

WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



***IARC Monographs on the Evaluation of  
Carcinogenic Risks to Humans***

**P R E A M B L E**

LYON, FRANCE  
2006

Plaintiff Exhibit

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# PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

## A. GENERAL PRINCIPLES AND PROCEDURES

### 1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended ‘ . . . that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.’ The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase ‘of chemicals’ was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been

1 established as being effective during previous *Monograph* meetings but remain,  
2 predominantly, the prerogative of each individual Working Group.

## 3 **2. Objective and scope**

4 The objective of the programme is to prepare, with the help of international Working  
5 Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations  
6 of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs*  
7 represent the first step in carcinogen risk assessment, which involves examination of all  
8 relevant information in order to assess the strength of the available evidence that an agent  
9 could alter the age-specific incidence of cancer in humans. The *Monographs* may also  
10 indicate where additional research efforts are needed, specifically when data immediately  
11 relevant to an evaluation are not available.

12 In this Preamble, the term ‘agent’ refers to any entity or circumstance that is subject to  
13 evaluation in a *Monograph*. As the scope of the programme has broadened, categories of  
14 agents now include specific chemicals, groups of related chemicals, complex mixtures,  
15 occupational or environmental exposures, cultural or behavioural practices, biological  
16 organisms and physical agents. This list of categories may expand as causation of, and  
17 susceptibility to, malignant disease become more fully understood.

18 A cancer ‘hazard’ is an agent that is capable of causing cancer under some circumstances,  
19 while a cancer ‘risk’ is an estimate of the carcinogenic effects expected from exposure to a  
20 cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the  
21 historical presence of the word ‘risks’ in the title. The distinction between hazard and risk is  
22 important, and the *Monographs* identify cancer hazards even when risks are very low at  
23 current exposure levels, because new uses or unforeseen exposures could engender risks that  
24 are significantly higher.

25 In the *Monographs*, an agent is termed ‘carcinogenic’ if it is capable of increasing the  
26 incidence of malignant neoplasms, reducing their latency, or increasing their severity or  
27 multiplicity. The induction of benign neoplasms may in some circumstances (see Part B,  
28 Section 3a) contribute to the judgement that the agent is carcinogenic. The terms ‘neoplasm’  
29 and ‘tumour’ are used interchangeably.

30 The Preamble continues the previous usage of the phrase ‘strength of evidence’ as a  
31 matter of historical continuity, although it should be understood that *Monographs* evaluations  
32 consider studies that support a finding of a cancer hazard as well as studies that do not.

33 Some epidemiological and experimental studies indicate that different agents may act at  
34 different stages in the carcinogenic process, and several different mechanisms may be  
35 involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of  
36 carcinogenicity at any stage in the carcinogenesis process, independently of the underlying  
37 mechanisms. Information on mechanisms may, however, be used in making the overall  
38 evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4  
39 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international  
40 scientific conferences to determine whether a broad-based consensus has emerged on how  
41 specific mechanistic data can be used in an evaluation of human carcinogenicity. The results  
42 of such conferences are reported in IARC Scientific Publications, which, as long as they still  
43 reflect the current state of scientific knowledge, may guide subsequent Working Groups.

44 Although the *Monographs* have emphasized hazard identification, important issues may  
45 also involve dose–response assessment. In many cases, the same epidemiological and  
46 experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–

1 response relationship. A *Monograph* may undertake to estimate dose–response relationships  
2 within the range of the available epidemiological data, or it may compare the dose–response  
3 information from experimental and epidemiological studies. In some cases, a subsequent  
4 publication may be prepared by a separate Working Group with expertise in quantitative  
5 dose–response assessment.

6 The *Monographs* are used by national and international authorities to make risk  
7 assessments, formulate decisions concerning preventive measures, provide effective cancer  
8 control programmes and decide among alternative options for public health decisions. The  
9 evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence  
10 for or against carcinogenicity provided by the available data. These evaluations represent  
11 only one part of the body of information on which public health decisions may be based.  
12 Public health options vary from one situation to another and from country to country and  
13 relate to many factors, including different socioeconomic and national priorities. Therefore,  
14 no recommendation is given with regard to regulation or legislation, which are the  
15 responsibility of individual governments or other international organizations.

### 16 **3. Selection of agents for review**

17 Agents are selected for review on the basis of two main criteria: (a) there is evidence of  
18 human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed  
19 exposures may occur in occupational and environmental settings and as a result of individual  
20 and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and  
21 compounds with biological or physical characteristics similar to those of suspected  
22 carcinogens may also be considered, even in the absence of data on a possible carcinogenic  
23 effect in humans or experimental animals.

24 The scientific literature is surveyed for published data relevant to an assessment of  
25 carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993,  
26 1998 and 2003 made recommendations as to which agents should be evaluated in the  
27 *Monographs* series. Recent recommendations are available on the *Monographs* programme  
28 website (<http://monographs.iarc.fr>). IARC may schedule other agents for review as it  
29 becomes aware of new scientific information or as national health agencies identify an urgent  
30 public health need related to cancer.

31 As significant new data become available on an agent for which a *Monograph* exists, a re-  
32 evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some  
33 cases it may be appropriate to review only the data published since a prior evaluation. This  
34 can be useful for updating a database, reviewing new data to resolve a previously open  
35 question or identifying new tumour sites associated with a carcinogenic agent. Major changes  
36 in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism  
37 does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full  
38 review.

### 39 **4. Data for the *Monographs***

40 Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in  
41 experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited  
42 but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

43 Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily  
44 cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section

1 4). Only those data considered by the Working Group to be relevant to making the evaluation  
2 are included.

3 With regard to epidemiological studies, cancer bioassays, and mechanistic and other  
4 relevant data, only reports that have been published or accepted for publication in the openly  
5 available scientific literature are reviewed. The same publication requirement applies to  
6 studies originating from IARC, including meta-analyses or pooled analyses commissioned by  
7 IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports  
8 that are publicly available are also considered. Exceptionally, doctoral theses and other  
9 material that are in their final form and publicly available may be reviewed.

10 Exposure data and other information on an agent under consideration are also reviewed.  
11 In the sections on chemical and physical properties, on analysis, on production and use and  
12 on occurrence, published and unpublished sources of information may be considered.

