Instructions to Authors

Instructions to Authors for the Preparation of Drafts for 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.

These instructions were prepared by staff of the *IARC Monographs* programme and are provided to authors preparing the first drafts of an *IARC Monograph* (members of the Working Group). Authors are also provided with details and instructions specific to each *Monograph* topic as appropriate, and are advised to consult a recent copy of the IARC *Monographs*. The outline for each Monograph is provided to each author and defines the detailed structure of the Monograph and individual writing assignments.

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

Table of contents

Section 1. Exposure data

Notes: The structure and content of Section 1 have been modified: please read these general instructions in their entirety. The* Monograph *outline provides specific writing assignments, including any modifications of the section structure. Please adhere to the suggested page limits for each section.

Section 1 identifies the agent, describes its measurement, main uses and production volume and summarizes the prevalence and level of human exposure worldwide. Methods of measurement and regulations are noted where relevant. 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 web site. **The data should present a representative overview, but all the available data are not comprehensively reviewed.**

1.1 Identification of the agent (1 page for a single chemical; 2–3 pages for mixtures, occupations or industries)

The agent being evaluated is unambiguously identified. For chemicals, provide the Chemical Abstracts Service Registry number, the latest primary name and the IUPAC systemic name and other names in common usage. Briefly describe physical and chemical properties relevant to occurrence, identification and biological activity and occurrence (e.g. liquid, solid or gaseous state; volatility, etc. for chemicals; composition, crystal structure and morphology for minerals; energy transfer for radiation, etc.). For a mixture, describe the main components, their sources and their relative proportions. Note impurities, contamination, bioaccumulation or transformations that may have an impact on the carcinogenicity evaluation (e.g. dioxin contamination of 2,4,5-T, or weathering of PCBs in the environment). For an occupation or industry, describe the nature of the work and the agents involved with a focus on exposure to potential carcinogens. If the material tested in animals or in-vitro systems is different from that to which humans are likely to be exposed, note the relevant differences.

1.2 Production & use (1–2 pages; may be modified or omitted if covered in 1.1.)

1.2.1 Uses. Describe the principal uses; if possible, indicate the amount or proportion attributed to each. Include minor or historical uses with significant exposure potential or that may aid interpretation of available epidemiological studies. A tabular summary may aid presentation if major and minor uses are numerous.

1.2.2 Production. When relevant, indicate production quantities and countries where the agent is produced. Note if nationally or internationally classified as of high production volume. Indicate production processes with significant potential for occupational exposure. If significant exposures have occurred

historically, note when production or exposure began and describe important changes in production processes, volume, or locations.

1.3 Methods of measurement and analysis

1.3.1. Detection and quantification (**up to 1 page + 1 optional table**; *may be omitted or modified according to relevance for the agent*) (see sample template for optional Table 1.3). An overview of analytical methods for detecting and quantifying the agent for research and regulatory purposes is provided as appropriate for the agent and specified in the Monograph outline. Describe in terms accessible to general readers the measurement methods for sample matrices that are important sources of human exposure (e.g. air, drinking-water) and for important validated exposure biomarkers (e.g. metabolites of the agent in urine). Address sampling issues (e.g. location, duration, personal versus environmental) pertinent to estimating population exposure. *A tabular summary with standard references may optionally be used for multiple analytical methods or sample matrices. NB: Technical details of chemical analyses are no longer required*.

1.3.2 Exposure assessment and biological markers (**up to 5 pages + 1 optional table**). This section is a critical review of the exposure assessment methods used in epidemiological studies that provide data relevant to the evaluation. When pertinent for the interpretation of those studies, describe and assess the strengths and limitations of exposure assessment methods that were used. Such methods might 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*.

1.4 Occurrence and exposure

Quantitative information regarding the prevalence and level of exposure is summarized for a concise overview of human exposure worldwide.

1.4.1. Exposures (**up to 5 pages each of text and tables**). Briefly describe the principal sources of population exposure (e.g. air, drinking-water, food, personal habits, or workplace). Naturally-occurring sources of exposures, if any, are noted. For those exposure sources that are significant, **representative** exposure data from research studies, government reports and web sites, and other citable, publicly available sources are tabulated. 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 is noted.

Exposure data for this section are tabulated using the IARC Table Builder online tool, which can be accessed through a link in the IARC Online Publications System (IOPS).

