Instructions for Authors

Instructions for Authors for the Preparation of Drafts for IARC Monographs

These Instructions for Authors were prepared by staff of the IARC Monographs programme and are provided to members of the Working Group to guide them in preparing the first drafts of a Monograph before the Working Group meeting.

Authors are also provided with details and instructions specific to each Monograph topic as appropriate, and are advised to consult a recent volume of the IARC Monographs. The outline for each Monograph is provided to each author and defines the detailed structure of the Monograph and the individual writing assignments.

Although individual authors (members of the Working Group) prepare the preliminary drafts, the final Monograph and resulting evaluation is a consensus document that is reviewed and validated by the entire Working Group.

The Instructions for Authors were modified in 2019 to be in line with the Preamble to the IARC Monographs as updated in January 2019, as recommended by the Advisory Group to Recommend an Update to the Preamble to the IARC Monographs.

This document should be read in conjunction with the Preamble to the IARC Monographs, which describes the scientific principles and procedures used in developing a Monograph, the types of evidence considered, and the scientific criteria that guide the evaluations.
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Section 1. Exposure Characterization

Note: The structure of this section may vary depending on the agent being evaluated; therefore, it is important to read these general instructions in their entirety.

Section 1 identifies the agent, describes its main uses and occurrence, and summarizes the prevalence of human exposure worldwide, including geographical patterns and time trends. Methods of measurement and regulations are noted where relevant. Exposure assessment methods used in key epidemiological studies reviewed by the Working Group are described, and their quality is critically reviewed.

Instructions at a glance

1. IARC uses online tools during the preparation and conduct of Monographs meetings: the HAWC Literature Search tool, the IARC Table Builder, and the IARC Online Publications System (IOPS). These tools are described in Shapiro et al. (2018). Information on how to access your account will be sent to you.

2. Section 1 presents a representative overview of exposure information, but not all available data are comprehensively reviewed. Information is obtained from research studies, government reports, and other publicly available sources, with all statements of scientific fact substantiated by a fully referenced article, report, or website.

3. It is important to search for and include data from low- and middle-income countries to the extent possible. Where data are lacking for important regions or countries, this should be noted.

4. Working Group members draft text in Microsoft Word and submit the drafts electronically via the IARC Online Publication System (IOPS). Tables may be created using the IARC Table Builder tool. Information on how to access your account will be sent to you. The included studies should be described in the text, providing only the essential details about the study and the key results. Information given in the tables does not need to be repeated in the text.
5. The Monograph text should reflect your expert interpretation of the pertinent studies. Text that is a direct copy and paste from original publications can be detected as plagiarism by specialized software. Please adhere to the suggested word limits for each section.

6. Your writing assignment should be prepared before the meeting according to the deadline provided to you.

7. You will be expected to conduct peer review of other sections. More information will be provided after the Working Group members submit their writing assignments.

8. At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. During the plenary session, each subgroup presents its drafts for scientific review and discussion for eventual adoption as a consensus Working Group product.

Detailed instructions

1.1 Identification of the agent (350 words for a single chemical; 700–1000 words for mixtures, occupations, or industries, or other complex exposures)

The agent being evaluated is unambiguously identified. Details will vary depending on the type of agent but will generally include physical and chemical properties relevant to the agent’s identification, occurrence, and biological activity. If the material that has been tested in experimental animals or in vitro systems is different from that to which humans are exposed, these differences are noted.

For chemical agents, the Chemical Abstracts Service Registry (CAS) number is provided, as well as the latest primary name and other names in common use, including important trade names, along with available information on the composition of common mixtures or products containing the agent, and potentially toxic and/or carcinogenic impurities that may have an impact on the carcinogenicity evaluation (e.g. dioxin contamination of 2,4,5-trichlorophenoxyacetic acid, or weathering of polychlorinated biphenyls in the environment). Physical properties relevant to understanding the potential for human exposure and measures of exposure used in studies in humans are summarized.
These may include physical state, volatility, aqueous and fat solubility, and half-life in the environment and/or in human tissues.

For biological agents, taxonomy and structure are described. Mode of replication, life-cycle, target cells, persistence, latency, and host responses, including morbidity and mortality through pathologies other than cancer, are also presented.

For foreign bodies, fibres, and particles, the following are summarized: composition, size range, relative dimensions, and accumulation, persistence, and clearance in target organs. Physical agents that are forms of radiation are described in terms of frequency spectrum and energy transmission.

In instances where exposures result from, or are influenced by, social and environmental factors (e.g. occupational factors or components of diet, sleep, and physical activity patterns), this section will include a description of the agent, its variability across human populations, and its composition or characteristics relevant to understanding its potential carcinogenic hazard to humans and to evaluating exposure assessments in epidemiological studies.

1.2 Production and use (350–700 words; may be modified or omitted if covered in Section 1.1)

Historical and geographical patterns and trends in production and use are included when they are available, to help readers understand the contexts in which exposures may occur, both within key epidemiological studies reviewed by the Working Group and in human populations generally. A tabular summary may aid presentation if these contexts are numerous.

Industries that produce, use, or dispose of the agent are described, including their global distribution, when available. National or international listing as a high-production-volume chemical or similar classification may be included. Production processes with significant potential for occupational exposure or environmental pollution are indicated. Trends in global production volumes, technologies, and other data relevant to understanding exposure potential are summarized.

Minor or historical uses with significant exposure potential or with particular relevance to key epidemiological studies are included. The amount or proportion attributed to each is indicated if possible. Particular effort may be directed towards finding data on production in low- and middle-
income countries, where rapid economic development may lead to higher exposures than those in high-income countries.

1.3 Detection and analysis (up to 700 words and 1 optional table)

Key methods of detection and quantification of the agent are presented, with an emphasis on those used most widely in surveillance, regulation, and epidemiological studies. Measurement methods for sample matrices that are deemed to be important sources of human exposure (e.g. air, drinking-water, food, residential dust) and for validated exposure biomarkers (e.g. the agent or its metabolites in human blood, urine, or saliva) are described. Information on detection and quantification limits is provided when it is available and is useful for interpreting studies in humans and in experimental animals. This is not an exhaustive treatise but is meant to help readers understand the strengths and limitations of the available exposure data and of the epidemiological studies that rely on these measurements. A tabular summary with standard references may optionally be used for multiple analytical methods or sample matrices.

