R. Schwartz

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

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CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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In reply please refer to: C2/12
Prière de rappeler la référence:

11 July 1978

Dear Mr Barnard,

Thank you for your letter of 23 June addressed to Dr Higginson.

... I enclose herewith a photocopy of the Preamble to Volume 17 of the IARC Monographs, which will appear shortly. This Preamble is the result of two Working Groups that met in Lyon in October 1977 and April 1978.

This advisory document to the Director of the IARC will serve as a basis upon which each volume of the monographs will be prepared, and it may be modified by successive Working Groups in order to improve its scientific standard.

Yours sincerely,

R. Montesano, M.D., Ph.D.
Unit of Chemical Carcinogenesis

Mr R.C. Barnard
Cleary, Gottlieb, Steen & Hamilton
1250 Connecticut Avenue, N.W.
Washington, D.C. 20036
USA

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June 23, 1978

Dr. John Higginson
Director
International Agency for
Research on Cancer
150 Cours Albert Thomas
69008 Lyon
France

Dear Dr. Higginson:

I represent the American Industrial Health Council, an organization made up of some 100 companies which is participating in the administrative proceeding regarding "The Proposed Regulation of the United States Occupational Safety and Health Administration for the Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk to Humans."

On April 4, 1978, Dr. L. Tomatis filed a statement regarding the proposed regulations, at the request of the U.S. Occupational Safety and Health Administration. Attached to Dr. Tomatis' statement was a preprint of an article from Cancer Research for April 1978 by Dr. Tomatis and others entitled "Evaluation of the Carcinogenicity of Chemicals: A Review of the Monograph Program of the International Agency for Research on Cancer." The preprint describes the formation of a working group in October 1977 "to update and revise the criteria on which the carcinogenicity to humans and/or experimental animals is assessed and on which evaluation of the possible carcinogenic risk they may represent for humans is made." The preprint summarizes the report of that group stating that their conclusions would appear in the introduction to IARC Monograph Volume 17 (described as in press).

Dr. David Rall, Director of the National Institute of Environmental Health Sciences also testified as to the conclusions reached as a result of the deliberations of the group.

At the hearing, which began May 16, 1978, Dr. Saffiotti and Dr. Schneiderman of the National Cancer Institute testified that a new group had been formed to review the criteria which had been previously recommended and had recommended modifications. Subsequently, Dr. Greisemer of the National Cancer Institute described some of the changes made as a result of the deliberations of the second group. (Dr. Griesemer said he did not have the text of the changes.)

There is great interest in the conclusions reached by the IARC on this important subject, and those conclusions are particularly relevant to the hearings on the proposed regulation. As the record presently stands, the conclusions of the meeting in October 1977 are in the record but the changes are not.

I am writing to request that you furnish to me for submission to OSHA the text of the proposed changes in the introduction to Monograph 17, which I understand is in press or about to go to press. Since the hearings will be over long before Volume 17 is published, this is the only way in which an accurate and correct copy of the IARC conclusions can be incorporated in the record and the present confusion eliminated.

I will appreciate your consideration of the request. Since the hearings will terminate next month, it would be very helpful if we can receive a pre-publication copy of that part of the introduction relating to the criteria upon which carcinogenicity is assessed as soon as convenient.

Thank you very much.

Very truly yours,

Robert C. Barnard

IARC MONOGRAPH PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

PREAMBLE

BACKGROUND

In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans centred on the production of critically evaluated monographs on individual chemicals. Since 1972, the programme has undergone considerable expansion, primarily with the scientific collaboration and financial support of the US National Cancer Institute.

The criteria established in 1971 to evaluate the carcinogenic risk of chemicals to humans were adopted in essence by all the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monograph* series. In October 1977, a joint IARC/WHO *ad hoc* Working Group met to reevaluate these guiding criteria; this preamble reflects the results of their deliberations[1].

OBJECTIVE AND SCOPE

The objective of the monograph programme is to collect all available relevant experimental and epidemiological data about groups of chemicals to which humans are known to be exposed, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to publish and disseminate the conclusions of those working groups as a series of monographs.