NB: Current exposures are of primary interest, but historical exposures may be as relevant for interpreting epidemiological studies and when agents are persistent or have long-term effects (cf. previous Monograph *– if available). Data regarding environmental media, plants or wildlife that are not important*

sources of direct human exposure can be excluded. Similarly, data concerning remote, unpopulated sites ("background" exposures) may not be pertinent.

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

If regulations or guidelines have been established for the agent, the approach taken is described in a brief narrative. The applicable populations, the media concerned, and the basis on cancer risk, other health risks, or environmental considerations may be relevant. National and international bans on production, use, and trade are noted. If exposure limits have been established, these may optionally be tabulated if informative for the interpretation of existing or historical exposure levels.

See sample template for optional Table 1.5

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.

Instructions at a glance

1. Section 2 is a systematic review of original research. Generally only analytical epidemiological studies (typically cohort and case–control studies) are included.
2. The literature search will be conducted using the HAWC Literature Search tool (a collaborative workspace for conducting risk assessments for human health; https://hawcproject.org/). Initial searches will be provided by the IARC secretariat and further refined by the Working Group.
3. Text is written in Word and submitted electronically via the IARC Monographs Online Publication System (IOPS).
4. Included studies are described individually**,** providing essential details about the study and the key results. Information given in the tables does not need to be repeated in the text.
5. Tables for Section 2 are constructed using the IARC Table Builder online tool linked to IOPS.
6. Your assignment *should be prepared before the meeting* according to the deadline provided to you.

The Working Group conducts a systematic review of original research. Normally only analytical epidemiological studies (typically cohort and case–control studies) are included. When *multiple publications* are available for a single study, only the most recent or most informative publication is described in detail. Well-conducted quantitative meta-analyses may also be reviewed. *Case reports and descriptive studies* (correlation or ecological studies) should be 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.

Identifying the relevant information

Searching the literature

The Working Group identifies relevant peer-reviewed literature through comprehensive searches of relevant databases (e.g. PubMed). Additional studies may be identified by hand searching or from past Monographs, government documents, authoritative reviews or, expert knowledge of the literature. The HAWC Literature Search tool documents the search topics, terms, sources, and identified studies. Search terms are drafted by the IARC secretariat and further refined by the Working Group. Further detail on these topics and associated search terms is available at https://hawcproject.org/.

Instructions on how to use the HAWC Literature Search tool can be found in this video.

Screening and organizing the results

The Working Group screens the retrieved literature for relevance. The IARC secretariat can assist with the initial screen focused on exclusion of studies that do not address the agent or cancer in humans. Other exclusion criteria (e.g. ecological studies and case reports) used by the Working Group are documented in HAWC using tags.

The Working Group considers all included studies. Using the literature tagging function in HAWC, the Working Group organizes the studies by cancer site and/or study design, and by additional subtopics according to the monograph outline. Studies may fall into more than one topic or category. Default tags for included and excluded studies are provided by the IARC secretariat and if necessary may be further refined by the Working Group.

Literature trees in HAWC document the number of studies identified, screened, excluded and categorized per category of evidence.

See page 8 of the Preamble to the IARC Monographs for further guidance about the types of studies included.

Summarizing the evidence

Once tagging is complete, the IARC secretariat reviews the results and may refine the outline and writing assignments, considering the extent of relevant evidence and needed expertise.

Text

Text is *written in Word and uploaded electronically* via the IARC Monographs Online Publication System (IOPS). Included studies are described individually**,** providing essential details about the study such as:

- the reference (first author et al., year)
- design
- location
- number of subjects
- exposure assessment method
- key results with the risk estimate (95% confidence interval, CI)

The level of detail should be proportional to the importance of the study and give only the minimum detail needed to evaluate the particular study in the context of all of the studies presented. Information given in the 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 study features such as response rates or covariates controlled in the

text, unless they are notable as limitations or strengths. Risk estimates and 95% CIs should be provided for the main results without descriptions of statistical significance. *P*-values for trend may be reported when available. When there are multiple publications on a single study, previous papers may be briefly indicated in the text as Working Group comments, or in the Comments field of the table.

Less informative studies may be either described in a brief, summary style giving key characteristics and results of the studies or in the aggregate.

For each study or group of studies, it is important to include an expert assessment of the strengths and limitations as well as important points of interpretation, which should be indicated in square brackets [ ]. Study strengths and limitations are noted in the tables (see below).

Subsections describing a number of studies may have a brief introduction describing the included literature, the reasons for exclusions, if any, and highlighting important issues of interpretation.

Tables

Tables for Section 2 are constructed using the IARC Table Builder online tool. Please fill in all of the fields provided for descriptive information and results for each study.