Note: Technical details of chemical analyses are no longer required.

1.4 Exposure (up to 1800 words of text and tables)

A concise overview of quantitative information on sources, prevalence, and levels of exposure in humans worldwide is provided. Representative data from research studies, government reports and websites, online databases, and other citable, publicly available sources are tabulated. Data from low- and middle-income countries are sought and included to the extent feasible; information gaps for key regions are noted. Naturally occurring sources of exposure, if any, are noted. Primary exposure routes (e.g. inhalation, ingestion, skin uptake) and other considerations relevant to understanding the potential for cancer hazard from exposure to the agent are reported.

For occupational settings, information on exposure prevalence and levels (e.g. in air or human tissues) is reported by industry, occupation, region, and other characteristics (e.g. process, task) where feasible. Information on historical exposure trends, protection measures to limit exposure, and potential co-exposures to other carcinogenic agents in workplaces is provided when available.
For non-occupational settings, the occurrence of the agent is described with environmental monitoring or surveillance data. Information on exposure prevalence and levels (e.g. concentrations in human tissues), persistence in the environment with potential for human exposure (e.g. through bioaccumulation), and exposure from and/or concentrations in food and beverages, consumer products, consumption practices, and personal microenvironments is reported by region (where relevant) and other relevant characteristics. Particular importance is placed on describing exposures in life stages or in states of disease or nutrition that may involve greater exposure or susceptibility.

Note: Current exposures are of primary interest; however, information on historical exposure trends is provided when available. Historical exposures may be relevant for interpreting epidemiological studies, and when agents are persistent or have long-term effects. Information gaps for important time periods are noted. Exposure data that are not deemed to have high relevance to human exposure (e.g. remote, unpopulated sites, or environmental media, plants, or wildlife that are not important sources of direct human exposure) are generally not considered.

1.5 Regulations and guidelines (up to 350 words and 1 optional table; may be omitted if not applicable)

If regulations or guidelines have been established for the agent (e.g. occupational exposure limits, maximum permitted levels in foods and water, pesticide registrations), these are briefly described to provide context about government efforts to limit exposure, and may be tabulated if they are informative for the interpretation of existing or historical exposure levels. Information on applicable populations, specific agents concerned, basis for regulation (e.g. human health risk, environmental considerations), and timing of implementation may be noted. National and international bans on production, use, and trade are also indicated.
1.6 Summary and critical review of exposure assessment methods in key epidemiological studies
(up to 1800 words and 1 optional table)

1.6.1 Exposure assessment methods

This section summarizes exposure assessment methods used in human health studies that are relevant to the overall evaluation. Such methods may include, for example, questionnaires, expert assessment, job-exposure matrices, exposure modelling, or biological markers. A table may be included to summarize methods and their strengths and limitations. This content will directly inform the review of the quality of the exposure assessment methods used in key human health studies (Section 1.6.2).

1.6.2 Critical review of exposure assessment

This section may be assigned in certain Monographs with important data from epidemiological studies, or with important human data from studies of mechanistic end-points. It serves to identify the studies with the most informative exposure assessment methods (referring to information summarized in Section 1.6.1) and is developed in collaboration with the subgroup reviewing studies of cancer in humans, as well as with the subgroup reviewing studies of other mechanistic end-points for carcinogenesis in humans.

For each selected study, the exposure assessment approach is summarized, referring to Section 1.6.1 where appropriate. The strengths and limitations of the approach as implemented are noted, with the assessment of the Working Group of their effect on the interpretation of the study.

(a) Studies of cancer in humans

The identification of key epidemiological studies, and the establishment of concepts for considering the quality of exposure assessment, will be done in collaboration with Working Group members reviewing studies of cancer in humans (Subgroup 2).

Once concepts for considering the quality of exposure assessment have been established, Working Group members of Subgroup 1 (exposure characterization) will apply them to studies of cancer in humans. For each selected study, the exposure assessment approach, along with its strengths and
limitations, is summarized. Concerns about exposure assessment methods applied and their impacts on overall quality for each study reviewed are indicated. In situations where information provided in the study is inadequate to properly review the exposure assessment, this is indicated. When adequate information is available, the likely direction of bias (overestimated effects, underestimated effects, or unknown) may be discussed. The full product of this review should be presented in Section 1.6.2, with a condensed version provided in Section 2 tables. (Note: Working Group members populate tables for Section 2 using the IARC Table Builder linked to the IARC Online Publications System (IOPS).)

(b) Other end-points in humans (mechanistic evidence)

Concepts for considering the quality of exposure assessment will be developed in collaboration with Working Group members tasked with reviewing studies of other end-points in humans (mechanistic data). These considerations will complement those applied in key studies of cancer in humans.

Note: Working Group members of Subgroup 4 (mechanistic evidence) will write initial drafts summarizing consideration of these concepts for human mechanistic studies; Working Group members of Subgroup 1 (exposure characterization) will provide peer review.

Reference

Section 2. Cancer in Humans

Section 2 summarizes all of the pertinent epidemiological studies and identifies tumour sites for which there is sufficient, limited, or inadequate evidence of carcinogenicity in humans.

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2. Section 2 is a systematic review of original epidemiological research. Generally, only analytical epidemiological studies (typically cohort and case–control studies) are included. Human studies reviewed in Section 2 have cancer as an outcome, whereas those reviewed in Section 4 have precancerous end-points as outcomes (e.g. biomarkers related to the 10 key characteristics of carcinogens; Guyton et al., 2018a, b).

3. The IARC Secretariat performs initial literature searches, does title and abstract screening, and organizes the included literature using the HAWC Literature Search tool. The Working Group reviews the searches performed by the IARC Secretariat, and identifies literature through other searches. The Working Group also reviews the initial screening and organization of the literature done by the IARC Secretariat.

4. The Working Group performs full-text review of the included studies, including an evaluation of the quality and informativeness, based on the considerations described in Part B, Section 2 of the Preamble to the IARC Monographs.