13 Inclusion of a study does not imply acceptance of the adequacy of the study design or of  
14 the analysis and interpretation of the results, and limitations are clearly outlined in square  
15 brackets at the end of each study description (see Part B). The reasons for not giving further  
16 consideration to an individual study also are indicated in the square brackets.

## 17 **5. Meeting participants**

18 Five categories of participant can be present at *Monograph* meetings.

19 (a) The Working Group is responsible for the critical reviews and evaluations that are  
20 developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that  
21 all appropriate data have been collected; (ii) to select the data relevant for the evaluation on  
22 the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the  
23 reader to follow the reasoning of the Working Group; (iv) to evaluate the results of  
24 epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the  
25 understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the  
26 carcinogenicity of the exposure to humans. Working Group Members generally have  
27 published significant research related to the carcinogenicity of the agents being reviewed, and  
28 IARC uses literature searches to identify most experts. Working Group Members are selected  
29 on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of  
30 interests. Consideration is also given to demographic diversity and balance of scientific  
31 findings and views.

32 (b) Invited Specialists are experts who also have critical knowledge and experience but  
33 have a real or apparent conflict of interests. These experts are invited when necessary to assist  
34 in the Working Group by contributing their unique knowledge and experience during  
35 subgroup and plenary discussions. They may also contribute text on non-influential issues in  
36 the section on exposure, such as a general description of data on production and use (see Part  
37 B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text  
38 that pertains to the description or interpretation of cancer data, or participate in the  
39 evaluations.

40 (c) Representatives of national and international health agencies often attend meetings  
41 because their agencies sponsor the programme or are interested in the subject of a meeting.  
42 Representatives do not serve as meeting chair or subgroup chair, draft any part of a  
43 *Monograph*, or participate in the evaluations.

44 (d) Observers with relevant scientific credentials may be admitted to a meeting by IARC  
45 in limited numbers. Attention will be given to achieving a balance of Observers from  
46 constituencies with differing perspectives. They are invited to observe the meeting and

1 should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair,  
2 draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting  
3 chair and subgroup chairs may grant Observers an opportunity to speak, generally after they  
4 have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC*  
5 *Monographs* meetings (available at <http://monographs.iarc.fr>).

6 (e) The IARC Secretariat consists of scientists who are designated by IARC and who  
7 have relevant expertise. They serve as rapporteurs and participate in all discussions. When  
8 requested by the meeting chair or subgroup chair, they may also draft text or prepare tables  
9 and analyses.

10 Before an invitation is extended, each potential participant, including the IARC  
11 Secretariat, completes the WHO Declaration of Interests to report financial interests,  
12 employment and consulting, and individual and institutional research support related to the  
13 subject of the meeting. IARC assesses these interests to determine whether there is a conflict  
14 that warrants some limitation on participation. The declarations are updated and reviewed  
15 again at the opening of the meeting. Interests related to the subject of the meeting are  
16 disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

17 The names and principal affiliations of participants are available on the *Monographs*  
18 programme website (<http://monographs.iarc.fr>) approximately two months before each  
19 meeting. It is not acceptable for Observers or third parties to contact other participants before  
20 a meeting or to lobby them at any time. Meeting participants are asked to report all such  
21 contacts to IARC (Cogliano *et al.*, 2005).

22 All participants are listed, with their principal affiliations, at the beginning of each  
23 volume. Each participant who is a Member of a Working Group serves as an individual  
24 scientist and not as a representative of any organization, government or industry.

## 25 **6. Working procedures**

26 A separate Working Group is responsible for developing each volume of *Monographs*. A  
27 volume contains one or more *Monographs*, which can cover either a single agent or several  
28 related agents. Approximately one year in advance of the meeting of a Working Group, the  
29 agents to be reviewed are announced on the *Monographs* programme website  
30 (<http://monographs.iarc.fr>) and participants are selected by IARC staff in consultation with  
31 other experts. Subsequently, relevant biological and epidemiological data are collected by  
32 IARC from recognized sources of information on carcinogenesis, including data storage and  
33 retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary  
34 working papers for specific sections are expected to supplement the IARC literature searches  
35 with their own searches.

36 Industrial associations, labour unions and other knowledgeable organizations may be  
37 asked to provide input to the sections on production and use, although this involvement is not  
38 required as a general rule. Information on production and trade is obtained from  
39 governmental, trade and market research publications and, in some cases, by direct contact  
40 with industries. Separate production data on some agents may not be available for a variety of  
41 reasons (e.g. not collected or made public in all producing countries, production is small).  
42 Information on uses may be obtained from published sources but is often complemented by  
43 direct contact with manufacturers. Efforts are made to supplement this information with data  
44 from other national and international sources.

1 Six months before the meeting, the material obtained is sent to meeting participants to  
2 prepare preliminary working papers. The working papers are compiled by IARC staff and  
3 sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

4 The Working Group meets at IARC for seven to eight days to discuss and finalize the  
5 texts and to formulate the evaluations. The objectives of the meeting are peer review and  
6 consensus. During the first few days, four subgroups (covering exposure data, cancer in  
7 humans, cancer in experimental animals, and mechanistic and other relevant data) review the  
8 working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure  
9 that each study summary is written or reviewed by someone not associated with the study  
10 being considered. During the last few days, the Working Group meets in plenary session to  
11 review the subgroup drafts and develop the evaluations. As a result, the entire volume is the  
12 joint product of the Working Group, and there are no individually authored sections.

13 IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad  
14 agreement among Working Group Members, but not necessarily unanimity. The chair may  
15 elect to poll Working Group Members to determine the diversity of scientific opinion on  
16 issues where consensus is not readily apparent.

17 After the meeting, the master copy is verified by consulting the original literature, edited  
18 and prepared for publication. The aim is to publish the volume within six months of the  
19 Working Group meeting. A summary of the outcome is available on the *Monographs*  
20 programme website soon after the meeting.

## 21 **B. SCIENTIFIC REVIEW AND EVALUATION**

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

30 The scope of the *IARC Monographs* programme has expanded beyond chemicals to  
31 include complex mixtures, occupational exposures, physical and biological agents, lifestyle  
32 factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph*  
33 has evolved to include the following sections:

- 34 1. Exposure data
- 35 2. Studies of cancer in humans
- 36 3. Studies of cancer in experimental animals
- 37 4. Mechanistic and other relevant data
- 38 5. Summary
- 39 6. Evaluation and rationale

40 In addition, a section of General Remarks at the front of the volume discusses the reasons  
41 the agents were scheduled for evaluation and some key issues the Working Group  
42 encountered during the meeting.