The critical evaluations of experimental data given in these monographs are intended to assist national and international authorities in formulating decisions concerning preventive measures. The WHO publications on food additives[2], drugs[3], pesticides and contaminants[4] and occupational carcinogens[5] are particularly informative.

Since the programme began in 1971, 17 volumes have been published[6-22] in the *IARC Monograph* series, and 380 separate chemicals have been evaluated (see cumulative index to the monographs, p. 353). Each volume is printed in 4000 copies and distributed *via* the World Health Organization (WHO) publications service (see inside covers for a listing of IARC publications and back outside cover for distribution and sales services).

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of environmental chemicals. The first users' survey, made in 1976, indicates that the monographs are consulted routinely by various agencies in 24 countries.

SELECTION OF CHEMICALS FOR MONOGRAPHS

The chemicals (natural and synthetic, mixtures and manufacturing processes) are selected for evaluation on the basis of two main criteria: (1) there is evidence of human exposure, and (2) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. *Inclusion of a chemical in a volume does not imply that the chemical is carcinogenic, only that the published data have been examined. The evaluations must be consulted to ascertain the conclusions of the Working Group. Equally, the fact that a chemical has not appeared in a monograph does not mean that the chemical is not carcinogenic.*

The scientific literature is monitored for published data relevant to the monograph programme. Additionally, the IARC Survey of Chemicals Being Tested for Carcinogenicity[23-29] often indicates those chemicals that are to be scheduled for future meetings. The major aims of the survey are to prevent unnecessary duplication of research, to increase communication among scientists, and to make a census of chemicals that are being tested and of available research facilities.

When new, relevant information becomes available concerning a chemical(s) which has already been evaluated, or when new principles for evaluating carcinogenic risk receive acceptance, reevaluations may be made at subsequent meetings, and a monograph(s) may be revised and published.

WORKING PROCEDURES

Approximately one year in advance of a working group meeting, a list of the substances to be considered is prepared by IARC in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; in this context, US Public Health Service Publication No. 149[10-15] has been particularly valuable and has been used in conjunction with other recognized sources of information on chemical carcinogenesis. The major effort in the collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production, use and occurrence and on analysis is made by SRI International under a separate contract with the US National Cancer Institute. Most of the data they provide on production, use and occurrence concern the United States and Japan; SRI and IARC try to supplement this information with that from other sources in Europe. Important bibliographical sources for mutagenicity and teratogenicity data are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, USA.

Six to nine months before the meeting, reprints of articles containing relevant biological data are sent to an expert(s), or are used by the IARC staff, for the preparation of first drafts of the monographs. These drafts are edited by IARC staff and are sent prior to the meeting to all participants of the Working Group for their comments. The Working Group then meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, then edited and prepared for reproduction. The monographs appear in print within six months after adjournment of the Working Group meeting.

DATA FOR EVALUATIONS

With regard to biological data, generally only reports that have been published or accepted for publication are reviewed by the working groups. The monographs do not cite all of the literature on a particular chemical:

only those data considered by the Working Group to be relevant to the evaluation of the carcinogenic risk of the chemical to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals for which monographs have appeared is urged to make them available to the Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

THE WORKING GROUP

During a meeting the tasks of the Working Group are generally fivefold: (1) to confirm that all relevant published data are included; (2) to ensure that the summaries of data enable the reader to follow the reasoning of the committee; (3) to judge the significance of the experimental and epidemiological results; (4) to select and summarize the data on which to base an evaluation; and (5) to formulate an evaluation of the carcinogenic risk of the chemical.

Working Group participants who contributed to the consideration and evaluation of chemicals within a particular volume are listed, with their addresses, at the beginning of each publication (see p. 3). Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies, organizations and industries.

GENERAL PRINCIPLES FOR EVALUATING THE CARCINOGENIC RISK OF CHEMICALS

The widely accepted meaning of the term 'chemical carcinogenesis', and that used in these monographs, is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found, although fundamentally different mechanisms may be involved in these three phenomena. Etymologically, the term 'carcinogenesis' means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours.

Within the monographs, the words 'tumour' and neoplasm' are used interchangeably (In scientific literature the terms 'tumourigen', 'oncogen' and 'blastomogen' have all been used synonymously with 'carcinogen', although occasionally 'tumourigen' has been used specifically to denote the induction of benign tumours).

