Ingested mutagens from opium and tobacco pyrolysis products and cancer of the œsophagus (submitted for publication)

Higginson, J. (1976) Primary cancer control in relation to community and individual responsibility. *Cancer Forum*, **9**, 154

Higginson, J. (1977) Environmental carcinogens in modern society. *Vop. Onkol.* **23**, 8–16

Higginson, J. (1978) Environment, cancer and research. *World Health,* June, 22–27

Higginson, J. (1978) *Perspectives and future developments in research on environmental carcinogenesis.* In: *Carcinogens: Identification and Mechanisms, Proceedings of the 31st Annual Symposium on Fundamental Cancer Research, Houston, 1978* (in press)

Higginson, J. (1978) The role of epidemiology and geographic pathology in environmental carcinogenesis. *Bull. Am. Coll. Surg.,* **63**, 14–19

Higginson, J. & Muir, C. S. (1977) Détermination de l'importance des facteurs environnementaux dans le cancer humain: rôle de l'épidémiologie. *Bull. Cancer,* **64**, 365–384

Ho, H. C., Kwan, H. C., Ng, M. H. & de-Thé, G. (1978) Serum IgA antibodies to EBV capsid antigen preceding symptoms of NPC. *Lancet,* **i**, 436

Huberman, E., Montesano, R., Drevon, C., Kuroki, T., Saint Vincent, L., Pugh, T. D. & Goldfarb, S. Gamma-glutamyl transpeptidase and malignant transformation of cultured liver cells (submitted for publication)

Huff, J. E. (1977) Life sciences information within the biomedical sciences section: information center complex. *Oak Ridge Nat. Lab. Rep.,* Oak Ridge, Tenn., Oak Ridge National Laboratory

Huff, J. E. (1978) Asbestos: a perspective. I. An overview. ORNL/TIRC-77/5, Oak Ridge, Tenn., Oak Ridge National Laboratory, pp. 1–19

Huff, J. E. (1978) Asbestos: a condensed panorama. *Toxicol. Annu.* (in press)

Huff, J. E. & Gerstner, H. B. (1978) Kepone: a literature summary. *J. environ. Pathol. Toxicol.,* **1**, 377–395

Huff, J. E., Hammons, A. S., Dinger, C. Y., Kline, B. W. & Whitfield, B. L. (1978) Asbestos: a perspective. II. An annotated literature collection, 1960–1974. ORNL/TIRC-77/5, Oak Ridge, Tenn., Oak Ridge National Laboratory, pp. 21–171

Hwang, W. S. & Shanmugaratnam, K. (1978) *Breast cancer in Singapore.* In: *An International Survey of Distributions of Histologic Types of Breast Cancer* (UICC Technical Report Series) (in press)

IARC Intestinal Microecology Group (1977) Dietary fibre, transit-time, faecal bacteria, steroids and colon cancer in two Scandinavian populations. *Lancet,* **ii**, 207–211

Jensen, O. M., Tuyns, A. J. & Péquignot, G. (1978) Usefulness of population controls in retrospective studies of alcohol consumption. Experience from a case-control study of œsophageal cancer in Ille-et-Vilaine, France. *J. Stud. Alcohol,* **39**, 175–182

Jensen, O. M., Tuyns, A. J. & Ravisse, P. (1978) Cancer in Cameroon. A relative frequency study. *Rev. Epidemiol. Santé publique* (in press)

Johannesson, G., Geirsson, G. & Day, N. E. (1978) The effect of mass-screening in Iceland 1965–74 on incidence and mortality of cervical carcinoma. *Int. J. Cancer,* **21**, 418–425

Joint Iran-IARC Study Group (1977) Œsophageal cancer studies in the Caspian littoral of Iran: results of population studies—a prodrome. *J. natl Cancer Inst.,* **59**, 1127–1138

Kirk, R. L., Blake, N. M., Serjeantson, S., Simons, M. J. & Chan, S. H. (1978) *Genetic components in susceptibility to nasopharyngeal carcinoma.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 283–297

Kirk, R. L., Keats, B., Blake, N. J., McDermid, E. J., Ala, F., Karimi, M., Nickbin, B., Shabazi, H. & Kmet, J. (1977) Genes and people in the Caspian littoral of Iran. *Am. J. phys. Anthropol.*, **46**, 377–390

Kmet, J., McLaren, D. & Siassi, F. Epidemiology of esophageal cancer with special reference to nutritional studies among Turkomans of Iran (submitted for publication)

Kuroki, T. & Bartsch, H. Mutagenicity of some *N*- and *O*-acyl derivatives of *N*-hydroxy-2-aminofluorene in V79 Chinese hamster cells (submitted for publication)