5. Working Group members populate tables for Section 2 using the IARC Table Builder linked to the IARC Online Publication System (IOPS). The IARC Secretariat has created the templates for suggested tables; however, it is within the scope of the Working Group to revise these or add new tables.
6. Working Group members draft text in Microsoft Word and submit the drafts electronically via the IARC Online Publications System (IOPS). The included studies should be described in the text, providing only the essential details about the study and the key results. Information given in the tables does not need to be repeated in the text. Detailed individual study descriptions are not needed; however, the text must present a detailed synthesis of the findings that enables the Working Group to arrive at an evaluation of the data.

7. Your writing assignment should be prepared before the meeting according to the deadline provided to you.

8. You will be expected to conduct peer review of other sections. More information will be provided after the Working Group members submit their writing assignments.

9. At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. During the plenary session, each subgroup presents its drafts for scientific review and discussion for eventual adoption as a consensus Working Group product.

**Detailed instructions**

Section 2 is a systematic review of original epidemiological research on cancer in humans. Generally, only analytical epidemiological studies (typically cohort and case–control studies) are included. When *multiple publications* are available for a single study group, only the most recent or most informative publication is used in the evaluation, and previous or less informative publications are only cited. Well-conducted quantitative meta-analyses may also be reviewed with a critical assessment of their quality, including their accuracy in reporting the results of original studies. *Case reports and descriptive studies* (correlation or ecological studies) are reviewed only when they are the only information available or when they add materially to other evidence. *Narrative reviews, commentaries, and letters* that do not provide relevant original data are not reviewed or cited, unless they are critical to the evaluation (e.g. as related to important aspects of study methodology).
Steps in the review process

Step 1. Comprehensive searches of the literature

Preliminary searches of the peer-reviewed literature are provided by the IARC Secretariat using the HAWC Literature Search tool, which documents the search topics, terms, sources, and identified studies. The Secretariat screens the search results to identify relevant epidemiological studies. The Working Group may add additional studies identified by expert knowledge of the literature, further electronic or manual searches, or other sources, such as government documents or authoritative reviews.

Further information and instructions on how to use the HAWC Literature Search tool can be found at https://hawcproject.org/ and in this video; see also Shapiro et al. (2018).

Step 2. Screening and organizing the results

Using the literature tagging function in the HAWC Literature Search tool (https://hawcproject.org/), the Secretariat and the Working Group organize the included studies by cancer site and/or study design, and by additional subtopics according to the Monograph outline. Studies may be tagged into more than one topic or category (e.g. by study population, design, and outcome). Default tags for included and excluded studies are provided by the IARC Secretariat and if necessary may be further refined for each evaluation, by either the Working Group or the Secretariat.

Literature trees document the number of studies identified, screened, excluded, and categorized for each Monograph section and for key topics within sections (for an example of a literature tree, see Fig. 1 in Shapiro et al., 2018).

The Working Group reviews the retrieved literature for relevance to the evaluation. Additional exclusion criteria set by the Working Group (e.g. studies based on proxy indicators for the agent) may be applied and documented in the HAWC Literature Search tool using tags.

See page 20 of the Preamble to the IARC Monographs for further guidance about the types of studies included.
Step 3. Evaluation of study quality

A key aspect of the Working Group’s focus will be on evaluating study quality, as described in the Preamble to the IARC Monographs. One important aspect of study quality is the quality of the exposure assessment methods used in the studies of cancer in humans. Members of Subgroup 2 (studies of cancer in humans) will work together with members of Subgroup 1 (exposure characterization) in this effort. An important first step is the identification of key studies that are most likely to be informative on whether there is limited or sufficient evidence of an association of the agent with cancer in humans. The quality of exposure assessment methods will be reviewed and summarized by members of Subgroup 1, as described in the Instructions for Authors for Section 1.

For each study or group of related studies, it is important to include an expert assessment of study quality and informativeness (including the strengths and limitations as well as important points of interpretation), which should be indicated in square brackets. Subgroup 1 will provide an assessment of the quality of the exposure assessment methodology, which should be taken into account in the overall appraisal here. Study strengths and limitations are noted in the tables (see below).

Step 4. Description of characteristics and results of included studies

Text is written in Microsoft Word and uploaded via the IARC Online Publications System (IOPS). The text should coherently summarize groups of studies and should not be lengthy. Included studies need not be described in detail individually unless they have particular features that affect interpretation, such as notable strengths or deficits in the exposure assessment, design, or analysis. The text should present a detailed synthesis of the findings, written in a manner that is transparent for the reader to understand the rationale for the Working Group’s evaluation of the data. Details of the studies should generally be placed in tables. Essential details can be included in the text, such as the reference (first author et al., year), location (usually country), number of subjects, and key results with the risk estimate (95% confidence interval).

The level of detail in the text should be proportional to the importance of the study, and only the minimum information should be given that is needed to evaluate that study in the context of all of those reviewed. Information given in tables does not need to be repeated in the text unless it is
especially important for interpreting the results. It is not necessary to cite in the text study features such as response rates or covariates controlled for, unless they are notable as limitations or strengths. Risk estimates and 95% confidence intervals should be provided for the main results, without descriptions of the magnitude of association or of statistical significance. $P$ values for trend may be reported when available.

Multiple publications on the same study population are identified so that the number of independent studies is accurately represented. Multiple publications may result, for example, from successive follow-ups of a single cohort, from analyses focused on different aspects of an exposure–disease association, or from inclusion of overlapping populations. In these situations, generally only the most recent, most comprehensive, or most informative report is reviewed in detail in the text and tables. Other reports are cited in the text but are not described in detail, unless they contain critical information (e.g. on exposure assessment methods) not contained elsewhere.

Less informative studies may be described either in a brief, summary style, giving key attributes and results of the studies, or in the aggregate, while noting the general limitations of these studies.

For some Monographs with abundant databases, the Working Group may decide to undertake a triage exercise to focus its effort on the data most likely to be informative on whether there is sufficient or limited evidence of carcinogenicity in humans. In this case, the Working Group conducts a preliminary review to identify cancer sites for detailed assessment. Studies for cancer sites that are judged to be likely to have inadequate evidence (typically because of the small number or the poor quality of available studies) are reviewed in summary style (described above), and details are not tabulated. Studies for other cancer sites are taken forward for a full review (described above).