Example of description of an individual study

Pesticide use and cancer of the breast (excluding prevalent and in-situ cancers) was investigated among 30 454 wives of farmers enrolled in the AHS (Engel et al., 2005). At enrolment, famers' wives were given a questionnaire to investigate personal ever versus never use of specific pesticides, while information on potential indirect exposure to pesticides was obtained from their husbands' responses concerning use of specific pesticides; 309 cases of cancer of the breast were identified. No elevation in risk was observed when considering wives' use of malathion in the entire cohort (RR, 0.9; 95% CI, 0.7–1.2), while an increase was observed when restricting the analysis to wives who had never used pesticides themselves, but whose husband had used malathion (RR, 1.4; 95% CI, 1.0–2.0), after adjusting for age, race, and state of residence. There was no apparent trend in relation to husband's use of malathion [data not shown]. [The Working Group noted inconsistency in the results in that there was no elevation in risk for personal use of malathion, but an increase was noted only for husband's use. The strengths of this study included its large sample size, comprehensive exposure assessment, extent of potential confounder control, and exploration of potential effect modulation, such as by family history. Because of the small number of cases in North Carolina, these were excluded from the analyses.]

Example of description when there are a 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) 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

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 due to 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), proximity to traffic (Vineis et al., 2006), to more advanced use of fixed monitors data (Jedrychowski et al., 1990), exposure modeling (Nyberg et al., 2000), and national spatio-temporal air pollution maps (Hystad et al., 2012, 2013).

Examples of tables

2.1 Cancer in humans: cohort studies

Actions

Volume 117: Mono 4 - Aldrin

Last updated: Oct 12th 2016, 10:21 am

Reference, location, follow-up/enrollment period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
van Amelsvoort et al. (2009) Pernis, The Netherlands 1954-2006 Cohort	570; Men employed ≥1 year in a pesticide production plant 1954-1970. **Exposure assess. method:** modelling; Exposure modelled from blood measures in subgroup (n = 343) to produce total dose for each worker. Range 11mg - 7755 mg dieldrin and aldrin combined.	All cancers combined	Estimated intake of aldrin+dieldrin				Earlier publications from this study are Swaen et al, 2002; Sielken et al, 1999; de Jong et al, 1997; Ribbens 1985. **Strengths:** Biomonitoring data modelled to give quantitative exposure assessment. **Limitations:** No internal comparisons made. Unable to separate exposure to dieldrin and aldrin. Small numbers
			All	82	0.76 (0.61–0.95)	Age, time	
			Low	27	1 (0.66–1.46)		
			Moderate	27	0.75 (0.5–1.09)		
			High	28	0.66 (0.44–0.96)		
		All cancers combined: Mortality	SMR				
			Assistant operator	28	0.86 (0.58–1.25)	age, time	
			Maintenance	11	0.66 (0.33–1.19)		
			Operator	41	0.78 (0.56–1.05)		
			Supervisor	2	0.45 (0.06–1.65)		
		Oesophagus	Estimated intake of aldrin+dieldrin				
			All	4	1.59 (0.43–4.08)	Age, time	
			Low	2	2.87 (0.35–10.35)		
			Moderate	1	1.17 (0.03–6.49)		
			High	1	1.08 (0.03–5.99)		

2.2 Cancer in humans: case-control studies

Actions

Volume 117: Mono 4 - Aldrin

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Reference, location, follow-up/enrollment period, study-design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lee et al. (2004) Iowa, Minnesota, Nebraska, USA 1980-86 Case-Control	**Cases:** 872; State Health Registry, hospitals and Nebraska Lymphoma Study Group **Controls:** 2336; population-based and matched on age, race and state **Exposure assess. method:** questionnaire; Telephone or personal interviews with subjects or next of kin in Nebraska	NHL (Non-hodgkin's lymphoma)	Ever use of aldrin				**Strengths:** Pooled study so larger numbers **Limitations:** Use of proxy respondents may have led to nondifferential misclassification. No adjustment for co-exposures.
			Aldrin among asthmatics	10	2.1 (0.9–5.1)	age, vital status, state	
			Aldrin among non-asthmatics	66	1 (0.7–1.5)		

Section 3. Cancer in animals

Section 3 summarizes all the pertinent carcinogenicity bioassays, classifies the evidence relevant to carcinogenicity in experimental animals into one of four defined categories (sufficient, limited, inadequate or suggesting lack of carcinogenicity), and *identifies tumour sites* for those agents for which the evidence for carcinogenicity will be *sufficient* in experimental animals.