43 This part of the Preamble discusses the types of evidence considered and summarized in  
44 each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

## 1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

### (a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

### (b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

### (c) Production and use

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

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily

1 comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily  
2 represent current practice nor does it imply judgement as to their therapeutic efficacy.

### 3 **(d) Occurrence and exposure**

4 Information on the occurrence of an agent in the environment is obtained from data  
5 derived from the monitoring and surveillance of levels in occupational environments, air,  
6 water, soil, plants, foods and animal and human tissues. When available, data on the  
7 generation, persistence and bioaccumulation of the agent are also included. Such data may be  
8 available from national databases.

9 Data that indicate the extent of past and present human exposure, the sources of exposure,  
10 the people most likely to be exposed and the factors that contribute to the exposure are  
11 reported. Information is presented on the range of human exposure, including occupational  
12 and environmental exposures. This includes relevant findings from both developed and  
13 developing countries. Some of these data are not distributed widely and may be available  
14 from government reports and other sources. In the case of mixtures, industries, occupations or  
15 processes, information is given about all agents known to be present. For processes,  
16 industries and occupations, a historical description is also given, noting variations in chemical  
17 composition, physical properties and levels of occupational exposure with date and place. For  
18 biological agents, the epidemiology of infection is described.

### 19 **(e) Regulations and guidelines**

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

## 26 **2. Studies of cancer in humans**

27 This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies  
28 of biomarkers are included when they are relevant to an evaluation of carcinogenicity to  
29 humans.

### 30 **(a) Types of study considered**

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

35 Cohort and case–control studies relate individual exposures under study to the occurrence  
36 of cancer in individuals and provide an estimate of effect (such as relative risk) as the main  
37 measure of association. Intervention studies may provide strong evidence for making causal  
38 inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for  
39 lung cancer.

40 In correlation studies, the units of investigation are usually whole populations (e.g. in  
41 particular geographical areas or at particular times), and cancer frequency is related to a  
42 summary measure of the exposure of the population to the agent under study. In correlation  
43 studies, individual exposure is not documented, which renders this kind of study more prone

1 to confounding. In some circumstances, however, correlation studies may be more  
2 informative than analytical study designs (see, for example, the *Monograph* on arsenic in  
3 drinking-water; IARC, 2004).

4 In some instances, case reports and case series have provided important information about  
5 the carcinogenicity of an agent. These types of study generally arise from a suspicion, based  
6 on clinical experience, that the concurrence of two events — that is, a particular exposure and  
7 occurrence of a cancer — has happened rather more frequently than would be expected by  
8 chance. Case reports and case series usually lack complete ascertainment of cases in any  
9 population, definition or enumeration of the population at risk and estimation of the expected  
10 number of cases in the absence of exposure.

11 The uncertainties that surround the interpretation of case reports, case series and  
12 correlation studies make them inadequate, except in rare instances, to form the sole basis for  
13 inferring a causal relationship. When taken together with case-control and cohort studies,  
14 however, these types of study may add materially to the judgement that a causal relationship  
15 exists.

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

#### 19 **(b) Quality of studies considered**

20 It is necessary to take into account the possible roles of bias, confounding and chance in  
21 the interpretation of epidemiological studies. Bias is the effect of factors in study design or  
22 execution that lead erroneously to a stronger or weaker association than in fact exists between  
23 an agent and disease. Confounding is a form of bias that occurs when the relationship with  
24 disease is made to appear stronger or weaker than it truly is as a result of an association  
25 between the apparent causal factor and another factor that is associated with either an  
26 increase or decrease in the incidence of the disease. The role of chance is related to biological  
27 variability and the influence of sample size on the precision of estimates of effect.

28 In evaluating the extent to which these factors have been minimized in an individual  
29 study, consideration is given to a number of aspects of design and analysis as described in the  
30 report of the study. For example, when suspicion of carcinogenicity arises largely from a  
31 single small study, careful consideration is given when interpreting subsequent studies that  
32 included these data in an enlarged population. Most of these considerations apply equally to  
33 case-control, cohort and correlation studies. Lack of clarity of any of these aspects in the  
34 reporting of a study can decrease its credibility and the weight given to it in the final  
35 evaluation of the exposure.

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

40 Secondly, the authors should have taken into account — in the study design and analysis  
41 — other variables that can influence the risk of disease and may have been related to the  
42 exposure of interest. Potential confounding by such variables should have been dealt with  
43 either in the design of the study, such as by matching, or in the analysis, by statistical  
44 adjustment. In cohort studies, comparisons with local rates of disease may or may not be  
45 more appropriate than those with national rates. Internal comparisons of frequency of disease  
46 among individuals at different levels of exposure are also desirable in cohort studies, since

1 they minimize the potential for confounding related to the difference in risk factors between  
2 an external reference group and the study population.

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

11 Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of  
12 cancer, confidence intervals and significance tests, and to adjust for confounding should have  
13 been clearly stated by the authors. These methods have been reviewed for case-control  
14 studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

### 15 (c) Meta-analyses and pooled analyses

16 Independent epidemiological studies of the same agent may lead to results that are  
17 difficult to interpret. Combined analyses of data from multiple studies are a means of  
18 resolving this ambiguity, and well-conducted analyses can be considered. There are two types  
19 of combined analysis. The first involves combining summary statistics such as relative risks  
20 from individual studies (meta-analysis) and the second involves a pooled analysis of the raw  
21 data from the individual studies (pooled analysis) (Greenland, 1998).

22 The advantages of combined analyses are increased precision due to increased sample  
23 size and the opportunity to explore potential confounders, interactions and modifying effects  
24 that may explain heterogeneity among studies in more detail. A disadvantage of combined  
25 analyses is the possible lack of compatibility of data from various studies due to differences  
26 in subject recruitment, procedures of data collection, methods of measurement and effects of  
27 unmeasured co-variables that may differ among studies. Despite these limitations, well-  
28 conducted combined analyses may provide a firmer basis than individual studies for drawing  
29 conclusions about the potential carcinogenicity of agents.

