International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Report of the Advisory Group to Recommend an Update to the Preamble to the *IARC Monographs*

Lyon, France
September 2019

Contents

INTRODUCTION

The Advisory Group to Recommend an Update to the Preamble to the *IARC Monographs* was convened at a time when significant shifts are occurring in the scientific evidence that contributes to the understanding of carcinogenicity, as well as in approaches to information gathering and evidence assessment and integration. Historically, for many agents, the *IARC Monographs* Working Groups have considered substantial bodies of epidemiological and animal bioassay research, along with evidence from mechanistic studies. The use of conventional animal bioassays is currently declining as alternative methods are developed and come into use. Simultaneously, studies of carcinogen mechanisms are increasing in availability and utility, and are contributing new types of evidence (e.g. from various –omics technologies, high-throughput screening systems, and in silico predictive methods that rely on structure–activity relationships). In addition, epidemiological research is available only for those agents for which exposures have taken place, studies have been conducted, and sufficient follow-up has occurred to provide useful results. For newer agents, epidemiological information may be unavailable or uninformative. However, epidemiological studies now include the collection of biological samples and the measurement of various biomarkers, and thus they offer enhanced assessment of exposures and outcomes, and the opportunity to bridge from laboratory findings on mechanisms to human populations. Epidemiological cohort studies are also evolving, to incorporate biobanks and large populations. All of these developments are relevant to the assessment of carcinogenic hazards.

The carcinogenicity classifications provided by the *IARC Monographs* have broad implications. Therefore, these classifications have been carefully considered by the scientific community and other stakeholders, including the general public. Recently, a tendency has emerged to dismiss evidence-based findings in some sectors, particularly if the conclusions affect the interests of stakeholders. Given this changing climate, IARC should renew its commitment to ensuring that the processes used to develop the *Monographs* are fully transparent and rigorous, and potential conflicts of interest of Working Group members are fully revealed and addressed.

IARC's continued attention to scientific rigour and full transparency is essential to ensure that the conclusions of the *Monographs* will be fully defensible in the face of questioning, which has become inevitable for some types of agents.

The Advisory Group noted that many recommendations for updates to the Preamble were aimed at increasing transparency about the processes that the *IARC Monographs* use, and particularly about the methods. Although IARC Working Groups have always conducted comprehensive reviews of evidence, the many advances in methods of systematic review provide a basis for enhancing transparency through more specific guidance to Working Group members. The *IARC Monographs* programme has embraced these systematic review methods, incorporating them into its procedures. The Advisory Group recommended updating the Preamble by specifying these procedures, for example, how reviews of the quality of the exposure assessment methods used can be integrated with results of studies of cancer in humans and with mechanistic data, how the principles of systematic review apply to *IARC Monographs* assessments, and how the rationale for expert judgement needs to be stated. The Advisory Group also recognized that there is a balance between transparency and specifying methods in the Preamble too rigidly. The Preamble is designed to accommodate flexibility as scientific methods evolve. The Instructions for Authors, which are updated more frequently than the Preamble is, describe how these methods are operationalized. The Advisory Group's recommendations for updates to the Preamble also confirmed renewed commitments to transparency, including disclosure and publication of conflicts of interest, engagement with the public throughout the process, and limiting the use of data or studies to only those that can be made publicly available.

Substantial revisions to the Preamble were recommended to reflect both the changing mix of scientific evidence considered by *Monographs* Working Groups – notably, that there will be a predominance of mechanistic evidence for some agents – and the evolution of review methods. The evolution of approaches for mechanistic research is reflected in the acknowledgement that three streams of evidence contribute to the classification of carcinogenicity: studies of cancer in humans, animal cancer bioassays, and mechanistic data. The key characteristics of carcinogens

provide a framework for organizing mechanistic evidence and assessing its strength. The overall evaluation draws on the evidence from mechanistic data, animal cancer bioassays, and studies of cancer in humans in a more integrated fashion, rather than using the mechanistic findings only to "upgrade" or "downgrade" a preliminary classification based on the evidence from studies in humans and experimental animals, as previously. One consequence of the recommendations for updates to the Preamble is greater harmonization of the approaches to evidence evaluation across the four subgroups of the Working Group, which deal with exposure in humans and findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic studies, respectively. This harmonization will facilitate the overall evaluation by the Working Group and enhance transparency.

Procedures and outcomes

On 12–14 November 2018, IARC convened an Advisory Group to Recommend an Update to the Preamble to the *IARC Monographs*. This meeting was announced on 2 February 2018 on the *IARC Monographs* website (http://monographs.iarc.fr), along with a Call for Experts. Before the meeting, IARC engaged with IARC Governing Council members, WHO staff, and senior IARC staff. In addition, in order to take into account scientific input from all stakeholders in a comprehensive and transparent way, IARC solicited comments in different ways:

(a) *Online submission of scientific comments:* Before the Advisory Group meeting, IARC solicited comments on the Preamble through a Call for Public Comments on the *IARC Monographs* website, so that the Advisory Group could take account of the scientific views of a variety of different stakeholders. Submitted comments were accompanied by a completed WHO Declaration of Interests form. These comments, which were made available to the Advisory Group, are available on the *IARC Monographs* website (https://monographs.iarc.fr/wp-content/uploads/2018/11/Preamble_PublicComments.pdf) and are included in this report (see Annexes 1–4).

(b) *Presentations at a scientific webinar:* IARC also solicited expert input during a scientific webinar, held before the Advisory Group meeting (on 17 September 2018). Presenters generally had published significant research related to the identification of the causes of human cancer. Presenters nominated by the public (see Call for Public Comments) were combined with those identified by IARC. Attention was given to achieving a balance of presentations from constituencies with differing perspectives (i.e. a national or international health agency or scientific advisory committee, an academic institution, industry bodies, a nongovernmental organization). The presentations encompassed general principles and procedures and/or scientific review and evaluation, as per the Preamble. The names and principal affiliations of the presenters, together with pertinent disclosures made via the WHO Declaration of Interests form that they were required to complete, were made available before the webinar on the *IARC Monographs* website (see Annexes 1–4). A recording of the webinar, which was made available to the Advisory Group, is available at https://videos.iarc.fr/videos/?video=MEDIA181109152410127.

A group of international experts was invited to be part of the Advisory Group tasked with reviewing and recommending updates to the Preamble to the *IARC Monographs*. These expert Advisory Group members had access to all public comments and attended the scientific webinar. During September and October 2018, the Advisory Group began to discuss the public comments and propose changes to the Preamble, working in subgroups by Preamble section. The Advisory Group then participated in a 3-day meeting, held on 12–14 November 2018 in Lyon, France. The meeting was attended by 21 Advisory Group members, two Invited Specialists, seven Representatives of national and international health agencies, and three Observers. IARC and WHO staff with pertinent expertise, including from the *IARC Monographs* programme, the WHO Guidelines Review Committee, and other WHO programmes, also participated in the meeting.

Annexes 1–4 provide details about the Advisory Group and other meeting participants, the public comments, the webinar agenda and list of participants, and the webinar presentations.

The outcome of the Advisory Group meeting was this report to the incoming IARC Director, and a revised Preamble, for her to consider for adoption.

Advisory Group recommendations

The recommendations noted below reflect the consensus of the Advisory Group on topics that were discussed during the 3-day meeting. These include specific considerations about whether a particular change should be made to the Preamble. Other specific suggestions, including recommendations to retain certain aspects of the current Preamble, are not discussed below but are reflected in the revised Preamble.

GENERAL PRINCIPLES AND PROCEDURES

Name of the *Monographs* series

The Advisory Group recommended changing the name of the *Monographs* series to *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*.

The Advisory Group was aware that library scientists had previously advised IARC of the consequences of changing the title of a serial publication, with new volumes regarded as belonging to a different series and being located separately. Nonetheless, the Advisory Group placed greater importance on the accuracy of the title, which should reflect that the objective of the *Monographs* series is to identify carcinogenic hazards. The Advisory Group noted that the historical presence of the word *risks* in the title predated the distinction between *hazard* and *risk* drawn by the United States National Research Council in 1983 (National Research Council, 1983).

The Advisory Group discussed the distinction between *hazard* and *risk*. *Hazard* refers to the strength of the evidence that an agent is a carcinogen, whereas *risk* refers to the probability that a given exposure will result in cancer. It is important that IARC clarify this distinction for the lay public and the news media. The Advisory Group emphasized that the role of IARC in identifying carcinogenic hazards has been of immense importance to public health. Although such actions are outside the scope of IARC, the *Monographs* are used in various ways by national and

international authorities and organizations, including to inform risk assessments, formulate decisions about preventive measures, and motivate effective cancer control programmes.

Objective and scope

The Advisory Group endorsed the description in the Preamble of the broad scope of coverage of agent types (e.g. chemical, physical, and infectious agents, working conditions, and other factors) and exposure circumstances (e.g. environmental, occupational, dietary, and other). The Advisory Group recognized that for a particular body of evidence, a specifically limited review might be carried out; for example, a review related to tobacco products and cancer might have a narrowly circumscribed scope so as to efficiently address the question of interest. Whatever limitations are placed, they need to be described with sufficient specificity.

Some topics related to the agents evaluated by the *Monographs* programme that were raised by the Advisory Group were beyond the scope and time constraints of the November 2018 meeting. Among them was the possibility of providing guidance about issues to consider when evaluating agents that are mixtures that contain an established carcinogen (as a constituent or contaminant) or agents whose metabolites include an established carcinogen. These can be complicated situations, because the existence of an established carcinogen within a mixture or as a metabolite does not necessarily indicate that the mixture or parent compound is carcinogenic. For example, mixtures could contain constituents that alter the toxicokinetics (i.e. absorption distribution, metabolism, or excretion) of the constituent that is an established carcinogen. In addition, the toxicokinetics of a carcinogenic metabolite produced from a parent compound at a particular tissue site may differ from those that result from direct administration (e.g. by oral or inhalation routes) of the established carcinogen.

Working procedures

Conflicts of interest

The Advisory Group recommended that the updates to the Preamble maintain and strengthen IARC's procedures for protecting hazard evaluations from conflicts of interest. The Advisory

Group supported IARC's current policy for disclosure of conflicts of interest and noted that publicly posting the names of potential Working Group members approximately 2 months before a meeting provides an opportunity for undisclosed conflicts of interest to be brought to IARC's attention. The Advisory Group reaffirmed the requirement that all Working Group members be free of conflicts of interest. Working Group members participate in discussions and evaluations and are responsible for preparing the text, tables, and evaluations in the *Monograph*. Only a Working Group member can serve as Meeting Chair. In addition, the Advisory Group strengthened and extended rules for Working Group members by requiring that they refrain from consulting and other activities for financial gain (such as serving as an expert witness) that are related to the topic under review, or use inside information from the meeting, until the final *Monograph* is published.

The Advisory Group affirmed IARC's commitment to transparency with respect to data sources, but acknowledged that modern systematic review methods require searches for data or studies that are not published in journals. For the evidence related to cancer in humans or in experimental animals, and for mechanistic evidence, IARC conducts comprehensive and transparent searches of bibliographic databases. Identified material is included only if there is sufficient information to permit an evaluation of the quality of the methods and results of the studies. The Advisory Group recommended explicitly clarifying the search criteria for pertinent unpublished studies for certain types of agents (e.g. regulated pesticides and pharmaceuticals), because research has shown that regulatory agencies may have access to relevant data that are not in the scientific literature. IARC provides the opportunity for regulatory authorities, and regulated parties through such authorities, to make pertinent unpublished studies publicly available by the date specified in the Call for Data. Consideration of such studies by the Working Group is dependent on the public availability of sufficient information to permit an independent evaluation of (a) whether there has been selective reporting (e.g. on outcomes, or from a larger set of conducted studies), (b) study quality (e.g. design, methodology, and reporting of results), and

(c) study results. This update to the Preamble will ensure that all useful data are identified, and will maintain transparency about which data are used in *IARC Monographs* evaluations.