In this section, only *published (or accepted for publication) sources of information* in the peer-reviewed literature can be used (also see the Preamble). Exceptionally, publicly available data from government agency reports are also considered. Studies of doubtful quality may also be summarized for discussion by members of the Working Group assigned to this section.

Summarizing the evidence

Tables of study design and results

Tables will be constructed using the IARC Table Builder online tool embedded in the IARC Online Publications System (IOPS). In the Table Builder, please fill in all the fields provided for descriptive information and results for each study. Study design and results of all pertinent individual studies will be presented, including:

- Species, strain (sex) [note if unspecified], age at start if unusual, duration, reference
- Route, dosing regimen, numbers of male and female animals/group at start
- Number of each tumour type/effective number of animals (incidence) and percentage, tumour multiplicity if provided
- Statistical significance of differences between groups, and statistical method used; if not provided, *P* values should be calculated by the Working Group and given in square brackets.
- Comments should include limitations of the study; survival data (if important); if any of the above items is not reported.

Text

Text is submitted in Word electronically via IOPS. For each study, indicate:

- Number of males and of females in each experimental and control group
- Strain
- Route of administration of test substance
- Treatment of controls (untreated, vehicle, “positive”)

- Doses as quoted in the original paper (conversions to SI units will be added by the Secretariat)
- Dosing schedules
- Duration of treatment
- Duration of observation
- Histological types of tumours in treated and control animals
- Increased/decreased incidence of each tumour type of interest (both benign and malignant) in treated compared to control animals; dose-response. Tumours with a low spontaneous incidence rate should also be reported if above incidence range in historical controls.
- Tumours at unusual sites, with early onset, etc…

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 study should be presented in square brackets: [inadequate duration, no controls, underpowered study, inadequate reporting of exposure or results, high mortality]

Preferred outline

For each agent:

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 Administration with known carcinogens or other agents
3.1.12 Carcinogenicity of metabolites

3.2 Rat

3.2.1 Oral administration…

3.3 Hamster …

3.4 Dog …

3.5 Monkey …

3.6 etc…

Checklist for quality control: might include the following standards:

- Were adequate numbers of animals used?
- Were they allocated randomly to groups?
- Was the schedule of exposure adequate?
- Was the agent clearly defined or characterized?
- Was the duration of exposure adequate?
- Was survival acceptable?
- Was the duration of observation adequate?
- Was the study adequately reported?
- Were appropriate comparisons and statistical methods used? (See also the Preamble)

Section 4. Mechanistic and other data

Section 4 provides a concise synthesis of the data on mechanisms of carcinogenesis for the agent under consideration, drawn from representative studies in humans, experimental animals, and in vitro, and judged to be important by the Working Group.

Rationale

Mechanistic data may provide evidence of carcinogenicity, and can play a role in up- or downgrading an evaluation based on cancer findings in animals or humans (see Appendix 1). Important determinations in the evaluation of mechanistic data are:

- Is there strong evidence of an operative carcinogenic mechanism(s)?
- Is the evidence from exposed humans, human in-vitro systems, or animals?
- Does the mechanism only operate in animals?
- Does the agent belong to a class of agents evaluated as Group 1 or Group 2A (e.g. as in *Monograph* Volume 100F)?

In a style of a review article, Section 4 of the *Monograph* summarizes human and animal evidence and data gaps informative for addressing these questions, covering:

- Toxicokinetics (metabolites, enzymes involved, kinetic factors, etc.)
- Carcinogenic mechanisms, based on 10 key characteristics of carcinogens (see Table 7; Smith et al., 2016)
- Other relevant evidence (e.g. structure–activity relationships, susceptibility, target-organ toxicity).

The approach to identifying, screening, organizing and summarizing these data is presented below. Two online tools facilitate this approach: the HAWC Literature Search (https://hawcproject.org/), and the IARC Table Builder.

Identifying the relevant information

Step 1. Searching the literature: With support from the IARC secretariat, the Working Group identifies relevant studies through comprehensive searches of peer-reviewed literature, supplemented by manual searching (e.g. of past *IARC Monographs* or other authoritative reviews). Databases (e.g. PubChem) and peer-reviewed government reports can also be searched. The HAWC Literature Search tool (https://hawcproject.org/) documents the search terms (covering the agent, metabolites, toxicokinetics, and mechanisms), sources, and results.

Step 2. Screening and organizing the results: The Working Group screens the retrieved literature for relevance, with assistance from the IARC secretariat.