30 IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular  
31 *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the  
32 results of multiple individual studies, ad-hoc calculations that combine data from different  
33 studies may be conducted by the Working Group during the course of a *Monograph* meeting.  
34 The results of such original calculations, which would be specified in the text by presentation  
35 in square brackets, might involve updates of previously conducted analyses that incorporate  
36 the results of more recent studies or de-novo analyses. Irrespective of the source of data for  
37 the meta-analyses and pooled analyses, it is important that the same criteria for data quality  
38 be applied as those that would be applied to individual studies and to ensure also that sources  
39 of heterogeneity between studies be taken into account.

### 40 (d) Temporal effects

41 Detailed analyses of both relative and absolute risks in relation to temporal variables,  
42 such as age at first exposure, time since first exposure, duration of exposure, cumulative  
43 exposure, peak exposure (when appropriate) and time since cessation of exposure, are  
44 reviewed and summarized when available. Analyses of temporal relationships may be useful  
45 in making causal inferences. In addition, such analyses may suggest whether a carcinogen

1 acts early or late in the process of carcinogenesis, although, at best, they allow only indirect  
2 inferences about mechanisms of carcinogenesis.

### 3 **(e) Use of biomarkers in epidemiological studies**

4 Biomarkers indicate molecular, cellular or other biological changes and are increasingly  
5 used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992;  
6 Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of  
7 exposure, of early effects, of cellular, tissue or organism responses, of individual  
8 susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This  
9 is a rapidly evolving field that encompasses developments in genomics, epigenomics and  
10 other emerging technologies.

11 Molecular epidemiological data that identify associations between genetic polymorphisms  
12 and interindividual differences in susceptibility to the agent(s) being evaluated may  
13 contribute to the identification of carcinogenic hazards to humans. If the polymorphism has  
14 been demonstrated experimentally to modify the functional activity of the gene product in a  
15 manner that is consistent with increased susceptibility, these data may be useful in making  
16 causal inferences. Similarly, molecular epidemiological studies that measure cell functions,  
17 enzymes or metabolites that are thought to be the basis of susceptibility may provide  
18 evidence that reinforces biological plausibility. It should be noted, however, that when data  
19 on genetic susceptibility originate from multiple comparisons that arise from subgroup  
20 analyses, this can generate false-positive results and inconsistencies across studies, and such  
21 data therefore require careful evaluation. If the known phenotype of a genetic polymorphism  
22 can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype  
23 may be useful in making causal inferences.

### 24 **(f) Criteria for causality**

25 After the quality of individual epidemiological studies of cancer has been summarized  
26 and assessed, a judgement is made concerning the strength of evidence that the agent in  
27 question is carcinogenic to humans. In making its judgement, the Working Group considers  
28 several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is  
29 more likely to indicate causality than a weak association, although it is recognized that  
30 estimates of effect of small magnitude do not imply lack of causality and may be important if  
31 the disease or exposure is common. Associations that are replicated in several studies of the  
32 same design or that use different epidemiological approaches or under different  
33 circumstances of exposure are more likely to represent a causal relationship than isolated  
34 observations from single studies. If there are inconsistent results among investigations,  
35 possible reasons are sought (such as differences in exposure), and results of studies that are  
36 judged to be of high quality are given more weight than those of studies that are judged to be  
37 methodologically less sound.

38 If the risk increases with the exposure, this is considered to be a strong indication of  
39 causality, although the absence of a graded response is not necessarily evidence against a  
40 causal relationship. The demonstration of a decline in risk after cessation of or reduction in  
41 exposure in individuals or in whole populations also supports a causal interpretation of the  
42 findings.

43 A number of scenarios may increase confidence in a causal relationship. On the one hand,  
44 an agent may be specific in causing tumours at one site or of one morphological type. On the  
45 other, carcinogenicity may be evident through the causation of multiple tumour types.  
46 Temporality, precision of estimates of effect, biological plausibility and coherence of the

1 overall database are considered. Data on biomarkers may be employed in an assessment of  
2 the biological plausibility of epidemiological observations.

3 Although rarely available, results from randomized trials that show different rates of  
4 cancer among exposed and unexposed individuals provide particularly strong evidence for  
5 causality.

6 When several epidemiological studies show little or no indication of an association  
7 between an exposure and cancer, a judgement may be made that, in the aggregate, they show  
8 evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to  
9 a sufficient degree, the standards of design and analysis described above. Specifically, the  
10 possibility that bias, confounding or misclassification of exposure or outcome could explain  
11 the observed results should be considered and excluded with reasonable certainty. In addition,  
12 all studies that are judged to be methodologically sound should (a) be consistent with an  
13 estimate of effect of unity for any observed level of exposure, (b) when considered together,  
14 provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow  
15 confidence interval, due to sufficient population size. Moreover, no individual study nor the  
16 pooled results of all the studies should show any consistent tendency that the relative risk of  
17 cancer increases with increasing level of exposure. It is important to note that evidence of  
18 lack of carcinogenicity obtained from several epidemiological studies can apply only to the  
19 type(s) of cancer studied, to the dose levels reported, and to the intervals between first  
20 exposure and disease onset observed in these studies. Experience with human cancer  
21 indicates that the period from first exposure to the development of clinical cancer is  
22 sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot  
23 provide evidence for lack of carcinogenicity.

### 24 **3. Studies of cancer in experimental animals**

25 All known human carcinogens that have been studied adequately for carcinogenicity in  
26 experimental animals have produced positive results in one or more animal species (Wilbourn  
27 *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar  
28 radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly  
29 suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio  
30 *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in  
31 experimental animals also cause cancer in humans, it is biologically plausible that agents for  
32 which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B,  
33 Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of  
34 additional scientific information, these agents are considered to pose a carcinogenic hazard to  
35 humans. Examples of additional scientific information are data that demonstrate that a given  
36 agent causes cancer in animals through a species-specific mechanism that does not operate in  
37 humans or data that demonstrate that the mechanism in experimental animals also operates in  
38 humans (see Part B, Section 6).