Role of peer review in *Monographs*

Scientific rigour, transparency, and peer review are related elements that are critical to the success of the cancer hazard evaluations of the *IARC Monographs*. The process consists of several cycles of peer review, starting before the meeting with the review and revisions of each Working Group member's draft by several Working Group scientists. At the meeting, each revised draft is reviewed by the entire subgroup, and subsequently by the entire Working Group. The final *Monograph* is considered the work of the entire Working Group, and sections are not ascribed to individual authors. The Advisory Group noted that it is important to communicate the steps and rigour of the *Monographs* peer-review process in the Preamble, because the process is more rigorous than the peer review of a typical journal manuscript.

SCIENTIFIC REVIEW AND EVALUATION

Exposure characterization

Evaluation of the quality of the exposure assessment in epidemiological studies

The type and quality of the exposure assessment methods used can have an important impact when interpreting epidemiological findings; thus, these are fundamental considerations when reviewing studies for cancer hazard identification. The Advisory Group noted that exposure assessment is particularly complicated for outcomes with long latency periods, such as cancer, for which detailed information on past exposures is often missing and exposure intensity and timing must be estimated. In describing the quality considerations to be evaluated by Working Groups in their review of epidemiological studies, the Advisory Group recommended adding an explicit consideration of the quality of the exposure assessment in each study. The Advisory Group recommended that this critical review should be performed by Working Group members with

expertise in exposure assessment as well as in epidemiology, and (when relevant studies are considered) also in carcinogen mechanisms.

Studies of cancer in humans

Importance of expert judgement

The application of informed judgement by experts is an integral and critical component of the *IARC Monographs* development process. In particular, evidence from studies of cancer in humans usually derives from observational designs that do not follow the structure of a randomized controlled trial. When evidence from observational studies is evaluated, the idiosyncratic nature of each study needs to be considered, and this invariably involves judgement. Reliance on standardized checklists and formulas would be counterproductive to a thoughtful evaluation of a study's strengths and limitations. The Preamble provides a framework for evaluating the strength of the evidence, and within a Working Group, experts will exercise their judgement as needed. To achieve transparency in its evaluation, the Working Group should lay out clear reasoning for its decisions, describe the role of expert judgement in those decisions, and explain the basis for that judgement.

Study quality and informativeness

In describing the quality considerations to be evaluated by Working Groups in their review of epidemiological studies, the Advisory Group recommended adding an explicit consideration of the *informativeness* of each study. As also noted above, the Advisory Group recommended that this assessment be informed by Working Group members with expertise in exposure assessment as well as in epidemiology, and possibly also in carcinogen mechanisms.

The informativeness of a study is its ability to show a true association, if there is one, between the agent and cancer, and the lack of an association, if no association exists. Cooper et al. (2016) used the term *sensitivity* to mean substantially the same aspect of a study. *Informativeness* means not only the absence of bias or confounding and having precise estimates of effect, but also that the results provide relevant information on the exposure–cancer association. An informative study

is one that is likely to detect an association if one actually exists. Considerations include: having a study population of sufficient size to obtain precise estimates of effect; sufficient elapsed time from exposure to measurement of outcome for an effect, if present, to be observable; presence of an adequate exposure contrast (intensity, frequency, and/or duration); biologically relevant definitions of exposure (Smith & Kriebel, 2010); and relevant and well-defined time windows for exposure and outcome.

Studies of cancer in experimental animals

Evidence summary and role within the overall evaluation

The Advisory Group discussed tailoring the evaluation of the studies of cancer in experimental animals to how the findings are used in the overall evaluation. A suggestion was made that the evaluations of the strength of the evidence of cancer in experimental animals might be simplified to *sufficient evidence* and *less than sufficient evidence*, because specifying among the designations other than *sufficient evidence of carcinogenicity* (i.e. *limited evidence of carcinogenicity*, *inadequate evidence regarding carcinogenicity*, and *evidence suggesting lack of carcinogenicity*) does not alter the overall evaluation. In addition, it was suggested that information from the mechanistic evidence and the evaluation of studies in experimental animals could be integrated before the overall classifications, so that data on cancers produced in experimental animals by a mechanism not relevant to humans would not be considered in the classification of the evidence of cancer in experimental animals or, by extension, in the overall evaluation. After discussion, the Advisory Group recommended continuing to consider the full range of classifications for the evidence in experimental animals and continuing to conduct the interpretation of mechanistic evidence of relevance to humans separately from the evaluation of the evidence in experimental animals. Although these features do not affect the overall evaluation, they provide more complete and transparent information on the strength of the evidence of cancer in experimental animals and how it is used in the overall evaluation.

Mechanistic evidence

Importance and role within the overall evaluation

The Advisory Group recognized that the availability and utility of mechanistic evidence to inform the evaluation of carcinogenicity has increased substantially since the Preamble was last updated, in 2006. For instance, several reports from the United States National Research Council and National Academies of Sciences, Engineering, and Medicine have described how toxicity testing, hazard identification, and risk assessment have been or are anticipated to be transformed by the use of mechanistic data: *Toxicology Testing in the 21st Century: A Vision and a Strategy* (National Research Council, 2007), *Using 21st Century Science to Improve Risk-Related Evaluations* (National Academies of Sciences, Engineering, and Medicine, 2017), and *Review of EPA's Integrated Risk Information System (IRIS) Process* (National Research Council, 2014). In addition, IARC's review of Group 1 carcinogens in *Monographs* Volume 100, as well as recent experiences of IARC Working Groups, have revealed several aspects of how mechanistic data can play a role in evaluations of carcinogenicity (Smith et al., 2016; Guyton et al., 2018):

- human carcinogenic agents often share one or more key characteristics that are related to how they cause cancer;
- different carcinogenic agents may exhibit different spectra of these key characteristics; and
- the key characteristics can form a transparent basis for systematically identifying and organizing mechanistic data.

As a result, the Advisory Group recommended important changes to the Preamble's description of the evaluation and role of mechanistic data in *IARC Monographs* evaluations:

- A substantial part of the evaluation of mechanistic evidence should be organized around the key characteristics of carcinogens (Smith et al., 2016). The Advisory Group recognized that the list of key characteristics of carcinogens may evolve with additional experience and scientific understanding.

- In addition, the ability to assess mechanistic class hypotheses, as well as evidence relevant to authoritative criteria for determining that tumours in experimental animals are induced by mechanisms that do not operate in humans, is retained.
- Mechanistic data should be explicitly considered as an independent stream of evidence in the overall evaluation. Previously, integration of mechanistic evidence usually occurred after the evaluation of evidence from studies of cancer in humans and in experimental animals. The Advisory Group recommended that all three streams of evidence be considered together.

The Advisory Group noted that these changes reflect recent practices of IARC Working Groups, but recommended that these practices be made clearer and more transparent.

Classifications

Group 2 categories

The Advisory Group considered the option of merging Group 2A and Group 2B, because some stakeholders indicated that the distinction between these two categories was not clear. The Advisory Group decided against this option, for several reasons:

- Group 2A and Group 2B have involved distinctly different strengths of evidence for carcinogenicity;
- merging Group 2A and Group 2B would lead to confusion about the interpretation of past evaluations; and
- national authorities that use *IARC Monographs* evaluations would need to revisit their hazard and risk assessment processes and procedures.

However, the Advisory Group recommended increasing clarity and transparency with respect to the distinction between Group 2A and Group 2B, particularly with respect to how they differ in the strength of evidence. Specifically, the Advisory Group recommended changes in the overall evaluation to clarify these classifications as follows:

- a classification in Group 2B can be supported by a single stream of evidence (evidence of cancer in humans, evidence of cancer in experimental animals, or mechanistic evidence), whereas
- a classification in Group 2A requires support from at least two streams of evidence, at least one of which involves evidence in exposed humans or in human cells or tissues.

All past evaluations remain in effect until the agent is re-evaluated in a future *Monograph*. This includes evaluations that were based solely on *limited evidence of carcinogenicity* in humans or that did not explicitly cite *strong evidence* in exposed humans or in human cells or tissues as a basis for classification in Group 2A.

The Advisory Group discussed the misunderstanding that arises if the classifications *probably carcinogenic* and *possibly carcinogenic* are incorrectly viewed as statements of the probability that an agent is a carcinogenic hazard. Recognizing this potential for misunderstanding, in 2006 the IARC Preamble clarified that "the terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*" (IARC, 2006). The present Advisory Group viewed this as an accurate statement about strength of evidence that requires no further elaboration.

Nonetheless, the Advisory Group did explore replacements for the terms *probably carcinogenic* and *possibly carcinogenic*. Terms used by other health agencies (e.g. *presumed human carcinogen* under the Globally Harmonized System or *reasonably anticipated to be a human carcinogen* in the United States National Toxicology Program) do not have quantitative implications but would introduce a different potential for misunderstanding, because the criteria for these terms do not match those of the *IARC Monographs*. In addition, the Advisory Group considered that there could be difficulties in translating new terms into French and other languages. Therefore, the Advisory Group did not recommend replacements for the terms *probably carcinogenic* or *possibly carcinogenic* at this time.

Group 4 category

The Advisory Group took note of the misunderstanding among the public associated with the Group 4 classification (*probably not carcinogenic to humans*). The scope of the *IARC Monographs* is to identify factors that can increase the risk of cancer in humans, and the programme has selected agents for review only if there is evidence of human exposure and some evidence or suspicion of carcinogenicity. It is not within the scope of the programme to review new agents without evidence to suspect carcinogenicity, and in practice, there are almost always some data indicating a potential carcinogenic hazard for agents that are reviewed. For this reason, the Advisory Group recommended combining Group 3 (*not classifiable as to its carcinogenicity to humans*) and Group 4, and encouraged future Working Groups to add the statement that an agent is *probably not carcinogenic to humans* when this is warranted by the body of evidence. Working Groups may wish to note when multiple, well-designed epidemiological studies have not found a positive association between the agent and cancer in humans. However, making a definitive evaluation of an absence of potential carcinogenic hazard to humans on the basis of epidemiological studies requires assurances that all susceptible populations, exposure circumstances, cancer outcomes, and relevant variables have been captured adequately in the body of available studies, and in practice such assurances are nearly impossible to obtain.

Instructions for Authors

The Preamble frequently mentions the Instructions for Authors, which are provided to Working Group members to guide them in developing the drafts before the Working Group meeting. The Instructions for Authors constitute the documentation for implementing the principles laid out in the Preamble. Therefore, this document needs to be dynamic and to be updated frequently as methods change. Its importance is amplified by the current issues related to the need for transparency and the scrutiny of *IARC Monographs* classifications. Consequently, the Advisory Group recommended that attention be given to modification of the Instructions for Authors in line with the adopted Preamble.