The Working Group organizes the relevant literature by mechanistic topic, noting if human or animal, in vivo or in vitro, using literature tags in the HAWC Literature Search tool. Authoritative, balanced review articles are identified. Literature trees document the number of studies identified, excluded and categorized per mechanistic topic and species.

Step 3. Summarizing the evidence: The Working Group develops a synthesis reflecting the extent of data available, addressing the range of study designs and doses tested, whether effects are observed at the physiological, cellular, or molecular level, and any consistencies or differences in results within and across experimental paradigms. Emphasis is given to data in humans, where such data exist. Gaps in evidence are identified.

Although based on comprehensive searches and review, the *Monograph* includes only information relevant to making the evaluation and does not necessarily cite all retrieved studies. **The length is similar to a review article, i.e. 25–50 pages of combined text, tables, figures and references in Section 4**. Authoritative, balanced reviews may be cited in lieu of numerous supporting references.

Section outline

Text is submitted in Word electronically via the IARC Online Publications System (IOPS).

4.1 Toxicokinetic data: Evidence on absorption, distribution, metabolism and elimination is described in subsections **4.1.1 Humans** and **4.1.2 Experimental systems**, totalling 3–5 pages. Evidence for the metabolic fate, including metabolites and the enzymes involved in the activation and detoxification, are presented. A metabolic schema may indicate the relevant pathways, products and whether supporting evidence is from humans and/or experimental animals. Kinetic factors that may affect dose–response relationships or cross-species comparisons (e.g. uptake, deposition, half-life in tissues, protein binding, metabolic activation) are presented. Evidence for modulation of metabolic enzymes is presented.

4.2 Mechanisms of carcinogenesis: Representative data on the 10 key characteristics are presented in Table 7. An expert Working Group convened by IARC concluded that Group 1 carcinogens commonly show one or more of these 10 key characteristics (Smith et al., 2016). These characteristics can provide a basis for systematically collating and analysing mechanistic information.

This section describes evidence for those key characteristics of carcinogens for which there are adequate data for evaluation. The evidence for these characteristics may be organized into mechanistic categories, using the colours in Table 7 as one example. Within each group, subsections summarize evidence from (1) humans and (2) experimental systems, with further organization (as appropriate) by

species, sex, strain, target organ, and end-point. Following the Working Group's discussion, the subsections can be reordered as needed to reflect the conclusions on strength of evidence.

For genetic and related effects, tables are prepared using the IARC Table Builder online tool and capture the experimental system, end-point (e.g. mutation or chromosomal damage), test (comet assay), dose (exposure), and result (see Tables 1-5; Table 6 shows a completed sample table summarizing genetic and related effects for *ortho*-toluidine; see also the *Monograph* on 2,4-D). As needed, these tables can be adapted for other mechanistic effects. Information in tables is not repeated in text, although essential design details and key results of influential studies can be highlighted. When considered 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 not detailed in tables.

4.3 Data relevant to comparisons across agents and end-points: If important to the evaluation, structure–activity relationships, any additional high-throughput/output data, etc., are summarized. This information is also organized and analysed by the 10 key characteristics of carcinogens (see the *Monograph* on 2,4-D as an example of the approach).

4.4 Cancer susceptibility: Cancer studies addressing differential susceptibility due to toxicokinetic or mechanistic factors (e.g. genetic polymorphisms, metabolic differences, etc.) are summarized.

4.5 Other adverse effects: If data on other topics are limited, relevant evidence confirming distribution to, or effects at, tumour sites is briefly summarized (up to one page of text). This discussion will typically identify important non-cancer endpoints not addressed in Sections 4.1–4.4 that have been observed in human studies or in rodent bioassays.

5.4 Mechanistic and other relevant data. Summary statements on the entirety of Section 4 covering toxicokinetics, major mechanisms, and other relevant data highlight key supporting evidence and gaps, and address:

(a) Is there strong evidence (i.e. from human or animal data) of an operative carcinogenic mechanism(s), based on the 10 key characteristics of human carcinogens?

(b) Does the agent belong to a class of agents evaluated in Group 1 or Group 2A? and

(c) Does the mechanism(s) of carcinogenicity *only* operate in animals?