Subsections describing a number of studies may have a brief introduction describing the included literature and the reasons for exclusions (if any), and highlighting important issues of interpretation.
Examples of text and tables from recent Monographs

Example of description when there are several independent publications from a single study

Three population-based case–control studies conducted in the 1980s by the National Cancer Institute in Nebraska (Hoar Zahm et al., 1990), Iowa and Minnesota (Brown et al., 1990; Cantor et al., 1992), and Kansas (Hoar et al., 1986), USA, provided information on several pesticides. All three studies assessed the risk for non-Hodgkin lymphoma (NHL). NHL cases and controls were combined from these studies to create a pooled data set to increase study precision to enable analyses for specific pesticides (Waddell et al., 2001; De Roos et al., 2003).

These studies also assessed other cancer sites. The study in Iowa and Minnesota included leukaemia (Brown et al., 1990) and NHL (Cantor et al., 1992), the study in Iowa included multiple myeloma (Brown et al., 1993b), the study in Nebraska included NHL, Hodgkin lymphoma, multiple myeloma, and chronic lymphocytic leukaemia (Hoar Zahm et al., 1990), and the study in Kansas included NHL, soft tissue sarcoma, and Hodgkin lymphoma (Hoar et al., 1986). In Iowa and Minnesota, 622 cases of NHL (Cantor et al., 1992) and 669 cases of leukaemia (Brown et al., 1990) among white men aged ≥ 30 years were identified from the Iowa state cancer registry and from a surveillance system of hospital and pathology laboratory records in Minnesota. In Iowa, cases of multiple myeloma (n = 173) were identified from the state cancer registry (Brown et al., 1993b).

Example of description in summary style, typically for less informative studies

Two recent hospital-based case–control studies (Gousias et al., 2009; Spinelli et al., 2010), one conducted in Greece and the other in France, examined associations between glioma and mobile-phone use. Neither was informative, because of small numbers and unclear exposure assessment methods.

Example of subsection introduction

Case–control studies investigating the association of air pollution and cancer of the lung are presented below according to the main type of exposure under study. Studies focused on all sources of
air pollution have been divided according to the methodology, qualitative or quantitative, used for exposure assessment. The main development in the design of the studies is the evolution of exposure assessment methods from rather crude classification of urban areas and air pollution zones (Vena, 1982; Samet et al., 1987), proximity to industry (Brown et al., 1984; Pershagen, 1985), and proximity to traffic (Vineis et al., 2006), to more advanced use of data from fixed monitors (Jedrychowski et al., 1990), exposure modelling (Nyberg et al., 2000), and national spatiotemporal air pollution maps (Hystad et al., 2012, 2013).
Example of table (from Shapiro et al., 2018, with permission)

Step 5. Synthesis and evaluation of strength of evidence

At the meeting, during subgroup sessions, the Working Group summarizes the overall strengths and limitations of the studies of cancer in humans. Subgroup drafts of consensus evaluations are developed. The Working Group then develops, and describes the rationale for, the consensus
evaluation of carcinogenicity that integrates the conclusions about the strength of evidence from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic evidence.

References


Section 3. Cancer in Experimental Animals

Instructions at a glance

1. IARC uses online tools during the preparation and conduct of Monographs meetings: the HAWC Literature Search tool, the IARC Table Builder, and the IARC Online Publications System (IOPS). These tools are described in Shapiro et al. (2018). Information on how to access your account will be sent to you.

2. Section 3 summarizes all the publicly available and pertinent carcinogenicity bioassays. Studies reviewed in Section 3 have cancer as an outcome, whereas those reviewed in Section 4 have precancerous end-points as outcomes (e.g. end-points related to the 10 key characteristics of carcinogens; Guyton et al., 2018a, b).

3. The IARC Secretariat performs initial literature searches, does title and abstract screening, and organizes the included literature using the HAWC Literature Search tool. The Working Group reviews the searches performed by the IARC Secretariat, and identifies literature through other searches. The Working Group also reviews the initial screening and organization of the literature done by the IARC Secretariat.

4. The Working Group performs full-text review of the included studies, including an evaluation of the quality based on the considerations described in Part B, Section 3 of the Preamble to the IARC Monographs (e.g. design, methodology, and reporting of results).

5. Working Group members populate tables for Section 3 using the IARC Table Builder linked to the IARC Online Publications System (IOPS), or using templates provided by the IARC Secretariat in Microsoft Word.

6. Working Group members draft text in Microsoft Word and submit the drafts electronically via the IARC Online Publications System (IOPS). The draft text presents a synthesis of the findings that enables the Working Group to arrive at an evaluation of the data. Detailed individual study
descriptions are not needed; the text highlights essential details about the studies and the key results. Information given in the tables does not need to be repeated in the text.

7. Your writing assignment should be prepared before the meeting according to the deadline provided to you.

8. After submission, working drafts are reviewed by the Working Group, and by the IARC Secretariat. The working drafts are then revised and resubmitted before the meeting.

9. At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. During the plenary session, each subgroup presents its drafts for scientific review and discussion for eventual adoption as a consensus Working Group product.

**Detailed instructions**

Section 3 summarizes all available long-term studies of cancer in experimental animals with the agent under review and, as appropriate, metabolites or derivatives of the agent (see Part A, Section 7 of the *Preamble to the IARC Monographs*). Studies that are judged to be irrelevant to the evaluation or are judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. After a thorough evaluation of the study features (see Part B, Section 3b of the *Preamble to the IARC Monographs*), the evidence relevant to carcinogenicity in experimental animals is classified into one of four defined categories (*sufficient*, *limited*, *inadequate*, or *suggesting lack of carcinogenicity*).

In this section, only published (or accepted for publication) sources of information in the peer-reviewed literature can be used (see Part A, Section 7 of the *Preamble to the IARC Monographs*). Exceptionally, publicly available data from government agency reports are also considered.