Lay summary and frequently asked questions

The *IARC Monographs* identify factors that are cancer hazards. Because the identification of carcinogens is a key step in cancer prevention, the *IARC Monographs* evaluations are an important international activity that provides information for decision-making to improve public health. The *Monographs* carcinogenicity classifications are considered authoritative and are used by many stakeholders, such as national health agencies, research scientists, industry, and the public. These stakeholders use this information in different ways, such as: to prioritize and rank carcinogens; to estimate the global burden of specific cancer types from specific occupational or environmental exposures; to identify research gaps, especially for agents that are *possibly carcinogenic* or *probably carcinogenic*; and to develop preventive actions to limit exposure to a potential carcinogen.

The *IARC Monographs* carcinogenicity classifications are of interest to a broad group of stakeholders, including the general public. Some agents, such as radiofrequency electromagnetic fields and shift work, affect large populations, whereas others may pose risks only to particular subgroups. A wide range of actions may be motivated by a particular classification. IARC has substantial experience in communicating its findings so as to reach targeted stakeholders, and also recognizes the challenges of reaching across the diversity of backgrounds of those interested in its *Monographs* programme and its findings.

The Advisory Group suggested that IARC continue to develop approaches to disseminate the findings of the *Monographs* beyond the brief publications in *The Lancet Oncology* and posts on the IARC and *Monographs* websites. One specific suggestion is the development of a *Monograph* lay summary, written to match the reading and scientific literacy levels of the general public. An accompanying set of frequently asked questions with answers should be developed, and updated and expanded as experience is gained.

The Advisory Group recommended that the *IARC Monographs* programme make hazard communication a high priority, and that communication of cancer hazards, which uses language and venues tailored to the specific stakeholders, be integrated into all parts of the programme. Key

issues for communication include differentiating the concepts of *hazard* and *risk*, and the meaning of different carcinogenicity classifications. These classifications reflect the strength, or the level of confidence, of the evidence that a substance is a carcinogen. For instance, the confidence that an agent is a carcinogen is greater for those agents classified as *probably carcinogenic* than for those agents classified as *possibly carcinogenic*, because of differences in the strength of evidence. The classification of an agent in Group 2A (*probably carcinogenic*) requires support from at least two streams of evidence, at least one of which involves evidence in exposed humans or in human cells or tissues. In contrast, the classification of an agent in Group 2B (*possibly carcinogenic*) can be supported by a single stream of evidence. This support is typically from studies in experimental animals or mechanistic studies, which require translation to humans, or from evidence of carcinogenicity in humans that is *limited*. Clear communication of these issues and of the nature of any scientific uncertainty will help strengthen trust in the *IARC Monographs* process and evaluations.

References

Cooper GS, Lunn RM, Ågerstrand M, Glenn BS, Kraft AD, Luke AM, et al. (2016). Study sensitivity: evaluating the ability to detect effects in systematic reviews of chemical exposures. Environ Int. 92–93:605–10. https://doi.org/10.1016/j.envint.2016.03.017 PMID:27156196

Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, et al. (2018). Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis. 39(4):614–22. https://doi.org/10.1093/carcin/bgy031 PMID:29562322

IARC (2006). Preamble to the *IARC Monographs*, amended January 2006. Available from: https://monographs.iarc.fr/previous-preamble/.

National Academies of Sciences, Engineering, and Medicine (2017). Using 21st century science to improve risk-related evaluations. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/24635 PMID:28267305

National Research Council (1983). Risk assessment in the federal government: managing the process. Washington (DC), USA: National Academies Press. PMID:25032414

National Research Council (2007). Toxicology testing in the 21st century: a vision and a strategy. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/11970

National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process. Washington (DC), USA: National Academies Press. https://doi.org/10.17226/18764

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect. 124(6):713–21. https://doi.org/10.1289/ehp.1509912 PMID:26600562

Smith TJ, Kriebel D (2010). A biologic approach to environmental assessment and epidemiology. New York (NY), USA: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195141566.001.0001

Annex 1.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
ADVISORY GROUP TO RECOMMEND AN UPDATE TO THE PREAMBLE
Lyon, France: 12−14 November 2018

List of Participants

IARC requests that you do not contact or lobby meeting participants, send them written materials, or offer favours that could appear to be linked to their participation. (You may send pertinent written materials to IARC.) IARC will ask participants to report all such contacts and will publicly reveal any attempt to influence the meeting. Thank you for your cooperation.

Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

Advisory Group Members

Frederick Beland, U.S. Food and Drug Administration, USA
Lisa Bero, University of Sydney, Australia
Patience Browne, Organisation for Economic Co-operation and Development (OECD), France
Weihsueh A. Chiu, Texas A&M University, USA[1]
Vincent Cogliano, U.S. Environmental Protection Agency, USA
Lin Fritschi, Curtin University, Australia
Jennifer Jinot, US Environmental Protection Agency, USA [retired]
Jun Kanno, Japan Organization of Occupational Health and Safety, Japan
David Kriebel, University of Massachusetts Lowell, USA
Dirk W. Lachenmeier, Chemical and Veterinary Investigation Agency Karlsruhe, Germany
Qing Lan, National Cancer Institute, USA
Gérard Lasfargues, Director General, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), France
Frank Le Curieux, European Chemicals Agency (ECHA), Finland
Ruth M. Lunn, National Institute of Environmental Health Sciences, USA
Susan Peters, Utrecht University, The Netherlands
Jonathan M. Samet, University of Colorado, USA [Overall Chair]
Pamela Shubat, Environmental Health Division, Minnesota Department of Health, USA [retired]
Hideko Sone, National Institute for Environmental Studies, Japan
Mary C. White, Center for Disease Control and Prevention, USA
Jon Williamson, University of Kent, United Kingdom
Marianna Yakubovskaya, Ministry of Health, Russian Federation

Invited Specialists

Jack Siemiatycki, University of Montreal, Canada[2]
Paul A. White, Health Canada, Canada[3]

Representatives of national and international health agencies

Ann Chao, US National Cancer Institute, United States (Geneva-based)

[1] Weishueh Chiu receives non-significant research support (< 1% of his total research support) from the Environment Defense Fund (EDF).
[2] Jack Siemiatycki has been retained as an expert witness in a court case in the U.S. on behalf of a plaintiff regarding talcum powder and ovarian cancer.
[3] Paul White, is Co-chair of the Health & Environmental Sciences Institute (HESI) Genetic Toxicology Technical Committee.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
ADVISORY GROUP TO RECOMMEND AN UPDATE TO THE PREAMBLE
Lyon, France: 12–14 November 2018

Paolo Guglielmetti, Directorate-General for Health and Food Safety, European Commission
An Jamers, Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, European Commission
Andrew Kraft, U.S. EPA Integrated Risk Information System (IRIS) Program, USA
Eun Young Park, National Cancer Center of Korea, Republic of Korea
Chris Roth, ANSES – French Agency for Food, Environmental and Occupational Health & Safety, France
Bernard Stewart, Cancer Council Australia; University of New South Wales, Australia

Observers

Neeraja Erraguntla, American Chemistry Council, USA[4]
Katya Tsaioun, Johns Hopkins Bloomberg School of Public Health, USA[5]
Daniele Wikoff, ToxStrategies, USA[6]

IARC/WHO Secretariat

Bruce Armstrong, IARC Senior Visiting Scientist
Lamia Benbrahim-Tallaa, *IARC Monographs* Group
Véronique Bouvard, *IARC Monographs* Group
Fatiha El Ghissassi, *IARC Monographs* Group
Yann Grosse, *IARC Monographs* Group
Kathryn Guyton, *IARC Monographs* Group
Amy Hall, *IARC Monographs* Group
JaeKwan Jun, IARC Senior Visiting Scientist
Béatrice Lauby-Secretan, *IARC Handbooks* Group (Group Head)
Heidi Mattock, *IARC Monographs* Group (Editor)
Susan Norris, Guidelines Review Committee, World Health Organization
Rodolfo Saracci, IARC Senior Visiting Scientist
Mary Schubauer-Berigan, *IARC Monographs* Group
Kurt Straif, *IARC Monographs* Group (Head, Section of Evidence Synthesis and Classification)
Angelika Tritscher, Department of Food Safety and Zoonoses, World Health Organization
Jiri Zavadil, IARC Molecular Mechanisms and Biomarkers Group (Group Head)

NOTE REGARDING CONFLICTS OF INTERESTS: Each participant first received a preliminary invitation with the request to complete and sign the IARC/WHO Declaration of Interests, which covers employment and consulting activities, individual and institutional research support, and other financial interests.

Official invitations were extended after careful assessment of any declared interests that might constitute a real or perceived conflict of interest. Pertinent and significant conflicts are disclosed

[4] Neeraja Erraguntla, is Director, Chemical Products & Technology Division, American Chemistry Council. Her employer will support her travel to attend the Preamble AG meeting.

[5] Katya Tsaioun, is employed by the Johns Hopkins Bloomberg School of Public Health. She serves as the Executive Director of the Evidence Based Toxicology Collaboration (EBTC), a collaboration with senior representation from stakeholders including from the chemical industry, consulting companies, academia and governmental agencies.

[6] Daniele Wikoff, is employed by ToxStrategies, a consulting firm that has provided research services to the American Beverage Association. ToxStrategies received financial support from the American Beverage Association for preparing written and oral comments, as well as travel support for Dr. Wikoff to participate as an observer.

here. Information about other potential conflicts that are not disclosed may be sent to the Head of the Monographs Programme at imo@iarc.fr.

Participants identified as Invited Specialists will not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or draft text that pertains to the description or interpretation of cancer data. The Declarations will be updated and reviewed again at the opening of the meeting.

Posted on 19 November 2018

Annex 2.

Table of Contents

Harold Seifried, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.1 1 Line 28 and 29
Current text	IARC seeks to identify the causes of human cancer.
Proposed update (revised text)	Identify the potential causes of human cancer through the evaluation of molecular models, animal studies, epidemiology and related mechanisms.
Brief rationale for update (max. 200 words)	There is a serious confusion in the public as well as in the scientific community as to the difference between hazard and risk, IARC identifies potential hazards with varying degrees of certainty but the actual risk of exposure is not mentioned so just like the NTP and the previous NCI programs of screening for carcinogenic potential, the results do not give the reader any idea of the extent of the risk, i.e. saccharin, the reference doasage RfD would be over 400 cases of diet soda daily, the risk of dying from edema far overshadows the risk of the hazard's exposure. This message needs to be worked into the preampble as we had similar message issues with the carcinogenesis bioassay program and this concern was factored into our nominations to the Nci and later the National Toxicology Program
References, if any (max. 5)	

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A2 2 18 – 24, 44- page 3, line 5
Current text	See paragraph
Proposed update (revised text)	Spell out the difference between risk and hazard
Brief rationale for update (max. 200 words)	This is very understated here, line 21 word ‘risks’ in the title. Hazard describes the degree of support the evidence provides that an agent is a cancer hazard, risk takes into account the probability that under current levels of exposure (from the daa available to the review group) there is a certain probability that exposure will lead to cancer. The stress on the level of certainty for the hazard evaluation is important but more important is giving some discussion of the exposures seen in humans versus those levels (MTD for example) seen in animal screening studies. EPA has done extensive work on reference dose comparison techniques.
References, if any (max. 5)	

August 28, 2018

SUBMITTED BY EMAIL

Dr. Kurt Straif
Section Head
Monographs Group
International Agency for Research on Cancer
150 Cours Albert Thomas
69372 Lyon CEDEX 08
France
Email: straif@iarc.fr

Dear Dr. Straif:

Attached please find comments on, and recommendations for, improving the Preamble to the IARC Monographs. These comments were prepared as a collaboration of the American Chemistry Council[1] and the Center for Advancing Risk Assessment Science and Policy.[2,3] We appreciate the opportunity to provide these recommendations to IARC. Improving the scientific procedures and practices of the Monographs Programme is critical to overcoming the many documented shortcomings of the Programme and to bring the Monographs' evaluation procedures up to current 21st century standards for conducting evidence-based analyses for establishing causality.