Kuroki, T. & Drevon, C. (1978) Direct or proximate contact between cells and metabolic activation systems is required for mutagenesis. *Nature*, **271**, 368–370

Kuroki, T. & Drevon C. Inhibition by protease inhibitors of chemical transformation in C3H 10T½ cells, but not mutagenesis in V79 Chinese hamster cells (submitted for publication)

Lamelin, J. P., Ellouz, R., de-Thé, G. & Révillard, J. P. (1977) Lymphocyte subpopulations and mitogenic responses in nasopharyngeal carcinoma, prior to and after radiotherapy. *Int. J. Cancer*, **20**, 723–728

Lamelin, J. P., Révillard, J. P., Gabbiani, G. & de-Thé, G. (1978) *Autoantibodies (cold lymphocytotoxins, antiactin antibodies and antinuclear factors) in nasopharyngeal carcinoma patients.* In: de-Thé, G. & Ito, Y., eds. *Nasopharyngeal Carcinoma—Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 523–536

Lamelin, J. P., Thomasset, N., André, C., Brochier, J. & Révillard, J. P. (1978) Study of human T and B lymphocytes with heterologous antisera. III. Immunofluorescence studies on tonsils sections. *Immunology* (in press)

Lamelin, J. P., Vincent, C., Charnay, B. & Révillard, J. P. (1978) *Circulating immune complexes in nasopharyngeal carcinoma patients and their household contacts.* In: *Proceedings of the 26th Colloquium on Protides of Biological Fluids, Brussels* (in press)

Lamelin, J. P., Vincent, C., Charnay, B., Souissi, T. & Révillard, J. P. Anti-Epstein-Barr virus antibodies, (^{125}I) Clq-binding activity and their relationship in sera from household contacts of nasopharyngeal carcinoma patients (submitted for publication)

Lamelin, J. P., Vincent, C., Souissi, T. & Révillard, J. P. (1978) Clq binding activity and its relationship with anti-Epstein-Barr virus antibodies in sera from nasopharyngeal carcinoma patients. *Eur. J. Cancer* (in press)

Lenoir, G. & de-Thé, G. (1978) *Epstein-Barr virus epithelial cell interaction and its implication in nasopharyngeal carcinoma etiology.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 377–384

Lenoir, G., de-Thé, G., Ooka, T. & Daillie, J. (1977) *Studies on Epstein-Barr virus early proteins.* In: May, P., Monier, R. & Weil, R., eds, *Early Proteins of Oncogenic DNA Viruses*, Paris, INSERM (*INSERM Symposia Series* Vol. 69), pp. 165–172

Lenoir, G., de-Thé, G., Virelizier, J. L. & Griscelli, C. (1978) *Epstein-Barr virus nuclear antigen (EBNA) positive cells in a lymph node of a child with severe primary EBV infection.* In: de-Thé, G., Henle, W. & Rapp, F., eds, *Oncogenesis and Herpesviruses III*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 24) (in press)

Levine, P. H., Lamelin, J. P. & Stevens, D. A. (1978) *Cell-mediated immunity, Epstein-Barr virus and nasopharyngeal carcinoma.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 483–494

Linsell, C. A. (1977) *Aflatoxins.* In: Lenihan, J. & Fletcher, W. W., eds, *Environment and Man. 6. The Chemical Environment,* Glasgow & London, Blackie, pp. 121–136

Linsell, C. A. (1977) The mycotoxins and human health hazards. *Pure Appl. Chem.* **49**, 1765–1769

Linsell, C. A. (1978) *Decisions on the control of a dietary carcinogen—aflatoxin.* In: Davis, W. & Rosenfeld, C., eds, *Carcinogenic Risks—Strategies for Intervention,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 25) (in press)

Linsell, C. A. & Peers, F. G. (1977) Aflatoxin and liver cell cancer. *Trans. R. Soc. trop. Med. Hyg.,* **71**, 471–473

Linsell, C. A. & Peers, F. G. (1977) *Field studies on liver cell cancer.* In: Hiatt, H. H., Watson, J. D. & Winsten, J. A., eds, *The Origins of Human Cancer,* Cold Spring Harbor (*Cold Spring Harbor Cell Proliferation Series* Vol. 4), pp. 549–556

Lowenfels, A. B., Tuyns, A. J., Walker, E. A. & Roussel, A. (1978) Nitrite studies in œsophageal cancer. *Gut,* **19**, 199–201

McHardy, J., Williams, E. H., Geser, A., de-Thé, G., Beth, E. & Giraldo, G. Kaposi's sarcoma: time-space clustering in West Nile province, Uganda (submitted for publication)