Besides conventional long-term bioassays, alternative studies (e.g. in genetically engineered mouse models) may be considered in assessing carcinogenicity in experimental animals, likewise after a critical evaluation of the study features; for chemical exposures, a range of genetically engineered models are available, including the *Trp53*−/−, Tg.AC, and rasH2 mouse models (see also Eastmond et
al., 2013). Other types of studies can provide supportive evidence. These include experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies), studies in which the end-point was not cancer but a defined precancerous lesion, and studies of cancer in non-laboratory animals (e.g. companion animals) exposed to the agent.

The approach to identifying, screening, organizing, and summarizing these studies is presented below. Two online tools facilitate this approach: the HAWC Literature Search tool (https://hawcproject.org/) and the IARC Table Builder (https://table-builder.com/). The draft documents are submitted via the IARC Online Publications System (IOPS).

**Steps in the review process**

**Step 1. Comprehensive searches of the literature**

The Working Group reviews the initial searches of the peer-reviewed literature performed by the IARC Secretariat, and identifies literature through other searches (e.g. from reference lists of retrieved articles). The initial searches conducted by the IARC Secretariat are available via the HAWC Literature Search tool, which records the search topics, terms, sources, and identified studies. The IARC Secretariat uses search terms for the agent and studies of cancer in animals, but also identifies literature through other searches (e.g. from past Monographs or other authoritative reviews).

**Step 2. Screening and organizing the results**

The Working Group reviews the initial screening and organization of the literature done by the IARC Secretariat, and performs full-text review of the included studies. Based on title, abstract, and (if needed) full-text review, the IARC Secretariat excluded studies if they were not about the agent, or if they reported no data on end-points relevant to cancer in animals. Included studies were further sorted according to the outline of Section 3 and the writing assignments.
Step 3. Description of characteristics and results of included studies, and evaluation of study quality

Tables of study design and results

Tables are constructed using the embedded IARC Table Builder in the IARC Online Publications System (IOPS). Study design and results of all pertinent individual studies are presented, including:

- Test agent (including nature and extent of impurities)
- Species, strain (sex), age at start, duration of study (total), reference
- Route, dosing regimen, numbers of male and female animals per group at start, and numbers surviving at the end of the study
- Tumour site (e.g. mammary gland, lung, haematopoietic and lymphoid tissues) and histology (e.g. adenoma, squamous cell carcinoma, lymphoma)
- Number of each tumour type/effective number of animals (incidence) and percentage, tumour multiplicity and/or total number of tumours if provided
- Statistical significance of trends and differences between groups, and statistical method used; if not provided, $P$ values should be calculated by the Working Group and given in square brackets. Note that the IARC Table Builder will calculate pairwise $P$ values using Fisher’s exact test, and $P$ values for trend using the Cochran–Armitage trend test.
- Comments should include strengths of the study (e.g. well-conducted study, good laboratory practice study, both sexes used), limitations of the study (e.g. missing survival data, or any of the above-mentioned items), and any other important comments (e.g. effect on survival and body weight, toxicity, historical control data).

Text of study design and results

For each study, the following are indicated:

- Species, strain, sex, age at start;
- Number of males and number of females in each experimental and control group;
- Test agent (including nature and extent of impurities);
• Route of administration of test substance;
• Treatment of controls (untreated, vehicle, “positive”);
• Doses as quoted in the original paper;
• Dosing schedules;
• Duration of treatment;
• Duration of observation;
• Effect on survival and body weight;
• Histological types of tumours in treated and control animals (giving results by sex, i.e. male and then female);
• Increased or decreased incidence (and multiplicity or number of tumours, if reported) of each tumour type of interest (both benign and malignant) in treated compared with control animals (indicate if increase is statistically significant); dose–response (indicate if trend is statistically significant). Tumours with a low spontaneous incidence rate should also be reported if the incidence rate is above the incidence range in historical controls.
• Tumours at unusual sites, with early onset, and so on.

Precancerous lesions and non-neoplastic histopathological lesions that may be relevant to interpretation of tumour incidence, i.e. in the same target organ, should also be described.

The author’s interpretation may be included if you consider it necessary, but it must be clearly identified as such.

Strengths and weaknesses of the study should be presented in square brackets [e.g. well-conducted good laboratory practice study, inadequate duration, absence of controls, underpowered study, inadequate reporting of experimental details or results, high mortality].

Preferred outline

For each agent, order studies by species (mouse, rat, hamster, dog, monkey, etc.). Within each species, order results by route of administration, as indicated in the example below.
3. Cancer in Experimental Animals

3.1. Mouse

3.1.1 Oral administration
3.1.2 Skin application
3.1.3 Subcutaneous administration
3.1.4 Inhalation
3.1.5 Intratracheal administration
3.1.6 Intrapleural administration
3.1.7 Intraperitoneal administration
3.1.8 Intravenous administration
3.1.9 Transplacental and perinatal
3.1.10 Other routes of exposure
3.1.11 Initiation–promotion studies
3.1.12 Administration with known carcinogens or other agents
3.1.13 Carcinogenicity of metabolites

Evaluation of study quality

Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2018).

The considerations may include the following standards:

- whether the agent was clearly characterized, including the nature and extent of impurities and contaminants and the stability of the agent, and, in the case of mixtures, whether the sample characterization was adequately reported;
- whether the dose was monitored adequately, particularly in inhalation experiments;
- whether the doses, duration and frequency of treatment, duration of observation, and route of exposure were appropriate;
- whether appropriate experimental animal species and strains were evaluated;
- whether there were adequate numbers of animals per group;
- whether animals were allocated randomly to groups;
- whether the body weight, food and water consumption, and survival of treated animals were affected by any factors other than the test agent;
- whether the histopathology review was adequate;
- whether the data were reported and analysed adequately (see also Part B, Section 3c of the Preamble to the IARC Monographs).
Step 4. Synthesis and evaluation of the evidence

The summary text of the various studies (Section 5.3 Cancer in experimental animals) will be developed within the subgroup, and the tentative evaluation will be proposed by the subgroup, during the meeting. Guidance will be provided at that time.

References


Section 4. Mechanistic Evidence and Other Relevant Data

Instructions at a glance

1. IARC uses online tools during the preparation and conduct of Monographs meetings: the HAWC Literature Search tool, the IARC Table Builder, and the IARC Online Publications System (IOPS). These tools are described in Shapiro et al. (2018). Information on how to access your account will be sent to you.