The term 'carcinogenic risk' in this *IARC Monograph* series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Experimental Evidence

Qualitative aspects

Both the interpretation and evaluation of a particular study as well as the overall assessment of the carcinogenic activity of a chemical involve several qualitatively important considerations, including: (1) the experimental conditions under which the chemical was tested, including route of administration and exposure, species, strain, sex, age, etc.; (2) the consistency with which the chemical has been shown to be carcinogenic, e.g., in how many species and at which tumour sites(s); (3) the spectrum of neoplastic response, from benign neoplasia to multiple malignant tumours (this consideration warrants special attention); (4) the stage of tumour formation in which a chemical may be involved: some chemicals act as complete carcinogens and have initiating and promoting activity, while others are promoters only; and 5) the possible role of modifying agents.

Many chemicals induce both benign and malignant tumours; few instances are recorded in which only benign neoplasms are induced by chemicals that have been studied extensively. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be 'end-points' which do not readily undergo transition to malignant neoplasms. If a substance is found to induce only benign neoplasms in experimental animals, the chemical should be suspected of being a carcinogen and requires further investigation.

Hormonal carcinogenesis

Hormonal carcinogenesis presents certain distinctive features: the chemicals involved occur both naturally and exogenously; in most instances, long exposure is required; tumours occur in the target issue in association with a stimulation of non-neoplastic growth, but in some cases, hormones promote the proliferation of tumour cells in a target organ. Hormones that occur in excessive amounts, hormone-mimetic agents and agents that cause hyperactivity or imbalance in the endocrine system may require evaluative methods comparable with those used to identify chemical carcinogens; particular emphasis must be laid on quantitative aspects and duration of exposure. Some chemical carcinogens have significant side effects on the endocrine system, which may also result in hormonal carcinogenesis. Synthetic hormones and anti-hormones can be expected to possess other pharmacological and toxicological actions in addition to those on the endocrine system, and in this respect they must be treated like any other chemical with regard to intrinsic carcinogenic potential.

Quantitative aspects

Dose-response studies are important in the evaluation of carcinogenesis: the confidence with which a carcinogenic effect can be established is strengthened by the observation of an increasing incidence of neoplasms with increasing exposure.

The assessment of carcinogenicity in animals is frequently complicated by recognized differences among the test animals (species, strain, sex, age), in route(s) of administration and in dose/duration of exposure; often, target organs at which a cancer occurs and its histological type may vary with these conditions. Nevertheless, indices of carcinogenic potency in particular experimental systems (for instance, the dose-rate required under continuous exposure to halve the probability of the animals remaining tumourless[16]) have been formulated in the hope that, at least among categories of fairly similar agents, such indices may be of some predictive value in other systems, including humans.

Chemical carcinogens differ widely in the dose required to produce a given level of tumour induction, although many of them share common

biological properties which include metabolism to reactive (electrophilic[37-39]) intermediates capable of interacting with DNA. The reason for this variation in dose-response is not understood but may be due either to differences within a common metabolic process or to the operation of qualitatively distinct mechanisms.

Statistical analysis of animal studies

Tumours which would have arisen had an animal lived longer may not be observed because of the death of the animal from unrelated causes, and proper allowance must be made for this possibility. Various analytical techniques have been developed which use the assumption of independence of competing risks to allow for the effects of intercurrent mortality on the final numbers of tumour-bearing animals in particular treatment groups.

For externally visible tumours and for neoplasms that cause death, methods such as Kaplan-Meier (i.e., 'life-table', 'product-limit' or 'actuarial') estimates[36], with associated significance tests[40,41], are recommended.

For internal neoplasms which are discovered 'incidentally'[40] at autopsy but which did not cause the death of the host, different estimates[42] and significance tests[40,41] may be necessary for the unbiased study of the numbers of tumour-bearing animals.

All of these methods[36,40,41,42] can be used to analyse the numbers of animals bearing particular tumour types, but they do not distinguish between animals with one or many such tumours. In experiments which end at a particular fixed time with the simultaneous sacrifice of many animals, analysis of the total numbers of internal neoplasms per animal found at autopsy at the end of the experiment is straightforward. However, there are no adequate statistical methods for analysing the numbers of particular neoplasms that kill an animal host.