MacLennan, R., Da Costa, J., Day, N. E., Law, C. H., Ng, Y. K. & Shanmugaratnam, K. (1977) Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. *Int. J. Cancer,* **20**, 854–860

MacLennan, R. & Meyer, F. (1977) Food and mortality in France. *Lancet,* **ii**, 133

MacLennan, R., Muir, C. S., Steinitz, R. & Winkler, A., eds (1978) *Methods of Cancer Registration,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 21) (in press)

Malaveille, C. & Bartsch, H. (1977) Short-term tests and mycotoxins. *Pure Appl. Chem.,* **49**, 1753–1757

Malaveille, C., Bartsch, H., Tierney, B., Grover, P. & Sims, P. (1978) *Microsome-mediated mutagenicity of the 3,4-dihydrodiol of benz(a)anthracene (BA), 7,-methyl-BA and 7–12, dimethyl-BA correlates with the carcinogenic activity of the parent hydrocarbon.* In: *Proceedings of the 7th International Congress of Pharmacology, 16–21 July 1978,* p. 160

Malaveille, C., Bartsch, H., Tierney, B., Grover, P. L. & Sims, P. (1978) Microsome-mediated mutagenicities of the dihydrodiols of 7,12-dimethylbenz[*a*]anthracene: high mutagenic activity of the 3,4-dihydrodiol. *Biochem. biophys. Res. Commun.* (in press)

Margison, G. P., Margison, J. M. & Montesano, R. Persistence of methylated bases in ribonucleic acid of Syrian golden hamster liver after administration of dimethylnitrosamine (submitted for publication)

Martel, N., Tuyns, A. J. & Sizeret, P. (1977) Alpha-foetoprotein levels in normal individuals. Relative stability over time. *Digestion,* **16**, 128–137

Montesano, R. (1978) The use of mutagenicity tests in screening chemical carcinogens. *Prog. biochem. Pharmacol.,* **14**, 157–162

Montesano, R., Brésil, H. & Margison, G. Increased excision of O^6-methyl-guanine from rat liver DNA after chronic administration of dimethylnitrosamine (submitted for publication)

Montesano, R., Drevon, C., Kuroki, T., Saint Vincent, L., Handleman, S., Sanford, K. K., DeFeo, D. & Weinstein, I. B. (1977) Test for malignant transformation of rat liver cells in culture: cytology, growth in soft agar and production of plasminogen activator. *J. natl Cancer Inst.*, **59**, 1651–1658

Montesano, R., Margison, G. P. & Likhachev, A. (1977) *The possible role of nucleic acid alkylation in the organ specificity of carcinogens.* In: Farber, E., Kawachi, T., Nagayo, T., Sugano, H., Sugimura, T. & Weisburger, J. H., eds, *Pathophysiology of Carcinogenesis in Digestive Organs,* Tokyo, University of Tokyo Press and Baltimore, University Park Press, pp. 221–231

Muenz, L. R., Sizaret, P., Bernard, C., Chayvialle, J. A., Kithier, K., Kohn, J., Krebs, B. P., Lehmann, F. G., Martel, N., Masseyeff, R., McIntire, R., Nishi, S., Orr, A. H., Princler, G. L., Reynaud, S. & Waldmann, T. (1977) Results of the second international study on the WHO alpha-foetoprotein standard. *J. biol. Stand,* **6**, 187–199

Muir, C. S. (1977) Predictive value of cancer statistics. *J. environ. pathol. Toxicol.*, **1**, 3–10

Muir, C. S. (1978) *Epidemiological identification of cancer hazards.* In: Nieburgs, H. E., ed., *Prevention and Detection of Cancer, Part II, Detection,* New York & Basel, Marcel Dekker, Inc., pp. 3–23

Muir, C. S. & Nectoux, J. (1977) The role of the cancer registry. *Natl Cancer Inst. Monogr.*, **47**, 3–6

Muir, C. S. & Nectoux, J. (1978) Ovarian cancer. Some epidemiological features. *World Health Stat. Rep.*, **31**, No. 1, 51–56

Muir, C. S. & Nectoux, J. (1978) The epidemiology of cancer of the testis and penis. *J. natl Cancer Inst. Monogr.* (in press)

Muir, C. S. & Wagner, G., eds (1977) *Directory of On-going Research in Cancer Epidemiology 1977,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 17)

Muir, C. S. & Wagner, G., eds (1978) *Directory of On-going Research in Cancer Epidemiology 1978,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 26)

Muñoz, N. (1978) Viruses and carcinogenesis of the uterine cervix. *Tumori* (in press)

Muñoz, N. (1978) Perinatal viral infections and the risk of certain cancers. *Prog. biochem. Pharmacol.*, **14**, 104–108