The Preamble summarizes the underlying scientific principles of the IARC Monographs, and in tandem with the Author Instructions, provides guidance to members of Working Groups writing the IARC Monographs. Currently, both of these documents are fairly general. Neither provides a detailed framework for selecting and reviewing studies, assessing their quality, or fully integrating scientific evidence to form causal conclusions. Given all the concerns raised about the Monographs Programme—including lack of transparency, inadequate review of or failure to fully review all relevant scientific information, questionable practices for evaluating and integrating mechanistic data, lack of independent peer review, and conflicts of interest—the Preamble requires a top-to-bottom, comprehensive review.

Unfortunately, the procedures the Programme has devised for commenting on the Preamble do not facilitate a comprehensive review, and instead severely limit the scope of the review. The Programme requires comments to be submitted using a procedure more fitted to copy editing, i.e., submitted in a tabular format, citing the Preamble by section and line number and including specific edits to the existing text. In effect, this process restricts suggestions for improvements almost solely to editorial changes or minor additions or mark-ups to the existing text of the Preamble. If the review goes forward in this manner, it will certainly not adequately address of the many documented shortcomings of the procedures used by the Monographs Programme.

Therefore, we are submitting general comments tied to specific parts of the text in our best attempt to adhere to the prescribed format. We also summarize below the most critical changes and best practices

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®; common sense advocacy designed to address major public policy issues; and health and environmental research and product testing. The business of chemistry is a $768 billion enterprise and a key element of the nation's economy. It is among the largest exporters in the nation, accounting for fourteen percent of all U.S. goods exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

[2] The Center for Advancing Risk Assessment Science and Policy (ARASP) is a coalition of independent groups and associations that promotes the development and application of up-to-date, scientifically sound methods for conducting chemical assessments.

[3] These comments were prepared, in part, through a contract with Gradient (Dr. Julie Goodman served as the lead scientist for Gradient).

for systematic review, evidence identification, evidence evaluation, and evidence integration that the Programme needs to address to improve the scientific basis and objectivity of the Monographs. These include:

- Instituting more formal approaches to chemical prioritization processes when selecting agents for evaluation, including a screening scoring system to objectively evaluate and document the selection process.

- Considering individuals with relevant expertise from all sectors for inclusion in IARC Working Groups (while adhering to strict conflict of interest rules), as is done for advisory committees of other agencies.

- Implementing formal and transparent systematic review procedures for each Monograph. IARC may wish to indicate in the Preamble its intent to use systematic review procedures, and then develop a separate, stand-alone document explicitly detailing the systematic review practices Working Groups should follow; this document could then be updated independently of the Preamble, as needed.

- Providing guidance for problem formulation regarding the use of potential modes of action (MOAs) as a central organizing principle for the evidence integration step of the evaluation.

- Implementing procedures that reflect a scientific understanding that a cancer hazard (classification) can be route- and dose-specific.[4]

- Providing guidance for problem formulation regarding the level of evidence needed for each line of evidence to accurately draw conclusions regarding causality, and how uncertainty/inadequacy in the lines of evidence will be addressed.

- Developing procedures for evaluating and characterizing scientific assessments developed by other agencies, including weighing alternative conclusions and providing a clear description of the reasons why the evidence better supports one conclusion over another if IARC's position differs from other agency assessments.

- Providing a clear methodology for study selection, including study inclusion and exclusion criteria for each line of evidence, to increase transparency in this process.

- Developing a formal, objective approach to study quality evaluations, including a discussion of how the factors that affect study quality impact the interpretation of results in individual studies, how results from low quality studies will be considered (particularly if inconsistent with results from higher quality studies), and how individual study quality evaluation information will be utilized when considering the totality of the body of literature.

- Developing a formalized process for resolution of conflicting study quality opinions among reviewers, in which each reviewer articulates their reasons for choosing specific ratings, and if still no consensus is reached, a third party is consulted to resolve any scoring issues.

- Providing explicit guidance for integrating studies within and across lines of evidence, including clear

[4] For example, ethanol is a known human carcinogen when ingested at significant levels chronically. However, low levels of ingestion (*e.g.*, small amounts, not associated with alcoholic beverages) are not associated with a cancer hazard, and there is no cancer hazard associated with skin contact. This principle is relevant to many other carcinogens as well.

descriptions regarding how study quality evaluations should be used to weigh the evidence and how null or negative data and questions regarding human relevance will be considered.

- Developing guidance for evaluating the totality of mechanistic evidence (including high-throughput assay data), considering how study strengths and limitations impact the interpretation of results and whether any observed MOAs plausibly operate in humans, and for integrating mechanistic evidence equally and concurrently with other lines of evidence.

- Specifying that studies evaluating whether certain people are more susceptible to a potential carcinogen should be evaluated using the same study quality evaluation criteria as evidence of apical outcomes.

- Requiring Working Groups to explicitly lay out how each of their conclusions was reached, including a discussion of situations in which scientific judgment was exercised and descriptions of all deviations from the methods specified in the Preamble, such that an independent party could fully track the decision-making process.

- Implementing transparent decision-making procedures. In cases where consensus amongst Working Group Members is not achieved, polling should take place. The polling results should be reported in the conclusions section of the Monograph. A two-thirds Working Group majority vote for classification of "Group 1 – carcinogenic to humans" should be required.

- Developing procedures for subjecting Monographs to public comment and independent peer review before they are finalized, with the IARC Director responsible for ensuring that Monograph revisions are fully responsive to all public and peer review comments before each Monograph is published.

- Including guidance for communicating the findings and conclusions of IARC Monographs to the general public, emphasizing the nature of Monograph conclusions as hazard classifications that do not consider risk at any specific exposure level, to avoid potential public misunderstanding and misapplication of the Monograph's conclusions.

Future conclusions of IARC Monographs must better reflect the totality of weight of the scientific evidence. Therefore, we recommend that the Monographs Programme conduct a thorough and comprehensive review of its guidance and procedures with the goal of upgrading these to meet contemporary 21st century standards and best practices for evidence-based systematic reviews. Full consideration should be given to incorporating the key concepts described above. The comprehensive review should start with a consideration of approaches adopted by other organizations that are consistent with systematic review best practices and that employ procedures for integrating mechanistic evidence equally and concurrently with other lines of evidence.

Thank you for considering the attached comments. Please do not hesitate to contact me if you have any questions, or require clarification, on any of the comments.

Sincerely

/ Richard A. Becker /

Richard A. Becker Ph.D. DABT

Specific Recommendations from ACC and ARASP for Updating IARC Monographs Preamble

Name and affiliation of commenter

Your name	Richard A. Becker Ph.D. DABT
Your principal affiliation	American Chemistry Council, 700 Second St. NE, Washington DC USA
If another party suggested that you submit this nomination, please identify	Not Applicable
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Sent in a separate e-mail to IARC (preamble@iarc.fr)

1. Selection of Agents for Evaluation

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.3 3 17-38
Current text	The Preamble lists two primary criteria for selecting agents for review: "a) there is evidence of human exposure and b) there is some evidence or suspicion of carcinogenicity." IARC indicates that it may review agents as it "becomes aware of new scientific information" or if national health agencies identify a public health need for review. If these agents have been evaluated, IARC states that, "in some cases it may be appropriate to review only the data published since a prior evaluation."
Proposed update (revised text)	General comment: Given an equal hazard potential, an agent with widespread exposure potential is of a higher concern to public health than an agent with a low exposure potential. However, the Preamble currently provides little information regarding how IARC weighs hazard and exposure to select agents for review. IARC should consider instituting more formal approaches to chemical prioritization processes, such as those used by Canada's Chemical Management Plan (CMP) (Health Canada, 2017) and Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2016). IARC should consider developing a screening scoring system to objectively evaluate and document the selection process, then thoroughly document this system in the Preamble and Author Instructions. This system could include a set of criteria used to evaluate and rank agents with regard to relative carcinogenic hazard and exposure potential, based on available evidence. Information sources could include industry reports for other programs, such as the robust study summaries submitted to the European Chemical Agency (ECHA) for Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) registration and information submitted to the US Environmental Protection Agency (US

	EPA) High Production Volume (HPV) challenge program, as well as chemical assessments by other agencies, and/or "21st century tools," such as those developed by US EPA (*e.g.*, ToxCast and ExpoCast) (US EPA, 2014).
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Health Canada. 2017. "Approach for the Prioritization of Substances on the Revised In Commerce List." http://www.chemicalsubstanceschimiques.gc.ca/plan/approach-approche/icl-lsc-eng.php National Industrial Chemicals Notification and Assessment Scheme (NICNAS). 2016. "Human Health Assessments: Inventory Multi-Tiered Assessment and Prioritisation (IMAP) Framework." Australia Department of Health. https://web.archive.org/web/20160329033919/http://www.nicnas.gov.au/__data/assets/word_doc/0003/5817/IMAP-Framework.docx US EPA. 2014. "EPA Science Matters Newsletter: EPA's ToxCast and ExpoCast: Chemical screening, better and faster." January. https://www.epa.gov/sciencematters/epa-science-matters-newsletter-epas-toxcast-and-expocast-chemical-screening-better

2. Working Group Composition and Stakeholder/Outside Expert Involvement

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.5 4 26-31
Current text	The Preamble states, "Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts." Further, Working Group Members must have expertise, and "an absence of real or apparent conflicts of interest." The section also notes that "Consideration is also given to demographic diversity and balance of scientific findings and views."
Proposed update (revised text)	General comment: At present, Working Group Members generally are not members of industry or consultants to industry. To ensure that Working Groups are composed of members with the highest level of expertise with respect to the agent under evaluation, it is important that IARC considers individuals with relevant expertise from all sectors for participation in Working Groups, with full disclosure of potential conflicts of interest. IARC should adopt the procedures of the National Academy of Sciences (2003) to ensure that Working Groups are composed of members with a balance of perspectives. Other agencies have scientific advisory committees and boards for which members of all sectors are allowed opportunities for participation. US EPA has several scientific advisory panels and committees, including the Science Advisory Board (SAB), Clean Air Scientific Advisory Committee