39 Consideration is given to all available long-term studies of cancer in experimental  
40 animals with the agent under review (see Part A, Section 4). In all experimental settings, the  
41 nature and extent of impurities or contaminants present in the agent being evaluated are given  
42 when available. Animal species, strain (including genetic background where applicable), sex,  
43 numbers per group, age at start of treatment, route of exposure, dose levels, duration of  
44 exposure, survival and information on tumours (incidence, latency, severity or multiplicity of  
45 neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that  
46 are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a

1 duration, too few animals, poor survival; see below) may be omitted. Guidelines for  
2 conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

3 Other studies considered may include: experiments in which the agent was administered  
4 in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies,  
5 co-carcinogenicity studies and studies in genetically modified animals); studies in which the  
6 end-point was not cancer but a defined precancerous lesion; experiments on the  
7 carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory  
8 animals (e.g. livestock and companion animals) exposed to the agent.

9 For studies of mixtures, consideration is given to the possibility that changes in the  
10 physicochemical properties of the individual substances may occur during collection, storage,  
11 extraction, concentration and delivery. Another consideration is that chemical and  
12 toxicological interactions of components in a mixture may alter dose–response relationships.  
13 The relevance to human exposure of the test mixture administered in the animal experiment is  
14 also assessed. This may involve consideration of the following aspects of the mixture tested:  
15 (i) physical and chemical characteristics, (ii) identified constituents that may indicate the  
16 presence of a class of substances and (iii) the results of genetic toxicity and related tests.

17 The relevance of results obtained with an agent that is analogous (e.g. similar in structure  
18 or of a similar virus genus) to that being evaluated is also considered. Such results may  
19 provide biological and mechanistic information that is relevant to the understanding of the  
20 process of carcinogenesis in humans and may strengthen the biological plausibility that the  
21 agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

#### 22 (a) Qualitative aspects

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

30 Considerations of importance in the interpretation and evaluation of a particular study  
31 include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately  
32 the sample characterization was reported; (ii) whether the dose was monitored adequately,  
33 particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route  
34 of exposure were appropriate; (iv) whether the survival of treated animals was similar to that  
35 of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both  
36 male and female animals were used; (vii) whether animals were allocated randomly to  
37 groups; (viii) whether the duration of observation was adequate; and (ix) whether the data  
38 were reported and analysed adequately.

39 When benign tumours (a) occur together with and originate from the same cell type as  
40 malignant tumours in an organ or tissue in a particular study and (b) appear to represent a  
41 stage in the progression to malignancy, they are usually combined in the assessment of  
42 tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic  
43 may in certain instances aid in assessing the biological plausibility of any neoplastic response  
44 observed. If an agent induces only benign neoplasms that appear to be end-points that do not  
45 readily undergo transition to malignancy, the agent should nevertheless be suspected of being  
46 carcinogenic and requires further investigation.

## 1           **(b) Quantitative aspects**

2           The probability that tumours will occur may depend on the species, sex, strain, genetic  
3 background and age of the animal, and on the dose, route, timing and duration of the  
4 exposure. Evidence of an increased incidence of neoplasms with increasing levels of  
5 exposure strengthens the inference of a causal association between the exposure and the  
6 development of neoplasms.

7           The form of the dose–response relationship can vary widely, depending on the particular  
8 agent under study and the target organ. Mechanisms such as induction of DNA damage or  
9 inhibition of repair, altered cell division and cell death rates and changes in intercellular  
10 communication are important determinants of dose–response relationships for some  
11 carcinogens. Since many chemicals require metabolic activation before being converted to  
12 their reactive intermediates, both metabolic and toxicokinetic aspects are important in  
13 determining the dose–response pattern. Saturation of steps such as absorption, activation,  
14 inactivation and elimination may produce non-linearity in the dose–response relationship  
15 (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair.  
16 The dose–response relationship can also be affected by differences in survival among the  
17 treatment groups.

## 18           **(c) Statistical analyses**

19           Factors considered include the adequacy of the information given for each treatment  
20 group: (i) number of animals studied and number examined histologically, (ii) number of  
21 animals with a given tumour type and (iii) length of survival. The statistical methods used  
22 should be clearly stated and should be the generally accepted techniques refined for this  
23 purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams,  
24 1993). The choice of the most appropriate statistical method requires consideration of  
25 whether or not there are differences in survival among the treatment groups; for example,  
26 reduced survival because of non-tumour-related mortality can preclude the occurrence of  
27 tumours later in life. When detailed information on survival is not available, comparisons of  
28 the proportions of tumour-bearing animals among the effective number of animals (alive at  
29 the time the first tumour was discovered) can be useful when significant differences in  
30 survival occur before tumours appear. The lethality of the tumour also requires consideration:  
31 for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset  
32 and can be assessed using life-table methods; non-fatal or incidental tumours that do not  
33 affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in  
34 tumour prevalence. Because tumour lethality is often difficult to determine, methods such as  
35 the Poly-K test that do not require such information can also be used. When results are  
36 available on the number and size of tumours seen in experimental animals (e.g. papillomas on  
37 mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other  
38 more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*,  
39 2003).

40           Formal statistical methods have been developed to incorporate historical control data into  
41 the analysis of data from a given experiment. These methods assign an appropriate weight to  
42 historical and concurrent controls on the basis of the extent of between-study and within-  
43 study variability: less weight is given to historical controls when they show a high degree of  
44 variability, and greater weight when they show little variability. It is generally not appropriate  
45 to discount a tumour response that is significantly increased compared with concurrent  
46 controls by arguing that it falls within the range of historical controls, particularly when  
47 historical controls show high between-study variability and are, thus, of little relevance to the

1 current experiment. In analysing results for uncommon tumours, however, the analysis may  
2 be improved by considering historical control data, particularly when between-study  
3 variability is low. Historical controls should be selected to resemble the concurrent controls  
4 as closely as possible with respect to species, gender and strain, as well as other factors such  
5 as basal diet and general laboratory environment, which may affect tumour-response rates in  
6 control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

7 Although meta-analyses and combined analyses are conducted less frequently for animal  
8 experiments than for epidemiological studies due to differences in animal strains, they can be  
9 useful aids in interpreting animal data when the experimental protocols are sufficiently  
10 similar.

#### 11 **4. Mechanistic and other relevant data**

12 Mechanistic and other relevant data may provide evidence of carcinogenicity and also  
13 help in assessing the relevance and importance of findings of cancer in animals and in  
14 humans. The nature of the mechanistic and other relevant data depends on the biological  
15 activity of the agent being considered. The Working Group considers representative studies  
16 to give a concise description of the relevant data and issues that they consider to be  
17 important; thus, not every available study is cited. Relevant topics may include  
18 toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-  
19 stages, other relevant data and other adverse effects. When data on biomarkers are  
20 informative about the mechanisms of carcinogenesis, they are included in this section.