Muñoz, N., Davidson, R. J. L., Withoff, B., Ericsson, J. E. & de-Thé, G. (1978) Infectious mononucleosis and Hodgkin's disease. *Int. J. Cancer* (in press)

Muñoz, N., Dunn, T. B. & Turusov, V. S. (1978) *Tumours of the vagina and uterus.* In: Turusov, V. S., editor-in-chief, *Pathology of Tumours in Laboratory Animals, Vol. II, Tumours of the Mouse,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 23) (in press)

Ng, W. S., Ng, M. H., Ho, H. C. & Lamelin, J. P. (1977) *In vitro* immune responses to PPD, extracts from Raji cells and nasopharyngeal carcinoma biopsies in nasopharyngeal carcinoma leukocytes. *Br. J. Cancer,* **36**, 713–722

Ooka, T., Daillie, J., Costa, O. & Lenoir, G. (1978) *Studies on Epstein-Barr virus DNA polymerase activities in various human lymphoblastoid cell lines.* In: de-Thé, G., Henle, W. & Rapp, F., eds, *Oncogenesis and Herpesviruses III,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 24) (in press)

Ooka, T., Lenoir, G. & Daillie, J. Characterization of an Epstein-Barr virus-induced DNA polymerase (submitted for publication)

Osoba, D., Dick, H. M., Voller, A., Goosen, T. J., Goosen, T., Draper, C. C., de-Thé, G. & Levin, A. G. Indirect evidence for immune response genes controlling the human antibody response to malaria under natural conditions (submitted for publication)

Peers, F. G. & Linsell, C. A. (1977) Dietary aflatoxins and human primary liver cancer. *Ann. Nutr. Aliment.*, **31**, 1005–1017

Péquignot, G., Tuyns, A. J. & Berta, J. L. (1978) Ascitic cirrhosis in relation to alcohol consumption. *Int. J. Epidemiol.* (in press)

Planche, G., Croisy, A., Malaveille, C., Tomatis, L. & Bartsch, H. Metabolic and mutagenicity studies on DDT and 15 derivatives. Detection of the 1,1-bis (*p*-chlorophenyl)-2,2-dichlorethane (DDD) and 1,1-bis (*p*-chlorophenyl)-2,2,2-trichloroethyl acetate (Kelthane acetate) as mutagens in *S. typhimurium* and of 1,1-bis(*p*-chlorophenyl)ethylene oxide (DDNU-oxide), a likely metabolite, as an alkylating agent (submitted for publication)

Ponomarkov, V. & Tomatis, L. (1978) Effects of long-term oral administration of styrene to mice and rats. *Scand. J. Work environ. Health* (in press)

Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds (1978) *Environmental Carcinogens—Selected Methods of Analysis. Volume 1. Analysis of Volatile Nitrosamines in Food,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 18)

Sabadie, N., Bartsch, H., Richter-Reichhelm, H. B., Schindler, W. & Mohr, U. (1978) *Pulmonary AHH-activity in surgical specimens from 70 lung cancer patients: effects of smoking.* In: *Proceedings of the 7th International Congress of Pharmacology, 16–21 July 1978,* p. 67

Sabadie, N., Camus A. M., Malaveille, C., Richter-Reichhelm, H. B., Mohr, U. & Bartsch, H. (1977) Carcinogen metabolism in human liver, normal and tumorous lung tissues. *Proc. Am. Assoc. Cancer Res.*, **18**, 37

Saracci, R. (1977) Wieviel Mehrfachbestimmungen sind bei der Qualitätskontrolle klinisch-chemischer Tests erforderlich? *Arzneim. Lab.*, **23**, 187–191

Saracci, R. (1978) Asbestos and lung cancer: an analysis of the epidemiological evidence on the asbestos-smoking interaction. *J. Continuing Educ. Lung Dis.* (in press)

Saracci, R. (1978) *Asbestos diseases and smoking patterns—an overview.* In: *Occupational Exposures to Fibrous and Particulate Dust and their Extension into the Environment,* Washington, Society for Occupational and Environmental Health (in press)

Saracci, R. (1978) *Brève introduction aux méthodes épidémiologiques en médecine du travail.* In: Lazar, P., ed., *Epidémiologie de la Pathologie Industrielle,* Paris, Flammarion (in press)

Saracci, R. (1978) Epidemiological strategies and environmental hazards. *Int. J. Epidemiol.* (in press)

Saracci, R. (1978) *Controlled studies.* In: Holland, W. W., ed., *Epidemiology and Health* (in press)