	(CASAC), and the Advisory Council on Clean Air Compliance Analysis (Council). SAB and CASAC boards seek a broad array of expertise, while still adhering to strict conflict of interest rules (US EPA, 2002). The National Academy of Sciences (NAS) follows a similar procedure for its advisory committees (National Academies, 2005). The European Food Safety Authority (EFSA) takes a hybrid approach that allows for the inclusion of experts who may have had a financial interest in a substance under review, with restrictions regarding timing of participation. Critically, however, "EFSA recognises that high quality scientific expertise is by definition based on prior experience. Moreover, having an interest does not necessarily imply that there is a conflict of interest" (EFSA, 2018). IARC should implement procedures used by the US National Academies of Sciences, Engineering, and Medicine (NASEM) to prohibit individuals from reviewing their own work. The NASEM policy states, "However, an individual should not serve as a member of a committee with respect to an activity in which a critical review and evaluation of the individual's own work, or that of his or her immediate employer, is the central purpose of the activity, because that would constitute a conflict of interest, although such an individual may provide relevant information to the program activity" (NASEM, 2003). Furthermore, in selecting Working Group Members, IARC should implement procedures similar to NASEM that prohibit participation of experts affiliated with any government organization that will directly be affected by the use of a Monograph in a legally-mandated process or action. As NASEM notes, this is because such an affiliation/employment relationship could impair an individual's objectivity.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	European Food Safety Authority (EFSA). 2018. "Independent science." https://www.efsa.europa.eu/en/howwework/independentscience National Academies. 2003. " Policy on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports." 3-5p. http://www.nationalacademies.org/coi/bi-coi_form-0.pdf National Academies. 2005. "The National Academies: Getting to Know the Committee Process." 20p. http://www.nationalacademies.org/site_assets/groups/nasite/documents/webpage/na_069620.pdf National Academies of Sciences, Engineering, and Medicine (NASEM). 2003. "Conflicts Of Interest Policy For Committees Used In The Development Of Reports." 4 p., May 12. http://www.nationalacademies.org/coi/index.html. US EPA. 2002. "Overview of the Panel Formation Process at the Environmental Protection Agency Science Advisory Board." Science

	Advisory Board, EPA-SAB-EC-02-010, 10p., September. https://yosemite.epa.gov/sab/ sabproduct.nsf/WebFiles/OverviewPanelForm/$File/ec02010.pdf

3. Systematic Review Procedures

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.1 1 41-43
Current text	"The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail."
Proposed update (revised text)	General comment: The Preamble does not provide guidance for conducting a systematic review of the evidence regarding the potential carcinogenicity of evaluated agents. IARC should implement formal and transparent systematic review procedures for each Monograph. If IARC does not wish to include these procedures in the Preamble, it should indicate in the Preamble the intent to use systematic review procedures, and then develop a separate, stand-alone document explicitly detailing the systematic review practices that Working Groups should follow. This document, describing the detailed procedures whereby a Working Group conducts a systematic review could then be updated independently of the Preamble, as needed.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	

4. Problem Formulation

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.2 2-3 All text in this section
Current text	Problem formulation is not discussed in the Preamble, beyond the statement that Monographs "are an exercise in evaluating cancer hazards."
Proposed update (revised text)	General comment: Based on the limited statement that Monographs are an exercise in evaluating cancer hazards, the problem formulation step for each evaluation only involves asking the simple question, "is the agent potentially carcinogenic to humans?" The importance of problem formulation in systematic reviews is well documented and supported (Rhomberg *et al*., 2013; NRC, 2014). The problem formulation step of an evaluation can identify critical concepts and potential issues that may be faced later in the evaluation process. The Preamble should provide explicit guidance regarding problem formulation, including consideration of the conditions under which an

	agent may pose a cancer hazard (*e.g.*, whether it is route- or dose-specific), the level of evidence needed for each line of evidence to accurately draw conclusions regarding causality, and how uncertainty/inadequacy in the lines of evidence will be addressed. Information on the potential mode of action (MOA) of an agent should be incorporated into problem formulation, if available, as MOA is a key driver for extrapolation of responses in experimental animals to human-relevant exposures. Existing frameworks, such as the World Health Organization (WHO)/International Program on Chemical Safety (IPCS) MOA/Human Relevance (HR) Framework (Meek *et al*., 2014) or other similar approaches (*e.g.*, Borgert *et al*., 2015), can be followed. These frameworks bring issues of human relevance into hazard identification conclusions; for example, identifying an MOA with a threshold can render carcinogenicity in humans as impossible under typical environmental conditions or other reasonable exposure scenarios (Borgert *et al*., 2015). If enough information is available to hypothesize an agent's MOA, it should be used as a central organizing principle for evidence integration (Rhomberg *et al*., 2013). For some agents, there is sufficient information available to identify plausible alternative MOAs. All hypothesized MOAs should be described during the problem formulation step, to enable the comparison of the extent to which the evidence supports one hypothesized MOA compared to another during the evidence integration process.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Borgert, CJ; Wise, K; Becker, RA. 2015. "Modernizing problem formulation for risk assessment necessitates articulation of mode of action." *Regul. Toxicol. Pharmacol.* 72(3):538-551. Meek, ME; Boobis, A; Cote, I; Dellarco, V; Fotakis, G; Munn, S; Seed, J; Vickers, C. 2014. "New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis." *J. Appl. Toxicol.* 34(1):1-18. National Research Council (NRC). 2014. "Review of EPA's Integrated Risk Information System (IRIS) Process." National Academies Press (Washington, DC), 204p. http://www.nap.edu/catalog.php?record_id=18764 Rhomberg, LR; Goodman, JE; Bailey, LA; Prueitt, RL; Beck, NB; Bevan, C; Honeycutt, M; Kaminski, NE; Paoli, G; Pottenger, LH; Scherer, RW; Wise, KC; Becker, RA. 2013. "A survey of frameworks for best practices in weight-of-evidence analyses." *Crit. Rev. Toxicol.* 43(9):753-784.

5. Evaluation of Equivalent Scientific Assessments by Other Agencies

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 All pages of this section All text in this section
Current text	The Preamble does not discuss procedures for evaluating equivalent scientific assessments developed by other agencies, or procedures for documenting the scientific justification of its conclusions when they differ from those of other agencies.
Proposed update (revised text)	General comment: Section B.6(e) of the Preamble indicates that when there are "significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative," but there is no such procedure for differences in scientific interpretation among other agencies. The Preamble should include a discussion of procedures for evaluating carcinogenicity assessments previously developed by other agencies, for any agent being evaluated by IARC. Such assessments should be identified along with the relevant studies for each agent under evaluation, and the Preamble should provide guidance regarding the procedures to follow if a Working Group evaluation results in a different carcinogenicity conclusion compared to other agencies. The Working Group should weigh the alternative conclusions of other agencies and provide documentation with a clear description of the reasons why it believes the evidence better supports its conclusion compared to that of another agency, based on a comparison of methodologies used for each assessment. Weighing of alternative hypotheses for causal inference and providing justification that the evidence supports one alternative better than another is a critical step in the hypothesis-based weight-of-evidence process (Rhomberg *et al*., 2011, 2013) and should be incorporated into the IARC evaluation process with regard to assessments by other agencies to ensure that the conclusions in each Monograph are scientifically defensible.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Rhomberg, LR; Bailey, LA; Goodman, JE; Hamade, A; Mayfield, D. 2011. "Is exposure to formaldehyde in air causally associated with leukemia? - A hypothesis-based weight-of-evidence analysis." *Crit. Rev. Toxicol.* 41(7):555-621. Rhomberg, LR; Goodman, JE; Bailey, LA; Prueitt, RL; Beck, NB; Bevan, C; Honeycutt, M; Kaminski, NE; Paoli, G; Pottenger, LH; Scherer, RW; Wise, KC; Becker, RA. 2013. "A survey of frameworks for best practices in weight-of-evidence analyses." *Crit. Rev. Toxicol.* 43(9):753-784.

6. Exposure Data

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.1(d) 8 3-18
Current text	"Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases. Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described."
Proposed update (revised text)	General comment: Temporal aspects of exposure should also be considered (US EPA, 2016). For example, each Monograph should indicate whether uses of the agent suggest infrequent exposure to high levels, or continuous exposure to low levels. The text in Section B.1 (d), page 8, lines 11-13 should be revised to include the statement below (italicized for emphasis): "Information is reported on a range of human exposures, including occupational and environmental exposures. *When available, temporal aspects of exposure are also presented.* This includes relevant data from both developed and developing countries."
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	US EPA. 2016. "Guidelines for Human Exposure Assessment (Peer Review Draft)." Risk Assessment Forum, 213 p., January 7. https://www.epa.gov/sites/production/files/2016-02/documents/guidelines_for_human_exposure_assessment_peer_review_draftv2.pdf

7. Study Selection

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.4 3 40-42
Current text	"Each Monograph reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized."
Proposed update (revised text)	General comment: The IARC Preamble presents no clear methods or decision criteria whereby literature is included or excluded in an IARC assessment, nor does it describe what constitutes "inadequate" or "irrelevant" for Working Group purposes. Decision criteria should be based on study quality and relevance to directly inform cancer causality in humans, considering any issues identified during the problem formulation step. Consistent with the principles of transparency fundamental to systematic review and weight-of-evidence analysis, the Preamble should be updated to include clear study inclusion and exclusion criteria for each line of evidence (animal, human, mechanistic, and any others). IARC can draw upon other existing systems that include such criteria, such as the literature search and screening processes outlined in the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) systematic review framework (NTP, 2015).
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	National Toxicology Program (NTP). 2015. "Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration." Office of Health Assessment and Translation (OHAT), 98p., http://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf

8. Study Quality Evaluation

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.2(b) 9-10 All text in this section
Current text	The Preamble provides a general discussion of how bias, confounding, and other study quality issues are evaluated, stating, "In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population…. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure."

Proposed update (revised text)	General comment: Although IARC acknowledges the importance of considering the quality of studies, the Preamble does not provide a formal, objective approach to assessing quality. The Preamble should include a discussion of how the factors that affect study quality impact the interpretation of results in individual studies, how results from low quality studies will be considered (particularly if inconsistent with results from higher quality studies), and how individual study quality information will be utilized when considering the body of literature as a whole. IARC should develop a more formal approach to assessing study quality, such as those used by many other agencies responsible for assessing the hazards of chemical substances, including US EPA, NTP, Texas Commission on Environmental Quality (TCEQ), and EFSA (see, for example, Lynch *et al*., 2016; US EPA, 2018; TCEQ, 2017; EFSA, 2017). These approaches have been informed by numerous existing study quality assessment frameworks, including but not limited to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, the Klimisch system, the Toxicological Data Reliability Assessment Tool (ToxRTool), and the Science in Risk Assessment and Policy (SciRAP) tool (Lynch *et al*., 2016; Beronius et al., 2018). IARC should consider the application of similar evaluation systems, or adapt its own system utilizing, but also expanding upon, the quality considerations currently described in the Preamble.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Beronius, A; Molander, L; Zilliacus, J; Ruden, C; Hanberg, A. 2018. "Testing and refining the Science in Risk Assessment and Policy (SciRAP) web-based platform for evaluating the reliability and relevance of in vivo toxicity studies." *J. Appl. Toxicol.* doi: 10.1002/jat.3648. European Food Safety Authority (EFSA). 2017. "Guidance on the use of the weight of evidence approach in scientific assessments." Scientific Committee, *EFSA J.* 15(8):4971, doi: 10.2903/j.efsa.2017.4971. Lynch, HN; Goodman, JE; Tabony, JA; Rhomberg, LR. 2016. "Systematic comparison of study quality criteria." *Regul. Toxicol. Pharmacol.* 76:187-198. Texas Commission on Environmental Quality (TCEQ). 2017. "TCEQ Guidelines for Systematic Review and Evidence Integration." Toxicology Division, 53p., December 20. https://www.tceq.texas.gov/assets/public/ implementation/tox/dsd/whitepaper/srguidelines.pdf US EPA. 2018. "Application of Systematic Review in TSCA Risk Evaluations (Final)." Office of Chemical Safety and Pollution Prevention, Office of Pollution Prevention and Toxics, EPA Document # 740-P1-8001, 248p., May. https://www.epa.gov/sites/production/files/ 2018-06/documents/final_application_of_sr_in_ tsca_05-31-18.pdf