21 These topics are not mutually exclusive; thus, the same studies may be discussed in more  
22 than one subsection. For example, a mutation in a gene that codes for an enzyme that  
23 metabolizes the agent under study could be discussed in the subsections on toxicokinetics,  
24 mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

##### 25 **(a) Toxicokinetic data**

26 Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents  
27 in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic  
28 factors that may affect dose–response relationships include uptake, deposition, biopersistence  
29 and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that  
30 indicate the metabolic fate of the agent in humans and in experimental animals are  
31 summarized briefly, and comparisons of data from humans and animals are made when  
32 possible. Comparative information on the relationship between exposure and the dose that  
33 reaches the target site may be important for the extrapolation of hazards between species and  
34 in clarifying the role of in-vitro findings.

##### 35 **(b) Data on mechanisms of carcinogenesis**

36 To provide focus, the Working Group attempts to identify the possible mechanisms by  
37 which the agent may increase the risk of cancer. For each possible mechanism, a  
38 representative selection of key data from humans and experimental systems is summarized.  
39 Attention is given to gaps in the data and to data that suggests that more than one mechanism  
40 may be operating. The relevance of the mechanism to humans is discussed, in particular,  
41 when mechanistic data are derived from experimental model systems. Changes in the affected  
42 organs, tissues or cells can be divided into three non-exclusive levels as described below.

## 1 (i) Changes in physiology

2 Physiological changes refer to exposure-related modifications to the physiology  
3 and/or response of cells, tissues and organs. Examples of potentially adverse  
4 physiological changes include mitogenesis, compensatory cell division, escape from  
5 apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or  
6 preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones  
7 and changes in immune surveillance.

## 8 (ii) Functional changes at the cellular level

9 Functional changes refer to exposure-related alterations in the signalling pathways  
10 used by cells to manage critical processes that are related to increased risk for cancer.  
11 Examples of functional changes include modified activities of enzymes involved in the  
12 metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA  
13 repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes  
14 in the patterns of post-translational modifications of proteins, changes in regulatory  
15 factors that alter apoptotic rates, changes in the secretion of factors related to the  
16 stimulation of DNA replication and transcription and changes in gap-junction-mediated  
17 intercellular communication.

## 18 (iii) Changes at the molecular level

19 Molecular changes refer to exposure-related changes in key cellular structures at the  
20 molecular level, including, in particular, genotoxicity. Examples of molecular changes  
21 include formation of DNA adducts and DNA strand breaks, mutations in genes,  
22 chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater  
23 emphasis is given to irreversible effects.

24 The use of mechanistic data in the identification of a carcinogenic hazard is specific to the  
25 mechanism being addressed and is not readily described for every possible level and  
26 mechanism discussed above.

27 Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation  
28 of mechanistic data.

29 Tests for genetic and related effects are described in view of the relevance of gene  
30 mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*,  
31 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample  
32 characterization is considered and, when necessary, commented upon; with regard to  
33 complex mixtures, such comments are similar to those described for animal  
34 carcinogenicity tests. The available data are interpreted critically according to the end-  
35 points detected, which may include DNA damage, gene mutation, sister chromatid  
36 exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The  
37 concentrations employed are given, and mention is made of whether the use of an  
38 exogenous metabolic system *in vitro* affected the test result. These data are listed in  
39 tabular form by phylogenetic classification.

40 Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and  
41 cultured mammalian cells suggest that genetic and related effects could occur in  
42 mammals. Results from such tests may also give information on the types of genetic  
43 effect produced and on the involvement of metabolic activation. Some end-points  
44 described are clearly genetic in nature (e.g. gene mutations), while others are  
45 associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for

1 tumour promotion, cell transformation and gap–junction intercellular communication  
2 may be sensitive to changes that are not necessarily the result of genetic alterations  
3 but that may have specific relevance to the process of carcinogenesis. Critical  
4 appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et*  
5 *al.*, 1999).

6 Genetic or other activity manifest in humans and experimental mammals is  
7 regarded to be of greater relevance than that in other organisms. The demonstration  
8 that an agent can induce gene and chromosomal mutations in mammals *in vivo*  
9 indicates that it may have carcinogenic activity. Negative results in tests for  
10 mutagenicity in selected tissues from animals treated *in vivo* provide less weight,  
11 partly because they do not exclude the possibility of an effect in tissues other than  
12 those examined. Moreover, negative results in short-term tests with genetic end-points  
13 cannot be considered to provide evidence that rules out the carcinogenicity of agents  
14 that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity  
15 with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992).  
16 Factors that may give misleading results in short-term tests have been discussed in  
17 detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

18 When there is evidence that an agent acts by a specific mechanism that does not involve  
19 genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and  
20 other deposits that cause chronic irritation), that evidence is presented and reviewed critically  
21 in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g.  
22 Capen *et al.*, 1999).

23 For biological agents such as viruses, bacteria and parasites, other data relevant to  
24 carcinogenicity may include descriptions of the pathology of infection, integration and  
25 expression of viruses, and genetic alterations seen in human tumours. Other observations that  
26 might comprise cellular and tissue responses to infection, immune response and the presence  
27 of tumour markers are also considered.

28 For physical agents that are forms of radiation, other data relevant to carcinogenicity may  
29 include descriptions of damaging effects at the physiological, cellular and molecular level, as  
30 for chemical agents, and descriptions of how these effects occur. ‘Physical agents’ may also  
31 be considered to comprise foreign bodies, such as surgical implants of various kinds, and  
32 poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are  
33 a result of their physical presence in tissues or body cavities. Other relevant data for such  
34 materials may include characterization of cellular, tissue and physiological reactions to these  
35 materials and descriptions of pathological conditions other than neoplasia with which they  
36 may be associated.

### 37 (c) Other data relevant to mechanisms

38 A description is provided of any structure–activity relationships that may be relevant to  
39 an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical  
40 and chemical properties, and any other data relevant to the evaluation that are not included  
41 elsewhere.