2. Section 4 provides a concise synthesis to reflect the extent of available mechanistic evidence, summarizing groups of included studies with an emphasis on characterizing consistencies or differences in results within and across experimental designs. Greater emphasis is given to informative mechanistic evidence from human-related studies than to that from other experimental test systems, and gaps are identified. Tabulation of data may facilitate this review.

3. The IARC Secretariat performs initial literature searches, does title and abstract screening, and organizes the included literature using the HAWC Literature Search tool. The Working Group reviews the searches performed by the IARC Secretariat, and identifies literature through other searches. The Working Group also reviews the initial screening and organization of the literature done by the IARC Secretariat.

4. The Working Group performs full-text review of the included studies, including an evaluation of the quality based on the considerations described in Part B, Section 4 of the Preamble to the IARC Monographs (e.g. design, methodology, and reporting of results).

5. Working Group members populate tables for Section 4 using the IARC Table Builder linked to the IARC Online Publications System (IOPS), or using templates provided by the IARC Secretariat in Microsoft Word.

6. Working Group members draft text in Microsoft Word and submit the drafts electronically via the IARC Online Publications System (IOPS). The draft text presents a synthesis of the findings that enables the Working Group to arrive at an evaluation of the data. Detailed individual study
descriptions are not needed; the text highlights essential details about the studies and the key results. Information given in the tables does not need to be repeated in the text.

7. Your writing assignment should be prepared before the meeting according to the deadline provided to you.

8. You will be expected to conduct peer review of other sections. More information will be provided after the Working Group members submit their writing assignments.

9. After submission, working drafts are reviewed by the Working Group, and by the IARC Secretariat. The working drafts are then revised and resubmitted before the meeting.

10. At the meeting, within subgroups, the Working Group members critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus subgroup drafts. During the plenary session, each subgroup presents its drafts for scientific review and discussion for eventual adoption as a consensus Working Group product.

**Detailed instructions**

Section 4 provides a concise synthesis to reflect the extent of available mechanistic evidence, summarizing groups of included studies with an emphasis on characterizing consistencies or differences in results within and across experimental designs. Greater emphasis is given to informative mechanistic evidence from human-related studies than to that from other experimental test systems, and gaps are identified. Tabulation of data may facilitate this review.

The evidence synthesis is focused on the key characteristics of carcinogens (Smith et al., 2016; Guyton et al., 2018a, b). The key characteristics (see Table 1), such as “is genotoxic”, “is immunosuppressive”, or “modulates receptor-mediated effects”, are based on empirical observations of the chemical and biological properties associated with the human carcinogens identified by the *IARC Monographs* programme up to and including Volume 100. Key characteristics are distinct from the hallmarks of cancer, which relate to the properties of cancer cells. Key characteristics are also distinct from hypothesized mechanistic pathways, which describe a sequence of biological events postulated to occur during carcinogenesis.
Table 1. Ten key characteristics of carcinogens (Smith et al., 2016)

1. Is electrophilic or can be metabolically activated to an electrophile
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

The key characteristics were introduced to facilitate systematic consideration of mechanistic evidence in *IARC Monographs* evaluations. When judged by the Working Group to be relevant to an evaluation of carcinogenicity and to be of sufficient importance to affect the overall evaluation, other information may also be described. This may include quantitative structure–activity information, evidence that falls outside of the recognized key characteristics of carcinogens (i.e. reflecting emerging knowledge or important novel scientific developments on carcinogen mechanisms), or information on criteria with respect to tumours in experimental animals induced by mechanisms that do not operate in humans (e.g. Capen et al., 1999; IARC, 2003).

The approach to identifying, screening, organizing, and summarizing these data is presented below. Two online tools facilitate this approach: the HAWC Literature Search tool (https://hawcproject.org/) and the *IARC Table Builder*. The draft documents are submitted via the IARC Online Publications System (IOPS).

**Steps in the review process**

**Step 1. Comprehensive searches of the literature**

The Working Group reviews the initial searches of the peer-reviewed literature performed by the IARC Secretariat, and identifies literature through other searches (e.g. from reference lists of retrieved articles). The initial searches conducted by the IARC Secretariat are available via the HAWC Literature Search tool, which records the search topics, terms, sources, and identified studies. The IARC Secretariat uses search terms for the agent and the key characteristics of carcinogens (Guyton et
al., 2018a), performs additional complementary literature searches incorporating terms for the agent in combination with terms related to carcinogenicity, and identifies literature through other searches (e.g. from past Monographs or other authoritative reviews).

**Step 2. Screening and organizing the results**

The Working Group reviews the initial screening and organization of the literature done by the IARC Secretariat, and performs full-text review of the included studies. Based on title and abstract review, the IARC Secretariat excluded studies if they were not about the agent, or if they reported no data on end-points relevant to the key characteristics of carcinogens (Guyton et al., 2018a). Included studies were further sorted into categories representing the 10 key characteristics (see Table 1), based on the mechanistic end-points and species evaluated. When the included literature on the key characteristics of carcinogens is especially voluminous, further categorization is by exposure type or setting, species, study type, end-point, and so on.

**Step 3. Evaluation of study quality**

The Working Group reviews the included studies and evaluates their quality based on considerations including the study design, methodology, and reporting of results as described in Part B, Section 4 of the Preamble to the IARC Monographs. Based on these considerations, the Working Group may accord greater weight to some of the included studies. In the working drafts, interpretation of the results and the strengths and limitations of a study are clearly indicated in square brackets.

For observational and other studies in humans, the quality of study design, exposure assessment, and assay accuracy and precision are considered, as are other important factors, including those described for evaluation of evidence on cancer in humans. Working Group members with expertise in exposure characterization (Subgroup 1) and in studies of cancer in humans (Subgroup 2) collaborate with those in Subgroup 4 (mechanistic evidence) in assessing the quality of mechanistic studies in humans.
In general, in experimental systems, studies of repeated doses and of chronic exposures are accorded greater importance than are studies of a single dose or time point. Consideration is also given to factors such as the suitability of the dosing range, the extent of concurrent toxicity observed, and the completeness of reporting of the study (e.g. the source and purity of the agent, the analytical methods, and the results). Route of exposure is generally considered to be a less important factor in the evaluation of experimental studies, recognizing that the exposures and target tissues may vary across experimental models and in exposed human populations. Non-mammalian studies can be synthetically summarized when they are considered to be supportive of evidence in humans or higher organisms.