9. Study Quality Rating Conflicts

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.2 to B.4 8-18 All text in these sections
Current text	Study quality rating systems, inter-rater reliability, and procedures for resolving conflicting opinions regarding study quality are not discussed in the Preamble.
Proposed update (revised text)	General comment: Inter-rater reliability and procedures for resolving conflicting opinions regarding study quality among reviewers are important aspects of study quality evaluations in systematic reviews, as flawed ratings could result in biased conclusions. Regardless of the study quality evaluation system used in IARC evaluations, Working Group Members should be provided with detailed guidance for applying them. A pilot phase in which reviewers rate the quality of a subsample of studies would allow for identification of areas of ambiguity, such that more specific guidance or rephrasing of items within the system can be provided to increase inter-rater reliability (University of Alberta, 2012; Oremus *et al*., 2012). For transparency, the detailed guidance and decision rules for the study quality evaluation systems should be provided in the Preamble to inform the public and peer reviewers on how the systems are applied. When conducting reviews, study quality should be assessed independently by a minimum of two Working Group Members with clear justification provided for each decision. Resolution of conflicting opinions among reviewers should be a formalized process in which each reviewer articulates their reasons for choosing specific ratings, and if still no consensus is reached, an additional Working Group Member should be consulted to resolve any scoring issues. This approach has been used for systematic reviews with study quality ratings in the published literature (*e.g*., Goodman *et al*., 2015; Prueitt *et al*., 2014). The specific strategy for conflict resolution can also be tested in a pilot phase, as recently suggested by US EPA in its systematic review framework for TSCA (US EPA, 2018). Overall, the Preamble should be revised to include information on inter-rater reliability, guidance and decision rules for applying study quality evaluation systems, and the specific process for resolution of conflicting opinions regarding study quality.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Goodman, JE; Prueitt, RL; Sax, SN; Pizzurro, DM; Lynch, HN; Zu, K; Venditti, FJ. 2015. "Ozone exposure and systemic biomarkers: Evaluation of evidence for adverse cardiovascular health impacts." *Crit. Rev. Toxicol.* 45(5):412-452.

	Oremus, M; Oremus, C; Hall, GB; McKinnon, MC; ECT & Cognition Systematic Review Team. 2012. "Inter-rater and test-retest reliability of quality assessments by novice student raters using the Jadad and Newcastle-Ottawa Scales." *BMJ Open* 2(4):e001368. doi: 10.1136/bmjopen-2012-001368. Prueitt, RL; Lynch, HN; Zu, Ke; Sax, SN; Venditti, FJ; Goodman, JE. 2014. "Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects." *Crit. Rev. Toxicol.* 44(9):791-822. University of Alberta. 2012. "Validity and Inter-rater Reliability Testing of Quality Assessment Instruments." Report to US Dept. of Health and Human Services (HHS), Agency for Healthcare Research and Quality (AHRQ). Evidence-based Practice Center, AHRQ Publication No. 12-EHC039-EF. March. 106p. US EPA. 2018. "Application of Systematic Review in TSCA Risk Evaluations (Final)." Office of Chemical Safety and Pollution Prevention, Office of Pollution Prevention and Toxics, EPA Document # 740-P1-8001, 248p., May. https://www.epa.gov/sites/production/files/ 2018-06/documents/final_application_of_sr_in_ tsca_05-31-18.pdf

10. Integration Within a Line of Evidence

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.5 through B.6(c) 18-21 All text in these sections
Current text	The Preamble does not provide specific guidance for integrating studies within a given line of evidence. It states that the results of studies for each line of evidence are summarized, and then describes general principles for categorizing each line of evidence as "sufficient," "limited," or "inadequate," with no specific methods for evidence integration.
Proposed update (revised text)	General comment: The general principles for categorizing each line of evidence incorporate study quality, but only in a broad sense (*e.g.*, epidemiology evidence is sufficient if chance, bias, and confounding can be ruled out with reasonable confidence; animal evidence can be sufficient if there is an increased tumor incidence in both sexes of a single species in one well-conducted study). As discussed above, IARC should develop a more formal approach to assessing study quality, and the Preamble should clearly describe how study quality evaluations will be used to weigh the evidence and reach conclusions regarding the strength of each line of evidence. The evidence integration process requires a structured yet flexible method to allow application to different cases and incorporation of all available evidence (Rhomberg *et al.*, 2013). IARC should consider reviewing and adapting portions of other established systematic review and weight-of-evidence frameworks that follow best practices for evidence integration. For example, the recent EFSA *Guidance on the Use of the Weight of Evidence Approach* in scientific

	assessments (EFSA, 2017) describes critical concepts in weight-of-evidence analyses, including consideration of relevance, reliability, and consistency within and across lines of evidence. Various options for causal frameworks are presented, and EFSA emphasizes that in many cases, a single method may not cover all steps, and differing methods (or a combination of methods) may be needed for a given assessment. In addition, IARC should include a discussion of how positive and negative study findings will be reconciled and addressed to draw conclusions regarding causality. The Preamble should clearly describe how Working Groups should consider null or negative data, including results that indicate no biologically or clinically significant effects, when integrating evidence. Study quality should be evaluated for all relevant studies within a given line of evidence, regardless of their results; therefore, all null and negative data should be fully integrated into the evaluation to inform the interpretation of positive data, with appropriate weight given, based on study quality (Rhomberg *et al*., 2013).
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	European Food Safety Authority (EFSA) Scientific Committee. 2017. "Guidance on the use of the weight of evidence approach in scientific assessments." *EFSA J*. 15(8):4971. doi: 10.2903/j.efsa.2017.4971. Rhomberg, LR; Goodman, JE; Bailey, LA; Prueitt, RL; Beck, NB; Bevan, C; Honeycutt, M; Kaminski, NE; Paoli, G; Pottenger, LH; Scherer, RW; Wise, KC; Becker, RA. 2013. "A survey of frameworks for best practices in weight-of-evidence analyses." *Crit. Rev. Toxicol.* 43(9):753-784.

11. Integration Across Lines of Evidence

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6(d) 22-23 All text in this section
Current text	The Preamble does not provide explicit guidance for evidence integration across lines of evidence. Section B.6(d) of the Preamble states that "the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans." The Preamble then describes how the strength of evidence conclusions for each line of evidence should be combined to determine the overall carcinogenicity categorization of an agent.
Proposed update (revised text)	General comment: Categorizing the carcinogenic potential of an agent by combining the conclusions for the strength of each line of evidence amounts to checking off a list of criteria for categorization, and this methodology does not integrate the evidence in a way that allows each line of evidence to inform the interpretation of the others. IARC should not provide guidance for integrating evidence based solely on combining conclusions for each line of evidence; rather, Working Groups should be advised to develop an integration narrative that fully describes

	how the information from each line of evidence supports a given conclusion or an alternative, with an agent's MOA as the central organizing principle for evidence integration (see, for example, the guidelines for integrating evidence in Rhomberg *et al*., 2013). In this way, Working Groups can clearly demonstrate how specific studies or data sources contributed to the final conclusion. This will ensure that the process whereby each Working Group reaches conclusions about exposure, hazard, and/or risk will be well developed and transparent. The guidance for integration across lines of evidence should include a description of how questions of human relevance should be considered, including information on human-relevant exposures, dose-dependent effects, and species-specific differences in endogenous exposures, toxicokinetics, and susceptibility (*e.g*., liver tumors in susceptible strains of mice). The Preamble should be clear with regard to how data should be weighed according to relevance when integrating the evidence. As discussed above, IARC should consider adapting other established systematic review and weight-of-evidence frameworks that follow best practices for evidence integration, which include approaches to account for the evaluation of human relevance in the integration process.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Rhomberg, LR; Goodman, JE; Bailey, LA; Prueitt, RL; Beck, NB; Bevan, C; Honeycutt, M; Kaminski, NE; Paoli, G; Pottenger, LH; Scherer, RW; Wise, KC; Becker, RA. 2013. "A survey of frameworks for best practices in weight-of-evidence analyses." *Crit. Rev. Toxicol.* 43(9):753-784.

12. Evaluation of Mechanistic Evidence

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4 15-18 All text in this section
Current text	General comment: There is limited information on the evaluation of mechanistic evidence in the Preamble. The Preamble states that for each possible carcinogenic mechanism identified, a representative selection of key data is summarized. In addition, there are no specific guidelines for ranking the strength of mechanistic evidence or assessing whether a particular mechanism is relevant to humans.
Proposed update (revised text)	The Preamble explicitly states that not all mechanistic studies need to be cited, but does not give direction on how to identify key mechanistic studies or a representative selection of them. To ensure a transparent and unbiased evaluation, all studies relevant to the carcinogenic mechanism of the agent should be considered in the evaluation, with study quality being the only reason for excluding a particular study. Recently, IARC developed and is currently using a framework to identify and organize mechanistic data around 10 "key" characteristics of known carcinogens (Smith *et al*., 2016). There is no explicit discussion of this

	framework in the current (2006) Preamble. The key characteristics framework does not describe how the quality, external validity, or relevance of the mechanistic evidence should be considered, or how positive and negative findings should be integrated to draw conclusions regarding the likelihood that a substance operates or causes cancer through a given mechanism. The key characteristics framework also does not consider that many of the characteristics are also shared by non-carcinogenic agents, and some might be operative only under specific exposure conditions (*e.g.*, specific route, or high dose only) that are not currently distinguished in *in vitro* assays. It is possible that some evaluated agents could be assumed to have a carcinogenic hazard based on mechanistic evidence alone, even if the epidemiology and animal toxicology evidence do not support this conclusion. Rather than focus on whether agents possess characteristics that are not necessarily specific to carcinogens, IARC should provide clear, explicit guidance for how to consider the totality of the mechanistic evidence, including study strengths and limitations, and how they impact the interpretation of results. This can be achieved by adapting available frameworks that address the issues of study quality and human relevance. The quality of mechanistic studies can be evaluated by adapting study quality frameworks such as the Klimisch System (Klimisch *et al*., 1997) or the related ToxRTool (EC, 2017). The organization and evaluation of evidence in support of a postulated mechanism can be conducted using the WHO/IPCS MOA/HR framework, which has been adopted by international agencies to assist in transparency and consistency in MOA assessments (Meek *et al*., 2014). This framework facilitates a thorough analysis of mechanistic evidence within a larger weight-of-evidence assessment to determine whether any observed MOAs plausibly operate in humans. It is more systematic, clear, and thorough than the IARC key characteristics framework, and could be easily adapted for evaluating mechanistic evidence by IARC Working Groups. IARC should also consider the recently proposed extension of the WHO/IPCS MOA/HR framework by Becker *et al*. (2017), in which a quantitative confidence scoring method is used to evaluate the weight of the evidence in support of a potential MOA for use in hazard characterization. Regardless of the framework chosen by IARC, the Preamble should maintain that the same systematic process for evaluating mechanistic evidence is followed across all Monographs.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Becker, RA; Dellarco, V; Seed, J; Kronenberg, JM; Meek, B; Foreman, J; Palermo, C; Kirman, C; Linkov, I; Schoeny, R; Dourson, M; Pottenger, LH; Manibusan, MK. 2017. "Quantitative weight of evidence to assess confidence in potential modes of action." *Regul. Toxicol. Pharmacol.* 86:205-220.