There are problems not only of differential survival but of differential toxicity, which may be manifested by unequal growth and weight gain in treated and control animals. These complexities should also be considered in the interpretation of data, or, better, in the experimental design.

Evidence of Carcinogenicity in Humans

Evidence of carcinogenicity in humans can be derived from three types of study, the first two of which usually provide only suggestive evidence: (1) reports concerning individual cancer patients (case reports), including a history of exposure to the supposed carcinogenic agent; (2) descriptive epidemiological studies in which the incidence of cancer in human populations is found to vary (spatially or temporally) with exposure to the agent); and (3) analytical epidemiological studies (e.g., case-control or cohort studies) in which individual exposure to the agent is found to be associated with an increased risk of cancer.

An analytical study that shows a positive association between an agent and a cancer may be interpreted as implying causality to a greater or lesser extent, if the following criteria are met: (1) There is no identifiable positive bias (By 'positive bias' is meant the operation of factors in study design or execution which lead erroneously to a more strongly positive association between an agent and disease than in fact exists. Examples of positive bias include, in case-control studies, more nearly complete ascertainment of exposure to the agent in cases than in controls and, in cohort studies, more nearly complete detection of cancer in individuals exposed to the agent than in individuals not exposed). (2) The possibility of positive confounding has been considered (By 'positive confounding' is meant a situation in which the relationship between an agent and a disease is rendered more strongly positive than it truly is as a result of an association between that agent and another agent which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking). (3) The association is unlikely to be due to chance alone. (4) The association is strong. (5) There is a dose-response relationship.

In some instances, a single epidemiological study may be strongly indicative of a cause-effect relationship, however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings.

Analytical epidemiological studies that show no association between an agent and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (1) There is no identifiable negative bias. (2) The possibility of negative confounding has been considered. (3) The possible effects of misclassification of exposure or outcome have been considered.

In addition, it must be recognized that in any study there are confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above this upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement.

Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

Experimental Data Relevant to the Evaluation of Carcinogenic Risk to Humans

No adequate criteria are presently available to interpret experimental carcinogenicity data directly in terms of carcinogenic potential for humans. Nonetheless, utilizing data collected from appropriate tests in animals, positive extrapolations to possible human risk can reasonably be approximated.

Information compiled from the first 17 volumes of the *Monographs*[43-45] shows that of about 26 chemicals or manufacturing processes now generally accepted to cause cancer in humans, all but possibly two (arsenic and benzene) of those which have been tested appropriately produce cancer in at least one animal species. For several (aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence

of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

In general, the evidence that a chemical produces tumours in experimental animals is of two degrees: (1) *sufficient evidence* of carcinogenicity is indicated by the production of malignant tumours; and (2) *limited evidence* of carcinogenicity reflects the qualitative and/or quantitative limitations of the experimental results.

For many of the chemicals evaluated in the first 17 volumes of the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable to regard for practical purposes such chemicals as if they were carcinogenic to humans.

Sufficient evidence of carcinogenicity is provided by experimental studies that show an increased incidence of malignant tumours: (a) in multiple species or strains, and/or (b) in multiple experiments (routes and/or doses), and/or (c) to an unusual degree (with regard to incidence, site, type and/or precocity of onset). Additional evidence may be provided by data concerning dose–response, mutagenicity or structure.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw/day) of a particular chemical required to produce cancer in test animals and the dose which would produce a similar incidence of cancer in humans. The available data suggest, however, that such a relationship may exist[46], at least for certain classes of carcinogenic chemicals. Data that provide *sufficient evidence* of carcinogenicity in test animals may therefore be used in an approximate quantitative evaluation of the human risk at some given exposure level, provided that the nature of the chemical concerned and the physiological, pharmacological and toxicological differences between the test animals and humans are taken into account. However, no acceptable methods are currently available for quantifying the possible errors in such a procedure, whether it is used to generalize between species or to extrapolate from high to low doses. The methodology for such quantitative extrapolation to humans requires further development.