42 High-output data, such as those derived from gene expression microarrays, and high-  
43 throughput data, such as those that result from testing hundreds of agents for a single end-  
44 point, pose a unique problem for the use of mechanistic data in the evaluation of a  
45 carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret  
46 changes in individual end-points (e.g. changes in expression in one gene) without considering  
47 the consistency of that finding in the broader context of the other end-points (e.g. other genes

1 with linked transcriptional control). High-output data can be used in assessing mechanisms,  
2 but all end-points measured in a single experiment need to be considered in the proper  
3 context. For high-throughput data, where the number of observations far exceeds the number  
4 of end-points measured, their utility for identifying common mechanisms across multiple  
5 agents is enhanced. These data can be used to identify mechanisms that not only seem  
6 plausible, but also have a consistent pattern of carcinogenic response across entire classes of  
7 related compounds.

#### 8 **(d) Susceptibility data**

9 Individuals, populations and life-stages may have greater or lesser susceptibility to an  
10 agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of  
11 host and genetic factors that affect individual susceptibility include sex, genetic  
12 polymorphisms of genes involved in the metabolism of the agent under evaluation,  
13 differences in metabolic capacity due to life-stage or the presence of disease, differences in  
14 DNA repair capacity, competition for or alteration of metabolic capacity by medications or  
15 other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical  
16 exposure, a suppressed immune system, periods of higher-than-usual tissue growth or  
17 regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction).  
18 Such data can substantially increase the strength of the evidence from epidemiological data  
19 and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

#### 20 **(e) Data on other adverse effects**

21 Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation  
22 are summarized. Adverse effects that confirm distribution and biological effects at the sites of  
23 tumour development, or alterations in physiology that could lead to tumour development, are  
24 emphasized. Effects on reproduction, embryonic and fetal survival and development are  
25 summarized briefly. The adequacy of epidemiological studies of reproductive outcome and  
26 genetic and related effects in humans is judged by the same criteria as those applied to  
27 epidemiological studies of cancer, but fewer details are given.

### 28 **5. Summary**

29 This section is a summary of data presented in the preceding sections. Summaries can be  
30 found on the *Monographs* programme website (<http://monographs.iarc.fr>).

#### 31 **(a) Exposure data**

32 Data are summarized, as appropriate, on the basis of elements such as production, use,  
33 occurrence and exposure levels in the workplace and environment and measurements in  
34 human tissues and body fluids. Quantitative data and time trends are given to compare  
35 exposures in different occupations and environmental settings. Exposure to biological agents  
36 is described in terms of transmission, prevalence and persistence of infection.

#### 37 **(b) Cancer in humans**

38 Results of epidemiological studies pertinent to an assessment of human carcinogenicity  
39 are summarized. When relevant, case reports and correlation studies are also summarized.  
40 The target organ(s) or tissue(s) in which an increase in cancer was observed is identified.  
41 Dose-response and other quantitative data may be summarized when available.

### 1 (c) Cancer in experimental animals

2 Data relevant to an evaluation of carcinogenicity in animals are summarized. For each  
3 animal species, study design and route of administration, it is stated whether an increased  
4 incidence, reduced latency, or increased severity or multiplicity of neoplasms or  
5 preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced  
6 tumours after prenatal exposure or in single-dose experiments, this is also mentioned.  
7 Negative findings, inverse relationships, dose–response and other quantitative data are also  
8 summarized.

### 9 (d) Mechanistic and other relevant data

10 Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and  
11 the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are  
12 summarized. In addition, information on susceptible individuals, populations and life-stages  
13 is summarized. This section also reports on other toxic effects, including reproductive and  
14 developmental effects, as well as additional relevant data that are considered to be important.

## 15 6. Evaluation and rationale

16 Evaluations of the strength of the evidence for carcinogenicity arising from human and  
17 experimental animal data are made, using standard terms. The strength of the mechanistic  
18 evidence is also characterized.

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

23 These categories refer only to the strength of the evidence that an exposure is  
24 carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may  
25 change as new information becomes available.

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

### 30 (a) Carcinogenicity in humans

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

33 **Sufficient evidence of carcinogenicity:** The Working Group considers that a causal  
34 relationship has been established between exposure to the agent and human cancer. That  
35 is, a positive relationship has been observed between the exposure and cancer in studies  
36 in which chance, bias and confounding could be ruled out with reasonable confidence. A  
37 statement that there is *sufficient evidence* is followed by a separate sentence that identifies  
38 the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans.  
39 Identification of a specific target organ or tissue does not preclude the possibility that the  
40 agent may cause cancer at other sites.

41 **Limited evidence of carcinogenicity:** A positive association has been observed between  
42 exposure to the agent and cancer for which a causal interpretation is considered by the

1 Working Group to be credible, but chance, bias or confounding could not be ruled out  
2 with reasonable confidence.

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

7 ***Evidence suggesting lack of carcinogenicity:*** There are several adequate studies covering the  
8 full range of levels of exposure that humans are known to encounter, which are mutually  
9 consistent in not showing a positive association between exposure to the agent and any  
10 studied cancer at any observed level of exposure. The results from these studies alone or  
11 combined should have narrow confidence intervals with an upper limit close to the null  
12 value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with  
13 reasonable confidence, and the studies should have an adequate length of follow-up. A  
14 conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the  
15 cancer sites, conditions and levels of exposure, and length of observation covered by the  
16 available studies. In addition, the possibility of a very small risk at the levels of exposure  
17 studied can never be excluded.

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

20 When the available epidemiological studies pertain to a mixture, process, occupation or  
21 industry, the Working Group seeks to identify the specific agent considered most likely to be  
22 responsible for any excess risk. The evaluation is focused as narrowly as the available data on  
23 exposure and other aspects permit.

#### 24 **(b) Carcinogenicity in experimental animals**

25 Carcinogenicity in experimental animals can be evaluated using conventional bioassays,  
26 bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on  
27 one or more of the critical stages of carcinogenesis. In the absence of data from conventional  
28 long-term bioassays or from assays with neoplasia as the end-point, consistently positive  
29 results in several models that address several stages in the multistage process of  
30 carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity  
31 in experimental animals.

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

34 ***Sufficient evidence of carcinogenicity:*** The Working Group considers that a causal  
35 relationship has been established between the agent and an increased incidence of  
36 malignant neoplasms or of an appropriate combination of benign and malignant  
37 neoplasms in (a) two or more species of animals or (b) two or more independent studies  
38 in one species carried out at different times or in different laboratories or under different  
39 protocols. An increased incidence of tumours in both sexes of a single species in a well-  
40 conducted study, ideally conducted under Good Laboratory Practices, can also provide  
41 *sufficient evidence*.