**Step 4. Description of characteristics and results of included studies**

Pertinent characteristics and results of included studies are reviewed and succinctly described; tabulation of data may facilitate this reporting. The draft text presents a synthesis of the findings that enables the Working Group to arrive at an evaluation of the data. Detailed individual study descriptions are not needed; the text highlights essential details about the studies and the key results. Information given in the tables does not need to be repeated in the text.

**Step 5. Synthesis and evaluation of strength of evidence**

At the meeting, during subgroup sessions, the Working Group summarizes the overall strengths and limitations of the mechanistic evidence. Subgroup drafts of consensus strength-of-evidence conclusions on the mechanistic evidence are developed, as described below in the instructions for Section 5.4.

The Working Group then develops, and describes the rationale for, the consensus evaluation of carcinogenicity that integrates the conclusions about the strength of evidence from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic evidence.

Although it is based on comprehensive searches and review, the Monograph includes only information relevant to making the evaluation and does not necessarily detail or cite all included studies. The length is similar to that of a review article, i.e. up to 10 000 words of text.
Section outline

4.1 Absorption, distribution, metabolism, and excretion

Studies of absorption, distribution, metabolism, and excretion in mammalian species are addressed in summary style; exposure characterization is addressed in Section 1. The metabolic fate of the agent in humans and experimental animals (mammalian species) is described. Identified metabolites and their reactivity are noted. A metabolic schema may indicate the relevant metabolic pathways and products and whether supporting evidence is from studies in humans and/or studies in experimental animals. When direct evidence is sparse, evidence on other adverse effects that indirectly confirm absorption, distribution, and/or metabolism at tumour sites is briefly summarized.

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes evidence from groups of related studies on those key characteristics of carcinogens for which there are adequate data for evaluation. Studies in exposed humans and in human primary cells or tissues that incorporate end-points relevant to key characteristics of carcinogens are emphasized when available. For each key characteristic with adequate evidence for evaluation, studies are grouped according to whether they involve (a) humans, or human primary cells or tissues or (b) experimental systems; further organization (as appropriate) is by end-point (e.g. DNA damage), duration, species, sex, strain, and target organ as well as strength of study design. Findings relevant to a specific tumour type may be noted (see Part B, Section 4 of the Preamble to the IARC Monographs).

For genetic and related effects, tables are usually prepared using the IARC Table Builder, for which detailed instructions are given. The tables capture the experimental system, end-point (e.g. mutation or chromosomal damage), test (comet assay), dose (exposure), and result (see Tables 2–6 in Annex 1). As needed, these tables can be adapted for other mechanistic effects. Information given in the tables is not repeated in the text, although essential design details and key results of influential studies can be highlighted. When they are considered to be supportive of evidence in humans or
higher organisms, non-mammalian studies (e.g. data from plants, lower eukaryotes) can be synthetically summarized, and representative studies cited, but results are not detailed in tables.

4.3 Other relevant evidence

When judged by the Working Group to be relevant to an evaluation of carcinogenicity and to be of sufficient importance to affect the overall evaluation, quantitative structure–activity information, or evidence that falls outside of the recognized key characteristics of carcinogens (reflecting emerging knowledge or important novel scientific developments on carcinogen mechanisms) may also be included. Available evidence relevant to criteria provided in authoritative publications (e.g. Capen et al., 1999; IARC, 2003) on thyroid, kidney, urinary bladder, or other tumours in experimental animals induced by mechanisms that do not operate in humans is also described.

References


Section 5. Summary of Data Reported

Section 5.1 Exposure characterization

Exposure data are summarized to identify the agent and describe its production, use, and occurrence. Information on exposure prevalence and intensity in different settings, including geographical patterns and time trends, may be included. Exposure assessment methods used in key epidemiological studies reviewed by the Working Group are described and evaluated.

Section 5.2 Cancer in humans

Results of epidemiological studies pertinent to an evaluation of carcinogenicity in humans are summarized. The overall strengths and limitations of the epidemiological evidence base are highlighted to indicate how the evaluation was reached. The target organ(s) or tissue(s) in which a positive association between the agent and cancer was observed are identified. Exposure–response and other quantitative data may be summarized when available. When the available epidemiological studies pertain to a mixed exposure, process, occupation, or industry, the Working Group seeks to identify the specific agent considered to be most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data permit.

Section 5.3 Cancer in experimental animals

Results pertinent to an evaluation of carcinogenicity in experimental animals are summarized to indicate how the evaluation was reached. For each animal species, study design, and route of administration, there is a statement about whether an increased incidence, increased multiplicity, increased severity, or reduced latency of neoplasms was observed, and the tumour sites are indicated. Special conditions resulting in tumours, such as prenatal exposure or single-dose experiments, are mentioned. Dose–response patterns, negative findings, inverse relationships, and other quantitative data are also summarized.
Section 5.4 Mechanistic evidence

Results pertinent to an evaluation of the mechanistic evidence on carcinogenicity are summarized to indicate how the evaluation was reached. The summary focuses on the informative studies on the key characteristics with adequate evidence for evaluation. It also addresses other aspects of sufficient importance to affect the overall evaluation (e.g. criteria with respect to tumours in experimental animals induced by mechanisms that do not operate in humans). For each topic addressed, the main supporting findings are highlighted from exposed humans, human cells or tissues, experimental animals, or in vitro systems. Gaps in the evidence are indicated (i.e. if no studies were available in exposed humans, in in vivo systems, etc.). Consistency or differences of effects across different experimental systems are emphasized.