	European Commission (EC). 2017. "ToxRTool - Toxicological data Reliability Assessment Tool: Instructions for use." Joint Research Centre, Institute for Health and Consumer Protection. 3p. Klimisch, HJ; Andreae, M; Tillmann, U. 1997. "A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data." *Regul. Toxicol. Pharmacol.* 25(1):1-5. Meek, ME; Boobis, A; Cote, I; Dellarco, V; Fotakis, G; Munn, S; Seed, J; Vickers, C. 2014. "New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis." *J. Appl. Toxicol.* 34(1):1-18. Smith, MT; Guyton, KZ; Gibbons, CF; Fritz, JM; Portier, CJ; Rusyn, I; DeMarini, DM; Caldwell, JC; Kavlock, RJ; Lambert, P; Hecht, SS; Bucher, JR; Stewart, BW; Baan, R; Cogliano, VJ; Straif, K. 2016. "Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis." *Environ. Health Perspect.* 124(6):713-721.

13. Evaluation of High-throughput Mechanistic Data

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4(c) 17-18 All text in this section
Current text	The Preamble discusses potential issues with interpreting high-throughput data, but does not provide guidance for evaluation of such data. This includes data from US EPA's ToxCast program and the Tox21 federal agency collaboration, which were initiated after the current Preamble was written in 2006.
Proposed update (revised text)	General comment: The Preamble should provide explicit guidance for incorporating high-throughput data, such as from ToxCast/Tox21 assays, into evaluations of mechanistic evidence. IARC has recently used these data in cancer hazard evaluations, by assigning various ToxCast/Tox21 assays to 7 of the 10 key characteristics of carcinogens (as discussed above in comment 10) using expert judgment and incorporating the assay results into the evaluation of mechanistic evidence (as discussed by Becker *et al*., 2017). This approach is problematic, however, as the assays were not specifically designed to evaluate key stages in chemical-induced carcinogenesis. In addition, this approach has not been explicitly documented and has not been subjected to independent scientific peer review. Using statistical and prediction modeling analyses, Becker *et al*. (2017) found that the current ToxCast/Tox21 assays and datasets do not predict cancer better than chance. In addition, Bus (2017) found a lack of strong supporting evidence for one of the key characteristics (oxidative stress) as a plausible human cancer mechanism in IARC's evaluation of glyphosate. These findings indicate a need for robust, explicit, and transparent procedures to evaluate the relevance and reliability of mechanistic data, including high-throughput data.

	The scientific confidence framework was designed to aid in the development, evaluation, and communication of scientific confidence in Tox21 assays and their prediction models (Cox *et al*., 2014; Patlewicz *et al*., 2015; Cox *et al*., 2016). This framework requires documentation of the justification for a specific decision, with sufficient detail to enable an independent reviewer to replicate the analysis. IARC should consider adopting such a framework to enhance the transparency and rigor of its process for evaluating and integrating mechanistic evidence from high-throughput assays.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Becker, RA; Dreier, DA; Manibusan, MK; Cox, LAT; Simon, TW; Bus, JS. 2017. "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?" *Regul. Toxicol. Pharmacol.* 90:185-196. Bus, BJ. 2017. "IARC use of oxidative stress as key mode of action characteristic for facilitating cancer classification: Glyphosate case example illustrating a lack of robustness in interpretative implementation." *Regul. Toxicol. Pharmacol.* 86:157-166. Cox, LA; Popken, D; Marty, MS; Rowlands, JC; Patlewicz, G; Goyak, KO; Becker, RA. 2014. "Developing scientific confidence in HTS-derived prediction models: lessons learned from an endocrine case study." *Regul. Toxicol. Pharmacol.* 69:443-450. Cox, LA; Popken, DA; Kaplan, AM; Plunkett, LM; Becker, RA. 2016. "How well can in vitro data predict in vivo effects of chemicals? Rodent carcinogenicity as a case study." *Regul. Toxicol. Pharmacol.* 77:54-64. Patlewicz, G; Simon, TW; Rowlands, JC; Budinsky, RA; Becker, RA. 2015. "Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes." *Regul. Toxicol. Pharmacol.* 71(3):463-477.

14. Integration of Mechanistic Evidence

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6(c) to B.6(e) 21-23 All text in these sections
Current text	The Preamble does not explicitly address how mechanistic evidence should be integrated with other lines of evidence. Section B.6(c) states that mechanistic evidence is evaluated and the strength of evidence that any carcinogenic effect observed is due to a particular mechanism is judged to be "weak," "moderate," or "strong." Section B.6(d) notes how mechanistic data fits into the overall classification groups, but there is no specific guidance on how to integrate mechanistic evidence with the evidence in humans and experimental animals.
Proposed update (revised text)	General comment:

	As mechanistic evidence is critical to understanding human cancer hazards, the Preamble should include transparent and systematic guidelines for evaluating and integrating mechanistic evidence in a robust manner, concurrently with other realms of evidence. Most recently, IARC has refined its approach and indicated that mechanistic evidence can be used to up- or down-grade a cancer classification based on human and animal evidence (Guyton, 2015). While mechanistic evidence is an important part of the overall evaluation, it should be given appropriate weight relative to human and animal evidence, and it should be appropriately considered when interpreting human and animal evidence. The evaluation of the weight of the body of mechanistic evidence should be incorporated into the larger assessment that considers mechanistic evidence equally and concurrently with the other lines of evidence to ensure that cancer classifications are based on rigorous, objective, and transparent assessments and integration of mechanistic data.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Guyton, KZ. 2015. "Systematic Identification of the Mechanistic Evidence for Cancer Hazard Assessment: Experience of the IARC Monographs Programme." Presented at the US EPA Advancing Systematic Review for Chemical Risk Assessment Workshop, Arlington, VA, December 16-17. 25p. https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=526753

15. Susceptible Populations

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4(d) 18 All text in this section
Current text	The Preamble does not specify how susceptibility data should be incorporated into carcinogenicity classifications. The only statement made is that evidence that provides some mechanistic understanding of susceptibility (*e.g.*, differences in DNA repair capacity) can increase the strength of evidence from epidemiological data and "enhance the linkage of in-vivo and in-vitro laboratory studies to humans."
Proposed update (revised text)	General comment: The Preamble should specify that studies informing susceptibility (*i.e.*, whether some people are more susceptible to a potential carcinogen than others) should be treated with the same methodological scrutiny as any other line of evidence. As such, data that provide this type of information should be evaluated using the same study quality evaluation criteria as evidence of apical outcomes. Evidence that is deemed robust may be suitable to include in a discussion of populations that may or may not be more sensitive to the carcinogenic effects of an agent; however, it is unclear if and how this evidence should be used in the overall hazard classification conclusions, because these conclusions are intended to be general and not potency-specific.

	The Preamble should also recognize susceptibility when evaluating rodent data, as it is well-recognized that different species/strains are highly susceptible to tumor development in different target organs, and thus results from studies of these animals may not be relevant to humans.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	

16. Presentation of Data and Conclusions for Independent Replication

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 19 16
Current text	The Preamble states that "evaluation of the strength of the evidence for carcinogenicity arising from human and experimental data are made, using standard terms…." and "It is recognized that criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate."
Proposed update (revised text)	General comment: This section of the Preamble is intended to describe the final conclusions of the Monograph, including a description of the findings for each line of evidence and how the evidence is weighed together to reach an overall conclusion regarding carcinogenic hazard. However, the existing Monographs do not always provide consistent descriptions of the rationale for conclusions. The Preamble should require Working Groups to explicitly lay out how each of the conclusions was reached, such that an independent party can replicate the decision-making process. While it is inevitable that scientific judgment will be exercised in reaching conclusions, a baseline set of considerations for the evaluation should be outlined and followed by each Working Group. Some agents may necessitate deviations from these baseline considerations; however, in this section of the Preamble, IARC should explicitly charge each Working Group with providing a written discussion of situations in which scientific judgment was exercised to move away from the baseline considerations and describe all deviations from the methods specified in the Preamble. This process may be aided by the addition of summary tables or other visual representations that aid the reader in understanding how the Working Group reached its conclusions.

	In cases where consensus amongst Working Group Members, with regard to their conclusions, is not achieved, polling should take place. The polling results should be reported in the conclusions section of the Monograph. A two-thirds Working Group majority vote for classification of "Group 1 – carcinogenic to humans" should be required.
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	

17. Independent Peer Review

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 All pages of this section All text in this section
Current text	The Preamble does not discuss procedures for subjecting Monographs to public comment or independent scientific peer review before they are finalized and prepared for publication. The Preamble notes that the current approach involves "peer review" by the same Working Group that authored each draft Monograph.
Proposed update (revised text)	General comment: Currently, there is no public review or independent peer review of draft IARC Monographs by outside experts. This is not consistent with best scientific practices for expert panel-generated reviews of biomedical studies, as exemplified in the procedures for Cochrane Reviews or those conducted by NASEM. Cochrane Reviews are conducted by a group of experts and all are subjected to independent peer review by at least one clinical/topic specialist and one statistician/methodologist to ensure that "…the research question is still valid, to identify whether any relevant and important studies have been excluded, the clinical context is correct and up-to-date, the methodology is appropriate and that the conclusions are based only upon the data available" (Cochrane Collaboration, 2018). NASEM reports undergo independent peer review by anonymous experts who were not involved in the report's preparation, which "provides authors with preliminary reactions from a diverse group of experts and, as a result, enhances the clarity, cogency, and credibility of the final document" (NAS, 2018). Draft IARC Monographs should be subjected to similar peer review. The Preamble should be revised to include the following text: "After each Working Group meeting, all Monographs are considered drafts to be released for a period of at least 60 days for public comment. Each draft Monograph and all relevant public comments are submitted to a group of experts for independent peer review. The peer review experts will be selected by the IARC Director and will not be involved in the Monograph Working Group. Peer reviewers provide written comments and these, along with the public comments, will be evaluated and used to revise the Monograph by the Working Group. The IARC Director will then review the revised Monograph to ensure the revisions are fully

	responsive to all relevant public and peer review comments. If the revisions are not fully responsive, the IARC Director will return the Monograph to the Monographs Programme Section Head for additional revision. Once the Monograph adequately addresses the public and independent peer review comments, the IARC Director will approve the finalization and publication of the Monograph."
Brief rationale for update (max. 200 words)	See above
References, if any (max. 5)	Cochrane Collaboration. 2018. "Cochrane peer review policy." 21p. http://community.cochrane.org/editorial-and-publishing-policy-resource/cochrane-review-management/cochrane-peer-review-policy/cochrane-peer-review-policy-guidance-implementation National Academy of Sciences (NAS). 2018. "Guidelines for the Review of Reports of the National Academies of Sciences, Engineering, and Medicine." http://www.nationalacademies.org/nasem/na_067075.html.