6. Evaluation and rationale. Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted (see Table 7).

Appendix 1. Role of mechanistic data in the overall evaluation

Group 1

- Sufficient evidence in humans OR
- Sufficient evidence in animals AND ***strong evidence in exposed humans*** *that the agent acts through a relevant mechanism*

Group 2A

- Limited in humans AND sufficient in animals
- Inadequate in humans AND sufficient in animals AND ***strong evidence*** *that the carcinogenesis is mediated by a mechanism that also* ***operates in humans***
- *Clearly belongs, based on mechanistic considerations, to a* ***class of agents*** *for which one or more members have been classified in Group 1 or Group 2A*

Group 2B

- Limited in humans AND less than sufficient in animals
- Inadequate in humans BUT sufficient in animals
- *Inadequate in humans AND less than sufficient in animals AND* ***supporting evidence*** *from mechanistic and other relevant data*

Group 3

- Inadequate in humans AND inadequate/limited in animals
- Inadequate in humans AND sufficient in animals AND *strong evidence that the mechanism of carcinogenicity in animals* ***does not operate in humans***

Table 7. Key characteristics of carcinogens

Characteristic[a]	Example of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g. epoxide, quinone, etc.), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein crosslinks, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signalling pathways related to cellular replication or cell-cycle control, angiogenesis

[a] Colours in this column indicate characteristics for which an individual Working Group Member or group of Members identify data and draft the initial language.

Any of the 10 characteristics in this table could interact with any other (e.g. oxidative stress, DNA damage and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor

From Smith et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–721. Available from: http://ehp.niehs.nih.gov/wp-content/uploads/124/6/ehp.1509912.alt.pdf.

Section 5. Summaries

Section 5 combines summaries of the data reviewed in Sections 1 to 4. Each subgroup (members of the Working Group assigned to a particular Section) is responsible for writing the summary of the text they reviewed. Summaries are composed *during the meeting*, and are the product of the entire subgroup and, subsequently, of the entire Working Group.

Overall comments

Summaries are the sections most read in the entire volume. In that sense, it is extremely important to provide essential and relevant information, and yet remain concise.

The summaries should not contain studies or other elements that have not been mentioned before, in the main text.

Summaries must be understandable by the lay public. Avoid technical jargon.

No references should be quoted.

Section 5.1

The agent and its use are briefly described. Human exposure is summarized on the basis of the data on production, use and occurrence.

Section 5.2

A concise summary should be provided of the epidemiological studies considered to be of adequate quality for use in making an evaluation of carcinogenicity to humans. Those considered uninformative and not used in making the evaluation need not be brought forward to the description of studies in the summary.

A statement should be made of the type and number of studies (cohort, case–control) and whether an association was found between the exposure and the occurrence of cancer at different sites and under what circumstances. Quantitative data are not given. Any limitations should be mentioned.

References should not be cited, but information such as geographical location should be given to allow the reader to identify a study.

Section 5.3

A concise summary should be provided of those studies considered to be of adequate quality for use in making an evaluation of carcinogenicity to animals. Studies with critical weaknesses and not used in making the evaluation need not be brought forward to the summary.

A statement should be made of the number of experiments, the species and by what routes the agent has been tested adequately and with what qualitative results, including the main organ sites at which tumours were observed. Studies in which tumours were produced following single doses should be identified. Dose–response relationships should be noted. Several studies of the same type and/or with concordant results may be summarized together. Any limitations should be mentioned. Studies in which the agent was given in combination with known carcinogens should be summarized only briefly. Studies on preneoplastic lesions may be described if relevant to the evaluation. Cancer bioassays with major metabolites may be summarized.

Section 5.4

Information on biological effects in humans relevant to an evaluation of carcinogenicity is summarized, e.g. kinetic and metabolic considerations, evidence of DNA binding, persistence of DNA lesions or genetic damage in exposed people. Similarly, data on kinetics and metabolism in experimental animals are given only if considered relevant. The results of tests for genetic and related effects are summarized for exposed humans, other mammalian species, cultured human and mammalian cells and non-mammalian systems. Other mechanistic considerations may be included.

Section 6. Evaluation

Section 6 is a statement of the Working Group's evaluations of the *strength of the evidence* for carcinogenicity arising from data from humans and experimental animals, using standard terms (see the Preamble). Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. Finally, the body of evidence is considered as a whole, in order to reach an *overall evaluation* of the carcinogenicity of the agent to humans, and the agent is classified in one of four groups:

Group 1 *Carcinogenic to humans*
Group 2A *Probably carcinogenic to humans*
Group 2B *Possibly carcinogenic to humans*
Group 3 *Not classifiable as to its carcinogenicity to humans*
Group 4 *Probably not carcinogenic to humans*

The rationale used by the Working Group to achieve its overall evaluation is summarized.