Saracci, R. & Bardelli, D. (1978) *Measuring the quality of life in cancer clinical trials: a literature sample survey.* In: *UICC tech. Rep. Ser. Monogr.* (in press)

Seigneurin, J. M., Vuillaume, M., Lenoir, G. & de-Thé, G. (1977) Replication of Epstein-Barr virus: ultrastructural and immunofluorescent studies of P3HR1 superinfected Raji cells. *J. Virol.*, **24**, 836–845

Shanmugaratnam, K. (1978) *Histological typing of nasopharyngeal carcinoma.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 3–12

Shanmugaratnam, K. (1978) *Variations in nasopharyngeal cancer incidence among specific Chinese communities (dialect groups) in Singapore.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 191–198

Shanmugaratnam, K., Tye, C. E., Goh, E. H. & Chia, K. B. (1978) *Etiological factors in nasopharyngeal carcinoma: a hospital-based retrospective, case-control, questionnaire study.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 199–212

Siemiatycki, J. (1978) Mantel's space-time clustering statistic: computing higher moments and a comparison of various data transforms. *J. Stat. Comput. Simul.,* **7**, 13–31

Simons, M. J. & Amiel, J. L. (1977) *HLA and malignant disease.* In: Dausset, J. & Svejgaard, A., eds, *HLA and Disease,* Copenhagen, Munksgaard, pp. 212–232

Simons, M. J. & Day, N. E. (1978) HLA patterns and NPC. *Natl Cancer Inst. Monogr.,* **47**, 143–146

Simons, M. J., Chan, S. H., Wee, G. B., Shanmugaratnam, K., Goh, E. H., Ho, J. H. C., Chau, J. C. W., Darmalingam, S., Prasad, U., Bétuel, H., Day, N. E. & de-Thé, G. (1978) *Nasopharyngeal carcinoma and histocompatibility antigens.* In: de-Thé, G. & Ito, Y., eds, *Nasopharyngeal Carcinoma—Etiology and Control,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 20), pp. 271–282

Simons, M. J., Wee, G. B., Singh, D., Darmalingam, S., Yong, N. K., Chau, J. W., Ho, J. H. C., Day, N. E. & de-Thé, G. (1978) Immunogenetic aspects of nasopharyngeal carcinoma (NPC). V. Confirmation of a Chinese-related HLA haplotype (HLA2-Singapore 2) associated with an increased risk in Chinese for NPC. *Natl Cancer Inst. Monogr.,* **47**, 147–151

Sohier, R. & de-Thé, G. (1978) EBNA antibodies are more useful than complement-fixing antibodies in infectious mononucleosis patients. *Biomedicine* (in press)

Sohier, R. & de-Thé, G. Séro-immunologie de la mononucleose infectieuse. I. Données immunologiques. II. Diagnostic séro-immunologique (submitted for publication)

Steel, C. M., Ennis, M., Levin, A. G. & Wasunna, A. (1977) The mitogenic response of cryopreserved human lymphocytes in a microculture system. *Cytobios,* **18**, 89–99

Stumpf, R., Margison, G. P., Montesano, R. & Pegg, A. E. Formation and loss of alkylated purines from deoxyribonucleic acid of hamster liver after administration of *N*-nitroso carcinogens (submitted for publication)

Tomatis, L. (1977) Comment on methodology and interpretation of results. *J. natl Cancer Inst.,* **59**, 1341

Tomatis, L. (1977) *The value of long-term testing for the implementation of primary prevention.* In: Hiatt, H. H., Watson, J. D. & Winsten, J. A., eds, *The Origins of Human Cancer,* Cold Spring Harbor (*Cold Spring Harbor Cell Proliferation Series* Vol. 4), pp. 1339–1357

Tomatis, L., Agthe, C., Bartsch, H., Huff, J., Montesano, R., Saracci, R., Walker, E. & Wilbourn, J. (1978) Evaluation of the carcinogenicity of chemicals: a review of the monograph programme of the International Agency for Research on Cancer (1971–1977). *Cancer Res.,* **38**, 877–885

Toussaint, G. & Walker, E. A. The use of high pressure liquid chromatography as a clean-up procedure in analysis of polycyclic aromatic hydrocarbons in alcoholic beverages (submitted for publication)

Tovey, M. G., Lenoir, G. & Begon-Lours, J. Activation of latent Epstein-Barr virus by antibody to human IgM (submitted for publication)

Trichopoulos, D., Tabor, E., Gerety, R. J., Xirouchaki, E., Sparros, L., Muñoz, N. & Linsell, C. A. Evidence of a causal relationship between hepatitis B virus and primary hepatic carcinoma in a European population (submitted for publication)