Evidence for the carcinogenicity of some chemicals in experimental animals may be limited for two reasons. Firstly, experimental data may be restricted to such a point that it is not possible to determine a causal relationship between administration of a chemical and the development of a particular lesion in the animals. Secondly, there are certain neoplasms, including lung tumours and hepatomas in mice, which have been considered of lesser significance than neoplasms occurring at other sites for the purpose of evaluating the carcinogenic risk of chemicals to humans. Such tumours occur spontaneously in high incidence in these animals, and their malignancy is often difficult to establish. An evaluation of the significance of these tumours following administration of a chemical is the responsibility of the particular Working Group preparing the individual monograph, and it has not been possible to set down rigid guidelines; the relevance of these tumours must be determined by considerations which include experimental design and completeness of reporting.

Some chemicals for which there is *limited evidence* of carcinogenicity in animals have also been studied in humans with, in general, inconclusive results. While such chemicals may indeed be carcinogenic to humans, more experimental and epidemiological investigation is required.

Hence, '*sufficient evidence*' of carcinogenicity and '*limited evidence*' of carcinogenicity do not indicate categories of chemicals: the inherent definitions of those terms indicate varying degrees of experimental evidence, which may change if and when new data on the chemicals become available. The main drawback to any rigid classification of chemicals with regard to their carcinogenic capacity is the as yet incomplete knowledge of the mechanism(s) of carcinogenesis.

In recent years, several short-term tests for the detection of potential carcinogens have been developed. When only inadequate experimental data are available, positive results in validated short-term tests (see p. 25) are an indication that the compound is a potential carcinogen and that it should be tested in animals for an assessment of its carcinogenicity. Negative results from short-term tests cannot be considered sufficient evidence to rule out carcinogenicity. Whether short-term tests will

eventually attain a stature similar to that of long-term tests in predicting carcinogenicity in humans will depend on further demonstrations of consistency with long-term experiments and with data from humans.

EXPLANATORY NOTES ON THE MONOGRAPH CONTENTS

Chemical and Physical Data (Section 1)

The Chemical Abstracts Service Registry Number and the latest Chemical Abstracts Primary Name (9th Collective Index) are recorded in section 1. Other synonyms and trade names are given, but this list is often not comprehensive. Further, some of the trade names are those of mixtures in which the compound being evaluated is only one of the ingredients.

The structural and molecular formulae, molecular weight and chemical and physical properties are given. The properties listed refer to the pure substance, unless otherwise specified, and include, in particular, data that might be relevant to carcinogenicity (for example, lipid solubility) and those that concern identification. A separate description of the composition of technical products includes available information on impurities and formulated products.

Production, Use, Occurrence and Analysis (Section 2)

The purpose of section 2 is to provide indications of the extent of past and present human exposure to this chemical.

Synthesis

Since cancer is a delayed toxic effect, the dates of first synthesis and of first commercial production of the chemical are provided. In addition, methods of synthesis used in past and present commercial production are described. This information allows a reasonable estimate to be made of the time before which no human exposure could have occurred.

Production

Since Europe, Japan and the United States are reasonably representative industrialized areas of the world, most data on production, foreign trade and uses are obtained from those countries. It should not, however, be

inferred that those nations are the sole or even the major sources of users of any individual chemical.

Production and foreign trade data are obtained from both governmental and trade publications by chemical economists in the three geographical areas. In some cases, separate production data on organic chemicals manufactured in the United States are not available because their publication could disclose confidential information. In such cases, an indication of the minimum quantity produced can be obtained from the number of companies reporting commercial production. Each company is required to report on individual chemicals if the sales value or the weight of the annual production of a chemical exceeds a specified minimum level. These levels vary for chemicals classified for different uses, e.g., medicinals, plastics; however, the minimal annual sales value is between $1000 and $50,000 and the minimal annual weight of production is between 450 and 22,700 kg. Data on production in some European countries are obtained by means of general questionnaires sent to companies thought to produce the compounds being evaluated. Information from the completed questionnaires is compiled by country, and the resulting estimates of production are included in the individual monographs.

Use

Information on uses is meant to serve as a guide only and is not complete. It is usually obtained from published data but is often complemented by direct contact with manufacturers of the chemical. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their clinical efficacy.