Section 6. Evaluation and Rationale

Consensus evaluations of the strength of the evidence of cancer in humans, the evidence of cancer in experimental animals, and the mechanistic evidence are made using transparent criteria and defined descriptive terms. Finally, the bodies of evidence included within each stream of evidence are considered as a whole, in order to reach a consensus overall evaluation of the carcinogenicity of the agent to humans. The three streams of evidence are integrated and the agent is classified into one of the following categories (see the Preamble to the IARC Monographs), indicating that the Working Group has established that:

- The agent is **carcinogenic to humans** (Group 1)
- The agent is **probably carcinogenic to humans** (Group 2A)
- The agent is **possibly carcinogenic to humans** (Group 2B)
- The agent is **not classifiable as to its carcinogenicity to humans** (Group 3).

The rationale used by the Working Group to achieve its overall evaluation is summarized.
### Annex 1. Examples of tables

**Table 2 Genetic and related effects of [agent] in exposed humans**

<table>
<thead>
<tr>
<th>End-point</th>
<th>Tissue, cell type (if specified)</th>
<th>Location, date, setting, scenario</th>
<th>No. of exposed and controls</th>
<th>Agent, exposure level (mean, range, units)</th>
<th>Response (significance)</th>
<th>Covariates controlled</th>
<th>Comments on study quality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA strand breaks (SSBs)</td>
<td>Peripheral blood</td>
<td>Germany, 1991, styrene production plant</td>
<td>25, 25</td>
<td>Styrene in air, 83.9, 73–3540, μg/m$^3$</td>
<td>–</td>
<td>Smoking</td>
<td>Inadequate exposure characterization</td>
<td>Holzing et al. (1995)</td>
</tr>
<tr>
<td><em>HPRT</em> mutation</td>
<td>Peripheral blood</td>
<td>Czech Republic, 1992–1995, Reinforced plastics workers</td>
<td>13, 13</td>
<td>Styrene in air, 161.7, ±98.2 (SD), mg/m$^3$</td>
<td>(+) ($P&lt;0.0039$)</td>
<td>None</td>
<td>Small sample size; inadequate adjustment for known confounders</td>
<td>Vodoicka et al. (1999)</td>
</tr>
</tbody>
</table>

*Factors to be considered for study quality include: exposure contrast; appropriate statistical methods; or other aspects of design or analysis (e.g. selection bias).*

+, positive; −, negative; +/−, equivocal (variable response in several experiments within an adequate study); SSBs, single-strand breaks (+) or (−), positive or negative in a study of limited quality (specify reason in comments, e.g. only a single dose tested; data or methods not fully reported; confounding exposures).

**Table 3 Genetic and related effects of [agent] in human cells in vitro**

<table>
<thead>
<tr>
<th>End-point</th>
<th>Tissue, cell line</th>
<th>Results</th>
<th>Concentration (LEC or HIC)</th>
<th>Comments on study quality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronucleus formation</td>
<td>Lymphocytes</td>
<td>–</td>
<td>NT 44.9 μg/mL</td>
<td>Concurrent toxicity</td>
<td>Murphy et al. (2018)</td>
</tr>
</tbody>
</table>

*Factors to be considered for study quality include: the methodology and design (e.g. the end-point and test method, the number of replicate samples, the suitability of the concentration range, the inclusion of positive and negative controls, and the assessment of cytotoxicity) as well as reporting (e.g. of the source and purity of the agent, and of the analytical methods and results).*

−, negative; HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested.
### Table 4 Genetic and related effects of [agent] in non-human mammals in vivo

<table>
<thead>
<tr>
<th>End-point</th>
<th>Species, strain (sex)</th>
<th>Tissue</th>
<th>Results</th>
<th>Agent, dose (LED or HID)</th>
<th>Route, duration, dosing regimen</th>
<th>Comments on study quality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronucleus formation</td>
<td>Mouse B6C3F1 (M, F)</td>
<td>Peripheral blood; normochromatic normochromatic erythrocytes</td>
<td>+</td>
<td>Isobutyl nitrite 150 (males); 75 (females) ppm</td>
<td>Inhalation; 6 h/day, 5 days/week, 13 weeks</td>
<td>Only one dose tested</td>
<td>NTP (1996)</td>
</tr>
</tbody>
</table>

*Factors to be considered for study quality include: suitability of the dosing range, the extent of concurrent toxicity observed, and the completeness of reporting of the study (e.g. the source and purity of the agent, the analytical methods, and the results).

+, positive; -, negative; F, female(s); h, hour(s); HID, highest ineffective dose; LED, lowest effective dose (units as reported); M, male(s); NT, not tested; ppm, parts per million

### Table 5 Genetic and related effects of [agent] in non-human mammals in vitro

<table>
<thead>
<tr>
<th>End-point</th>
<th>Species, tissue, cell line</th>
<th>Results</th>
<th>Agent, concentration (LEC or HIC)</th>
<th>Comments on study quality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sister-chromatid exchange</td>
<td>Chinese hamster ovary cells</td>
<td>+</td>
<td>Isobutyl nitrite, 50 (without rat liver S9); 160 (with rat liver S9) μg/mL</td>
<td>Concurrent toxicity &gt; 50%</td>
<td>NTP (1996)</td>
</tr>
</tbody>
</table>

*Factors to be considered for study quality include: the methodology and design (e.g. the end-point and test method, the number of replicate samples, the suitability of the concentration range, the inclusion of positive and negative controls, and the assessment of cytotoxicity) as well as reporting (e.g. of the source and purity of the agent, and of the analytical methods and results).

+, positive; HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested
### Table 6 Genetic and related effects of [agent] in non-mammalian systems

<table>
<thead>
<tr>
<th>Test system (species, strain)</th>
<th>End-point Results</th>
<th>Agent, concentration (LEC or HIC)</th>
<th>Comments on study quality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without metabolic activation</td>
<td>With metabolic activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em> TA1535</td>
<td>Reverse mutation</td>
<td>+</td>
<td>Isobutyl nitrite 1000 µg/plate</td>
<td>Purity, NR</td>
</tr>
</tbody>
</table>

* Factors to be considered for study quality include: the methodology and design (e.g. the end-point and test method, the number of replicate samples, the suitability of the concentration range, the inclusion of positive and negative controls, and the assessment of cytotoxicity) as well as reporting (e.g. of the source and purity of the agent, and of the analytical methods and results).

+, positive; HIC, highest ineffective concentration; LEC, lowest effective concentration, NR, not reported