42 A single study in one species and sex might be considered to provide *sufficient evidence*  
43 *of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to  
44 incidence, site, type of tumour or age at onset, or when there are strong findings of  
45 tumours at multiple sites.

1 **Limited evidence of carcinogenicity:** The data suggest a carcinogenic effect but are limited  
2 for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is  
3 restricted to a single experiment; (b) there are unresolved questions regarding the  
4 adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the  
5 incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the  
6 evidence of carcinogenicity is restricted to studies that demonstrate only promoting  
7 activity in a narrow range of tissues or organs.

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

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

### 16 (c) Mechanistic and other relevant data

17 Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity  
18 and of sufficient importance to affect the overall evaluation is highlighted. This may include  
19 data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–  
20 activity relationships, metabolism and toxicokinetics, physicochemical parameters and  
21 analogous biological agents.

22 The strength of the evidence that any carcinogenic effect observed is due to a particular  
23 mechanism is evaluated, using terms such as ‘weak’, ‘moderate’ or ‘strong’. The Working  
24 Group then assesses whether that particular mechanism is likely to be operative in humans.  
25 The strongest indications that a particular mechanism operates in humans derive from data on  
26 humans or biological specimens obtained from exposed humans. The data may be considered  
27 to be especially relevant if they show that the agent in question has caused changes in  
28 exposed humans that are on the causal pathway to carcinogenesis. Such data may, however,  
29 never become available, because it is at least conceivable that certain compounds may be  
30 kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity  
31 in experimental systems.

32 The conclusion that a mechanism operates in experimental animals is strengthened by  
33 findings of consistent results in different experimental systems, by the demonstration of  
34 biological plausibility and by coherence of the overall database. Strong support can be  
35 obtained from studies that challenge the hypothesized mechanism experimentally, by  
36 demonstrating that the suppression of key mechanistic processes leads to the suppression of  
37 tumour development. The Working Group considers whether multiple mechanisms might  
38 contribute to tumour development, whether different mechanisms might operate in different  
39 dose ranges, whether separate mechanisms might operate in humans and experimental  
40 animals and whether a unique mechanism might operate in a susceptible group. The possible  
41 contribution of alternative mechanisms must be considered before concluding that tumours  
42 observed in experimental animals are not relevant to humans. An uneven level of  
43 experimental support for different mechanisms may reflect that disproportionate resources  
44 have been focused on investigating a favoured mechanism.

45 For complex exposures, including occupational and industrial exposures, the chemical  
46 composition and the potential contribution of carcinogens known to be present are considered  
47 by the Working Group in its overall evaluation of human carcinogenicity. The Working

1 Group also determines the extent to which the materials tested in experimental systems are  
2 related to those to which humans are exposed.

3 **(d) Overall evaluation**

4 Finally, the body of evidence is considered as a whole, in order to reach an overall  
5 evaluation of the carcinogenicity of the agent to humans.

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

12 The agent is described according to the wording of one of the following categories, and  
13 the designated group is given. The categorization of an agent is a matter of scientific  
14 judgement that reflects the strength of the evidence derived from studies in humans and in  
15 experimental animals and from mechanistic and other relevant data.

16 **Group 1: The agent is *carcinogenic to humans*.**

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

22 **Group 2.**

23 This category includes agents for which, at one extreme, the degree of evidence of  
24 carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other  
25 extreme, there are no human data but for which there is evidence of carcinogenicity in  
26 experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to*  
27 *humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological  
28 and experimental evidence of carcinogenicity and mechanistic and other relevant data.  
29 The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative  
30 significance and are used simply as descriptors of different levels of evidence of human  
31 carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than  
32 *possibly carcinogenic*.

33 **Group 2A: The agent is *probably carcinogenic to humans*.**

34 This category is used when there is *limited evidence of carcinogenicity* in humans and  
35 *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent  
36 may be classified in this category when there is *inadequate evidence of carcinogenicity* in  
37 humans and *sufficient evidence of carcinogenicity* in experimental animals and strong  
38 evidence that the carcinogenesis is mediated by a mechanism that also operates in  
39 humans. Exceptionally, an agent may be classified in this category solely on the basis of  
40 *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category  
41 if it clearly belongs, based on mechanistic considerations, to a class of agents for which  
42 one or more members have been classified in Group 1 or Group 2A.

1 **Group 2B: The agent is *possibly carcinogenic to humans*.**

2 This category is used for agents for which there is *limited evidence of carcinogenicity*  
3 in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It  
4 may also be used when there is *inadequate evidence of carcinogenicity* in humans but  
5 there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances,  
6 an agent for which there is *inadequate evidence of carcinogenicity* in humans and less  
7 than *sufficient evidence of carcinogenicity* in experimental animals together with  
8 supporting evidence from mechanistic and other relevant data may be placed in this  
9 group. An agent may be classified in this category solely on the basis of strong evidence  
10 from mechanistic and other relevant data.

11 **Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.**

12 This category is used most commonly for agents for which the evidence of  
13 carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental  
14 animals.

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

19 Agents that do not fall into any other group are also placed in this category.

20 An evaluation in Group 3 is not a determination of non-carcinogenicity or overall  
21 safety. It often means that further research is needed, especially when exposures are  
22 widespread or the cancer data are consistent with differing interpretations.

23 **Group 4: The agent is *probably not carcinogenic to humans*.**

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

29 **(e) Rationale**

30 The reasoning that the Working Group used to reach its evaluation is presented and  
31 discussed. This section integrates the major findings from studies of cancer in humans,  
32 studies of cancer in experimental animals, and mechanistic and other relevant data. It  
33 includes concise statements of the principal line(s) of argument that emerged, the conclusions  
34 of the Working Group on the strength of the evidence for each group of studies, citations to  
35 indicate which studies were pivotal to these conclusions, and an explanation of the reasoning  
36 of the Working Group in weighing data and making evaluations. When there are significant  
37 differences of scientific interpretation among Working Group Members, a brief summary of  
38 the alternative interpretations is provided, together with their scientific rationale and an  
39 indication of the relative degree of support for each alternative.

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