Statements concerning regulations and standards (e.g., pesticide registrations, maximum levels permitted in foods, occupational standards and allowable limits) in specific countries are mentioned as examples only. They may not reflect the most recent situation, since such legislation is in a constant state of change; nor should it be taken to imply that other countries do not have similar regulations.

Occurrence

Information on the occurrence of a chemical in the environment is obtained from published data, including that derived from the monitoring and surveillance of levels of the chemical in occupation environments, air, water, soil, foods and tissues of animals and humans. When available, data on the generation, persistence and bioaccumulation of a chemical are also included.

Analysis

The purpose of the section on analysis is to give the reader an indication, rather than a complete review, of methods cited in the literature. No attempt is made to evaluate critically or to recommend any of the methods.

Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans (Section 3)

In general, the data recorded in section 3 are summarized as given by the author; however, certain shortcomings of reporting, of statistical analysis or of experimental design are commented upon by the Working Group in square brackets. The nature and extent of impurities/contaminants in the chemicals being tested are given when available.

Carcinogenicity and related studies in animals

The monographs are not intended to cover all reported studies. Some studies are purposely omitted (1) because they are inadequate, as judged from previously described criteria[27-30] (e.g., too short a duration, too few animals, poor survival); (2) because they only confirm findings that have already been fully described; or (3) because they are judged irrelevant for the purpose of the evaluation. In certain cases, however, such studies are mentioned briefly, particularly when the information is considered to be a useful supplement to other reports or when it is the only data available. Their inclusion does not, however, imply acceptance of the adequacy of their experimental design and/or of the analysis and interpretation of their results.

Mention is made of all routes of administration by which the compound has been adequately tested and of all species in which relevant tests have

been done[49,50]. In most cases, animal strains are given (general characteristics of mouse strains have been reviewed[51]). Quantitative data are given to indicate the order of magnitude of the effective carcinogenic doses. In general, the doses and schedules are indicated as they appear in the original paper; sometimes units have been converted for easier comparison. Experiments on the carcinogenicity of known metabolites, chemical precursors, analogues and derivatives, and experiments on factors that modify the carcinogenic effect are also reported.

Other relevant biological data

Lethality data are given when available, and other data on toxicity are included when considered relevant. The metabolic data are restricted to studies that show the metabolic fate of the chemical in animals and man, and comparisons of data from animals and humans are made when possible. Information is also given on absorption, distribution, excretion and placental transfer.

Embryotoxicity and teratogenicity

Data on teratogenicity from studies in experimental animals and observations in humans are also included. There appears to be no necessary causal relationship between teratogenicity[52] and carcinogenicity, but chemicals often have both properties. Evidence of teratogenicity suggests transplacental transfer, which is a prerequisite for transplacental carcinogenesis.

Mutagenicity and other short-term tests

Data from indirect tests are also included. Since most of these tests have the advantage of taking less time and being less expensive than mammalian carcinogenicity studies, they are generally known as 'short-term' tests. They comprise assay procedures which rely on the induction of biological and biochemical effects in *in vivo* and/or *in vitro* systems. The end-point of the majority of these tests is not the production of neoplasms in animals but changes at the molecular, cellular or multicellular level: these include the induction of DNA damage and repair, mutagenesis in bacteria and other organisms, transformation of mammalian cells in culture, and other systems.

The short-term tests are proposed for use (1) in predicting potential carcinogenicity in the absence of carcinogenicity data in animals, (2) as a contribution in deciding which chemicals should be tested in animals, (3) in identifying active fractions of complex mixtures containing carcinoges, (4) for recognizing active metabolites of known carcinogens in human and/or animal body fluids and (5) to help elucidate mechanisms of carcinogenesis.