Tulinius, H., Day, N. E., Johannesson, G., Bjarnason, O. & Gonzales, M. (1978) Reproductive factors and risk for breast cancer in Iceland. *Int. J. Cancer*, **21**, 724–730

Tuyns, A. J. (1978) Alcohol and cancer. *Alcohol Health Res. World*, **2**, 20–21

Tuyns, A. J. (1978) Les registres du cancer. *Epidemiol. Prev.* (in press)

Tuyns, A. J. (1978) *Cancer and alcoholic beverages.* In: *Monograph on Fermented Food Beverages in Nutrition*, Rochester, Mayo Clinic (in press)

Tuyns, A. J. (1978) L'épidémiologie du cancer primitif du foie. *Actual. pharm.* (in press)

Tuyns, A. J., Péquignot, G. & Jensen, O. M. (1978) Nutrition, alcool et cancer de l'œsophage. *Bull. Cancer*, **65**, 59–64

Tuyns, A. J., Péquignot, G. & Jensen, O. M. (1978) Role of diet, alcohol and tobacco in œsophageal cancer, as illustrated in two contrasting high incidence areas in North Iran and West of France. *Front. Gastrointest. Res.* (in press)

Virelizier, J. L., Lenoir, G. & Griscelli, G. Persistent Epstein-Barr virus infection in a child with hypergammaglobulinemia and immunoblastic proliferation associated with a selective defect in immune interferon secretion (submitted for publication)

Voller, A., Lenoir, G., Bidwell, D. E. & de-Thé, G. A microplate enzyme linked immunosorbent assay (Elisa) for the detection of antibodies to Epstein-Barr virus (submitted for publication)

Vuori, H., Kokko, S. & MacLennan, R. (1977) Colon cancer and diet in two Scandinavian populations. *Duodecim*, **93**, 1603–1614

Walker, E. A. (1977) Some facts and legislation concerning polycyclic aromatic hydrocarbons in smoked foods. *Pure appl. Chem.*, **49**, 1673–1686

Walker, E. A. (1978) *The problems in collaborative studies on analysis of chemical carcinogens.* In: Nieburgs, H. E., ed., *Prevention and Detection of Cancer, Part I, Prevention*, New York & Basel, Marcel Dekker, Inc., pp. 2059–2069

Walker, E. A., Castegnaro, M., Garren, L. & Pignatelli, B. (1978) *Limitations to the protective effect of rubber gloves for handling nitrosamines.* In: Walker, E. A., Castegnaro, M., Griciute, L. & Lyle, R. E., eds, *Environmental Aspects of N-Nitroso Compounds*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 19), pp. 535–543

Walker, E. A., Castegnaro, M. & Griciute, L. (1978) *N*-nitrosamines in the diet of experimental animals. *Cancer Lett.* (in press)

Walker, E. A., Castegnaro, M., Griciute, L. & Lyle, R. E., eds (1978) *Environmental Aspects of N-Nitroso Compounds*, Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 19)

Walker, E. A., Castegnaro, M. & Pignatelli, B. (1978) *A method for analysis of volatile* N-*nitrosamines in food by electron capture and Coulson detection of their* N-*nitramine derivatives.* In: Egan, H., editor-in-chief, *Environmental Carcinogens—Selected Methods of Analysis.* Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds, *Vol. 1: Analysis of Volatile Nitrosamines in Food,* Lyon, International Agency for Research on Cancer (*IARC Scientific Publications* No. 18), pp. 175–187

Walker, E. A., Pignatelli, B. & Castegnaro, M. The catalytic effect of *p*-nitrosophenol on the nitrosation of diethylamine (submitted for publication)

Wassom, J. S., Huff, J. E. & Loprieno, N. (1978) A review of the genetic toxicology of chlorinated dibenzo-*p*-dioxins. *Mutat. Res.* (in press)

Waters, E. M., Gerstner, H. B. & Huff, J. E. (1977) Trichloroethylene: an overview. *J. Toxicol. environ. Health,* **2**, 671–707

Waters, E. M., Huff, J. E. & Gerstner, H. B. (1977) Mirex: an overview. *Environ. Res.,* **14**, 212–222

Williams, E. H., Smith, P. G., Day, N. E., Geser, A., Ellice, J. & Tukei, P. (1978) Space-time clustering of Burkitt's lymphoma in the West Nile district of Uganda. *Br. J. Cancer,* **37**, 109–122

Yokota, T. Sizaret, P. & Martel, N. (1978) Tumour-specific antigens on rat liver cells transformed *in vitro* by chemical carcinogens. *J. natl Cancer Inst.,* **60**, 125–129

IARC Fellows:

Albrecht-Buehler, G. (1976) *The function of filopodia in spreading 3T3 mouse fibroblasts.* In: Goldman, R. D., *et al.,* eds, *Cell Motility,* Cold Spring Harbor, N.Y., Cold Spring Harbor Laboratory, pp. 247–264

Börzsönyi, M. & Csik, M. (1975) Induction of malignant lymphomas in Swiss mice by *N*-nitroso compounds formed *in vivo. Int. J. Cancer,* **15**, 830–838

Börzsönyi, M., Pintér, A., Nadasdi, L. & Csik, M. (1976) The carcinogenic effect of *N*-nitroso compounds in mice derived *in vivo* from benzimidazol-carbamate containing pesticides. *Magy. Onkol.,* **20**, 89–93

Rannie, G. H. & **Donald, K. J.** (1977) Estimation of the migration of thoracic duct lymphocytes to non-lymphoid tissues. *Cell Tissue Kinet.,* **10**, 523–541

Dux, K. Janik, P. & Szaniawska, B. (1977) Kinetics of proliferation, cell differentiation, and IgM secretion in the omental lymphoid organ of B10/Sn mice following intraperitoneal immunization with sheep erythrocytes. *Cell Immun.,* **32**, 97–109

Hakulinen, T. & Rahiala, M. (1977) An example of the risk dependence and additivity of intensities in the theory of competing risks. *Biom. Soc.,* **33**, 557–559

Hirsch, I., Cabral, G., Patterson, M. & Biswal, N. (1977) Studies on the intracellular replicating DNA of herpes simplex virus type 1. *Virology,* **81**, 48–61

Hizi, A. & Joklik, W. K. (1977) RNA-dependent DNA polymerase of avian sarcoma virus B77. Isolation and partial characterization of the α, ß2, and αß forms of the enzyme. *J. biol. Chem.,* **252**, 2281–2289

Hizi, A., Leis, J. P. & Joklik, W. K. (1977) RNA-dependent DNA polymerase of avian sarcoma virus B77. Comparison of the catalytic properties of the α, ß2 and αß enzyme forms. *J. biol. Chem.,* **252**, 2290–2295

Hizi, A., Leis, J. P. & Joklik, W. K. (1977) The RNA-dependent DNA polymerase of avian sarcoma virus B77. Binding of viral and nonviral ribonucleic acids to the α, ß2, and αß forms of the enzyme. *J. biol. Chem.*, **252**, 6878–6884

Hizi, A. & Joklik, W. K. (1977) The ß subunit of the DNA polymerase of avian sarcoma virus strain B77 is a phosphoprotein. *Virology*, **78**, 571–575

Tomita, Y., Ichihara, A. & **Kuroki, T.** (1976) Further studies on the isozyme patterns of branched-chain amino-acid transaminase in cultured rat hepatocytes. *Gann*, **67**, 747–749

Lai, P. K., Alpers, M. P. & MacKay-Scollay, E. M. (1977) Development of cell-mediated immunity to Epstein-Barr herpesvirus in infectious mononucleosis as shown by leukocyte migration inhibition. *Infect. Immun.*, **17**, 28–35

Lai, P. K., Alpers, M. P. & MacKay-Scollay, E. W. (1977) Epstein-Barr herpesvirus infection: inhibition by immunologically induced mediators with interferon-like properties. *Int. J. Cancer*, **20**, 21–29

Likhachev, A. J., Margison, G. P. & Montesano, R. (1977) Alkylated purines in the DNA of various rat tissues after administration of 1,2-dimethylhydrazine. *Chem.-Biol. Interactions*, **18**, 235–240

Montesano, R., Margison, G. P. & **Likhachev, A. J.** (1977) The possible role of nucleic acids alkylation in the organ specificity of carcinogens. In: Farber, E., Kawachi, T., Nagayo, T., Sugano, H., Sugimura, T. & Weisburger, J. H., eds, *Physiopathology of Carcinogenesis in the Digestive Organs*, Tokyo, University of Tokyo Press and Baltimore, University Park Press, pp. 221–231

Lotan, R., Beattie, G. Hubbell, W. & Nicolson, G. L. (1977) Activities of lectins and their immobilized derivatives in detergent solutions. Implications on the use of lectin affinity chromatography for the purification of membrane glycoproteins. *Biochemistry*, **16**, 1787–1794

Nomura, T. (1976) Comparison of tumour susceptibility among various organs of foetal, young and adult ICR/Jcl mice. *Br. J. Cancer*, **33**, 521–534

Nomura, T. (1976) Diminution of tumorigenesis initiated by 4-nitroquinoline-1-oxide by post-treatment with caffeine in mice. *Nature*, **260**, 547–549