Although the theory that cancer is induced as a result of somatic mutation suggests that agents which damage DNA *in vivo* may be carcinogens, the precise relevance of short-term tests to the mechanism by which cancer is induced is not known. Predictions of potential carcinogenicity are currently based on correlations between responses in short-term tests and data from animal carcinogenicity and/or human epidemiological studies. This approach is limited because the number of chemicals known to be carcinogenic in humans is insufficient to provide a basis for validation, and most validation studies involve chemicals that have been evaluated for carcinogenicity only in animals. The selection of chemicals is in turn limited to those classes for which data on carcinogenicity are available. The results of validation studies could be strongly influenced by such selection of chemicals and by the proportion of carcinogens in the series of chemicals tested; this should be kept in mind when evaluating the predictivity of a particular test. The usefulness of any test is reflected by its ability to classify carcinogens and noncarcinogens, using the animal data as a standard; however, animal tests may not always provide a perfect standard. The attainable level of correlation between short-term tests and animal bioassays is still under investigation.

Since many chemicals require metabolism to an active form, test systems that do not take this into account may fail to detect certain potential carcinogens. The metabolic activation systems used in short-term tests (for example, the cell-free systems used in bacterial tests) are meant to simulate the intact human. Each has its advantages and limitations; thus, more confidence can be placed in the conclusions when negative or positive results for a chemical are confirmed in several such test systems. Deficiencies in metabolic competence may lead to misclassification of chemicals,

which means that not all tests are suitable for assessing the potential carcinogenicity of all classes of compounds.

The present state of knowledge does not permit the selection of a specific test(s) as the most appropriate for identifying potential carcinogenicity. Before the results of a particular test can be considered to be fully acceptable for predicting potential carcinogenicity, certain criteria should be met: (1) the test should have been validated with respect to known animal carcinogens and found to have a high capacity for discriminating between carcinogens and noncarcinogens, and (2) when possible, a structurally related carcinogen(s) and noncarcinogen(s) should have been tested simultaneously with the chemical in question. The results should have been reproduced in different laboratories, and a prediction of carcinogenicity should have been confirmed in additional test systems. Confidence in positive results is increased if a mechanism of action can be deduced and if appropriate dose-response data are available. For optimum usefulness, data on purity must be given.

The short-term tests in current use that have been the most extensively validated are the *Salmonella typhimurium* plate-incorporation assay[53-57], the X-linked recessive lethal test in *Drosophila melanogaster*[58], unscheduled DNA synthesis[59] and *in vitro* transformation[57,60]. Each is compatible with current concepts of the possible mechanism(s) of carcinogenesis.

An adequate assessment of the genetic activity of a chemical depends on data from a wide range of test systems. The monographs include, therefore, data not only from those already mentioned, but also on the induction of point mutations in other systems[61-66], of structural[67] and numerical chromosome aberrations, including dominant lethal effects[68], of mitotic recombination in fungi[61] and of sister chromatid exchanges[69,70].

The existence of a correlation between quantitative aspects of mutagenic and carcinogenic activity has been suggested[4,68-74], but it is not sufficiently well established to allow general use.

Further information about mutagenicity and other short-term tests is given in references 71-77.

Case reports and epidemiological studies

Observations in humans are summarized in this section.

Summary of Data Reported and Evaluation (Section 4)

Section 4 summarizes the relevant data from animals and humans and gives the critical views of the Working Group on those data.

Experimental data

Data relevant to the evaluation of the carcinogenicity of a chemical in animals are summarized in this section. Results from validated mutagenicity and other short-term tests are reported if the Working Group considered the data to be relevant. Dose-response data are given when available. An assessment of the carcinogenicity of the chemical in animals is made on the basis of all of the available data.

The animal species mentioned are those in which the carcinogenicity of the substance was clearly demonstrated. The route of administration used in experimental animals that is similar to the possible human exposure is given particular mention. Tumour sites are also indicated. If the substance has produced tumours after prenatal exposure or in single-dose experiments, this is indicated.

Human data

Human exposure to the chemical is summarized, and the significance of data on production, use and occurrence and other relevant biological data is discussed. Case reports and epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are described. Adequate dose-response data are given when available. An assessment of the carcinogenicity of the chemical in humans is made on the basis of all of the available evidence.

Evaluation

This section comprises the overall evaluation by the Working Group of the carcinogenic risk of the chemical to humans. All of the data in the monograph, and particularly the summarized information on experimental and human data, are considered in order to make an evaluation. In addition, recommendations are made regarding areas in which further investigation is considered to be necessary.

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