Nomura, T. (1977) Similarity of the mechanism of chemical carcinogen-initiated teratogenesis and carcinogenesis in mice. *Cancer Res.*, **37**, 969–973

Nomura, T. & Kanzaki, T. (1977) Induction of urogenital anomalies and some tumours in the progeny of mice receiving diethylstilbestrol during pregnancy. *Cancer Res.*, **37**, 1099–1104

Nomura, T. & Kondo, S. (1976) The enhancement effect of phenobarbital on toxicity of furylfuramidine in mouse embryo. *Mutat. Res.*, **35**, 167–172

Laerum, O. D., Hülser, D. F. & **Rajewsky, M. F.** (1976) Electrophysiological properties of ethylnitrosourea-induced neoplastic neurogenic rat cell lines cultured *in vivo*. *Cancer Res.*, **36**, 2153–2161

Riazzudin, S. & Lindahl, T. *E. coli* 3–methyladenine-DNA glycosylase (submitted for publication)

Rohrbach, R. (1975) The regulation of cell proliferation by chalone. Experimental investigations on epidermal hyperplasia. *Veröff. Pathol.*, **99**, 1–67

Iversen, O. H., Clausen, O. P. F., Elgjo, K., Iversen, U. M. & **Rohrbach, R.** (1976) Growth parameters of the hairless mouse epidermis after bleomycin treatment: possible interaction with epidermal chalones. *Prog. Biochem. Pharmacol.*, **11**, 110–118

Iversen, O. H., Clausen, O. P. F., Iversen, U. M. & **Rohrbach, R.** (1976) Some effects of bleomycin on the proliferation, maturation time and protein synthesis of hairless mouse epidermis. *Cell Tissue Kinet.*, **9**, 77–97

Iversen, O. H., Clausen, O. P. F., Elgjo, K., Iversen, U. M. & **Rohrbach, R.** (1977) Effects of bleomycin on the epidermal content of growth-regulatory substances (chalones). *Cell Tissue Kinet.*, **10**, 71–79

Rohrbach, R., Iversen, O. H., Elgjo, K., Riede, U. N. & Sandritter, W. (1976) Effects of croton oil on epidermal growth regulators (chalones). *Beitr. Pathol.*, **159**, 143–156

Rohrbach, R., Iversen, O. H., Elgjo, K. & Sandritter, W. (1976) Effects of methylcholanthrene on epidermal growth regulators. Variations in the S-factor. *Beitr. Pathol.*, **158**, 145–158

Sarasin, A. R., Smith, C. A. & Hanawalt, P. C. (1977) Repair of DNA in human cells after treatment with activated aflatoxin B_1. *Cancer Res.*, **37**, 1786–1793

Hampton, A., Slotin, L. A., Kappler, F., **Sasaki, T.** & Perini, F. (1976) Design of substrate-site-directed inhibitors of adenylate kinase and hexokinase. Effect of substrate substituents on affinity for the adenine nucleotide sites. *J. Med. Chem.*, **19**, 1371–1377

Hampton, A., **Sasaki, T.,** Perini, F., Slotin, L. A. & Kappler, F. (1976) Design of substrate-site-directed irreversible inhibitors of adenosine 5'-phosphate aminohydrolase. Effect of substrate substituents on affinity for the substrate site. *J. Med. Chem.*, **19**, 1029–1033

Schmauz, R., Findlay, M., Lalwak, A., Katsumbira, N. & Buxton, E. (1977) Variation in the appearance of giant condyloma in an Ugandan series of cases of carcinoma of the penis. *Cancer*, **40**, 1686–1696

Ghysdael, J., Hubert, E., **Travnicek, M.,** Bolognesi, D. P., Burny, A., Cleuter, Y., Huez, G., Kettman, R., Marbaix, G., Portetelle, D., & Chantrenne, H. (1977) Frog oocytes synthesize and completely process the precursor polypeptide to virion structural proteins after microinjection of avian myeloblastosis virus RNA. *Proc. natl Acad. Sci.*, **74**, 3230–3234

Yokota, T., Sizaret, P. & Martel, N. (1978) Tumor specific antigens on rat liver cells transformed *in vitro* by chemical carcinogens. *J. natl Cancer Inst.*, **60**, 125–129

Morrison, A. S., Lowe, C. R., MacMahon, B., Ravnihar, B. & **Yuasa, S.** (1976) Some international differences in treatment and survival in breast cancer. *Int. J. Cancer*, **18**, 269–273

Morrison, A. S., Lowe, C. R., MacMahon, B., Ravnihar, B. & **Yuasa, S.** (1977) Incidence risk factors and survival in breast cancer: Report on five years of follow-up observation. *Eur. J. Cancer*, **13**, 209–214

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