18. Communication to the Public

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 5-6 All text in this section
Current text	When describing the working procedures for the Monographs program, the Preamble does not discuss how the findings and conclusions of IARC Monographs should be communicated to the general public.
Proposed update (revised text)	The conclusion of each Monograph is a classification of an agent's carcinogenic hazard. The Preamble should describe procedures for communicating the findings of each Monograph to the public that emphasizes the nature of Monograph conclusions as hazard classifications that do not consider risks at any specific exposure level, including human-relevant exposures. Classification of carcinogenic hazards alone can lead to public misunderstanding and anxiety (Borgert *et al*., 2015; Boobis *et al*., 2016), and several health organizations have recently had to explain IARC's methodology to the public in order to alleviate unnecessary concern (Boobis *et al*., 2016). Even so, this is not always successful, and the public is left confused. IARC should present its own approach for public communication of Working Group findings in the Preamble. Other organizations have incorporated strategies for public communication into their risk assessment process. For example, US EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* includes development of an approach to communicate conclusions regarding risk characterization to the public and other stakeholders (US EPA, 2014). This approach ensures that communication products are developed to meet the needs of the intended audience, carrying forward key issues and describing conclusions in a lay person's context rather than a technical one.
Brief rationale for update (max. 200 words)	See above

References, if any (max. 5)	Boobis, AR; Cohen, SM; Dellarco, VL; Doe, JE; Fenner-Crisp, PA; Moretto, A; Pastoor, TP; Schoeny, RS; Seed, JG; Wolf, DC. 2016. "Classification schemes for carcinogenicity based on hazard identification have become outmoded and serve neither science nor society." *Regul. Toxicol. Pharmacol.* 82:158-166. Borgert, CJ; Wise, K; Becker, RA. 2015. "Modernizing problem formulation for risk assessment necessitates articulation of mode of action." *Regul. Toxicol. Pharmacol.* 72(3):538-551. US EPA. 2014. "Framework for Human Health Risk Assessment to Inform Decision Making." Risk Assessment Forum. EPA/100/R-14/001, 76p., April.

Dear Kurt,

In following up on below exchange I wanted to submit a comment for consideration by the Advisory group for the Preamble meeting. Unfortunately the Public Comment Form is currently not accessible through the web, and since I am on leave from tomorrow on, please allow me to submit a quick comment via this means for consideration by the Advisory Group.

My comment refers to the criteria for nomination:

The current criteria for selection of agents for review are very broad: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity.
Further consideration and refinement should be given to such broad criteria, taking into account that a lot of advances have been made in the scientific arena since this was formulated, and that more detailed information may be available from other existing scientific and regulatory programmes.

Happy to discuss further if needed, but I would appreciate if this could be consider as official submission of comments.

Many thanks and best regards

Angelika

Dr. Angelika Tritscher
WHO/FOS

Comments in IARC monograph preamble

Professor J. David Miller PhD FAIHA

Carleton University, Ottawa

August 31, 2018

General Principles

In my opinion, the existing preamble is not a good basis for minor edits. My comments therefore cover 14 key areas that I believe need attention. For some recommendations (e.g. articulating a modern and transparent information and review procedure and considering modern scholarship on expert panel function), this may deserve a separate process in consultation with the governing council.

1. The opening paragraph explains that soon after the founding in 1965, "frequent requests were received for advice on the carcinogenic risk of chemicals…"

In 2018, it seems unlikely to me that any government would ask for an analysis of risk not least because this is the province of national authorities. They are best suited to understand conditions and extent of exposure. In addition, at the WHO level, the JECFA and the JMPR are meant to consider exposure in developing their reports related to food and hence comment on risk.

This section of the preamble needs to be re-written to explain that these monographs contain hazard characterizations that can potentially be used in a variety of contexts.

Objective and Scope

2. Eliminate the concept of risk from the text.

3. The current text reads "…information on mechanisms may, however, be used in making the overall evaluation." [citing documents ranging in age from 12-27 years old]. In 2018, it seems irresponsible not to ensure to the extent possible that the mechanism of carcinogenesis in relevant animal models is described carefully and further that it is known to apply in humans. This principle was established a lot time ago with the 2u-globulin rodent carcinogens. The rubric of other cognizant authorities e.g. the US Report on Carcinogens requires mechanism to be considered (see Process for Preparation of the Report on Carcinogens 14th edition, https://ntp.niehs.nih.gov/ntp/roc/content/process_508.pdf).

4. A requirement to incorporate information on the toxicokinetics of the compound or carcinogenic metabolites in relevant animal models and where possible, humans, should be mentioned.

Selection of agents for review

5. As with the WHO Global Burden of Disease, it seems to me most important to spend time on exposures, work environments, dietary or traditional practices (e.g. smoking & etcetera) that mater or might matter the most for public health. It seems to me that the process for selecting agents for review should be re-imagined for the 21st Century. IARC spends a lot of time on the World Cancer Review. I would wish to ensure that any selection process was guided by impact and that information was kept current.

Data for the Monographs

6. These generalities need to be strengthened with a modern vision for literature searching and review. In the interests of transparency, it is not sufficient to offer hand waving such as "reviews all pertinent epidemiological studies and cancer bioassays". The complexity of literature searching is a defining problem for science and regulation. Circa 1980, there were 60,000 papers published in English per year, now it is north of 2 million and most of it is junk.

As a result, protocols such as the OHAT review process have been developed (https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html) around which variants are produced to meet the needs to the task (Arch Toxicol 91:2551; Environ Health Perspect 2018 PMID:30024384). These are similar to those required to draw evidence-based conclusions in medicine such as modified Cochrane review procedures. These outline a transparent step-by-step process for capturing and documenting how literature is to be gathered and included or not included in an evidence-based report. In general, after a search is done by a subject matter expert(s), 2-3 experts on a panel evaluate a number of features against variants of Klimisch criteria (Reg Tox Pharm 25:1) and more than one person extracts data. Increasingly, this process is managed within software such as DistillerLR.

Meeting Participants

7. For reasons I allude to above, the issue of publications defining an expert must be approached with reasonable caution. I think it was easier to identify key subject matter experts 30 years ago than today.

I examined a number of recent monographs and looked at the expertise based on publications and citations in pubmed/scifinder. I found several who, in my opinion, could not be credentialed in a common law court as an expert in the subject.

For what it is worth, people with leading roles in a monograph or other publication should be qualified (education), experienced in the subject under consideration (means a clear publication record in the area that would be recognized by a reasonable person as having impact) and they work within generally accepted rules of the relevant art.

While there are those who believe that people who have worked on a compound should not be involved in a monograph (Int J Epidemiol 39:1679), this entails the perverse implication that all scientists are motivated by self-interest (Int J Epidemiology 40:253). To go in that direction

would go against all post war experience in the design and operation of international processes that have implications for trade and the economy.

Bias is everywhere (Human & Exper Tox 24:161) and the best work comes from the most qualified and experienced people finding and carefully reviewing the best available evidence and indulging in vigorous debate to resolve differences (Environ Health Perspect 2018 PMID:30024384).

The Harvard Professor Michele Lamont among others have shown that in expert panels, people tend to defer to the person members regard as the most expert. This emphasizes the critical role of a strong chair to ensure that all reasonable effort is made to elicit comment from the shy but also the lazy who might not have done their homework.

There is an immense literature on the working of expert panels funded by US and EU agencies as well as by academic granting agencies. In view of the economic impact of some monographs, it would seem important to understand this literature more carefully for lessons learned. This, in my view, would be better than using language like "the strongest possible process" in public communications.

Objective and scope

8. Referring to comment 3, the language that mechanism "may be used" needs to be eliminated and an indication that a mechanism (adverse outcome pathway) must be articulated to the extent possible. I would hope that a monograph would not consider a compound unless a reasonable understanding of the mechanism was documented.

Scientific Review and evaluation.

9. In my opinion, the section on 'occurrence and exposure' needs clarification. By comparison to JECFA or JNPR, the exposure sections in monographs are typically selective and not representative. In both JECFA and JNPR and certainly national agencies, those responsible for assessing exposure have skills in the analytical quality of data, dietary or time activity patterns and the relevant statistical modelling. Reliable information is needed on exposure to assess risk which I posit should be outside the scope of a monograph. What is needed is a sense of (1) the relative size of the population who might be materially affected and (2) whether exposure at levels that have resulted in cancer in relevant animal models could be achieved even within a threshold of concern perspective. There are 2A carcinogens, rightly or wrongly classified, that it exposure would have to be very higher than those in relevant animals or higher than at which other acute effects could be seen.

10. Quality of studies considered

As indicated above, transparency as to the quality of studies can only be achieved by a formal risk of bias process.

If the primary epidemiological or animal data are not available, it seems to me that the reviewers should contact the author and ask for it. My experience is that such requests if made by a bona fide researcher are often granted. Major funding agencies and some journals often require data be available. This is important because a number of governments require that the data from studies used to make economically important decisions must be available for other researchers to re-analyze.

11. The language about biomarkers is framed in terms of papers that are 14-27 years old. In my opinion, biomarkers should not normally be used for decision-making unless they can be interpreted in the context of the human toxicokinetics (e.g. Environ Health Perspect 123:A166).

12. In my opinion, the language concerning the quality of the animal studies needs to be framed in a formal protocol.

13. The long sections on animal data were fine 10-20 years ago but surely the immense effort to consider the relevance of animal models in relation to human data needs to be reflected in new text.

14. Finally, it seems to me that the classification 'probably carcinogenic' versus 'possibly carcinogenic' involves a lot of opinion. While the current text states the two terms have "no quantitative' difference, the linguistic difference is immense. The OED states: "a sentence adverb qualifying a whole statement: almost certainly." In contrast, the OED indicates that possibly means "Qualifying a statement, and expressing contingency or uncertainty (cf. possible adj. 3): according to what may be (as far as one knows); perhaps, maybe."

This speaks to a crucial issue in public policy in common law jurisdictions namely to clearly illustrate the uncertainty in plain language around a decision. Where are the uncertainties, what would it take to resolve them & etcetera.

In my opinion, the classifications largely make sense but with both 2A and 2B, it would be important to illustrate uncertainties and context.

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Dr Michael Wilde
Your principal affiliation	University of Kent, United Kingdom
If another party suggested that you submit this nomination, please identify	Click here to enter text.
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Attached.

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.2(f) 11 46
Current text	"Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations."
Proposed update (revised text)	"Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations. However, where considerations of biological plausibility affect the interpretation of the epidemiological data, care should be taken to ensure that the same considerations are not employed in a mechanistic upgrade or downgrade, at the risk of overstating the evidence. A systematic set of procedures for incorporating mechanistic evidence in a principled way is given in Parkkinen et al (2018). "
Brief rationale for update	In a discussion of whether there is sufficient

(max. 200 words)	epidemiological data for carcinogenicity in humans, an appeal is currently made to the role of the viewpoints on causation provided by Austin Bradford Hill [B.2(f), p.11, l.28]. One of the viewpoints appealed to here is biological plausibility, which might depend upon mechanistic evidence [B.2(f), p.11, l.46]. However, if mechanistic evidence is given a role in both the interpretation of the epidemiological data as well as in upgrading the combined results of the evidence in experimental animals and evidence in humans, then there is a worry that the mechanistic evidence is being double-counted, that is, the same evidence influencing the overall classification more than once. To avoid these sorts of problems, a systematic set of procedures for incorporating mechanistic evidence in a principled way has been developed in Parkkinen et al (2018). It would be helpful to include a reference to this text.
References, if any (max. 5)	Parkkinen, V. P., Wallmann, C., Wilde, M., Clarke, B., Illari, P., Kelly, M.P., Norrell, C., Russo, F., Shaw, B., Williamson, J. (2018) *Evaluating Evidence of Mechanisms in Medicine*. Springer.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4(b) 15 36-37
Current text	"To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer."
Proposed update (revised text)	"To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. Mechanistic studies influence the classification by confirming or disconfirming specific mechanism hypotheses. There are a wide variety of such hypotheses. Examples include: • the ten key characteristics of carcinogenicity (Smith et al., 2016); • the hypothesis that an agent belongs to a class of agents for which one or more members have been classified in Group 1 or Group 2A; • the hypothesis that any pathways of carcinogenicity proceed via one or more other agents that are under consideration or have been previously classified in Group 1 or Group 2A. The mechanistic working group may consider any specific mechanism hypothesis that is relevant to the classification of the agents in question. Explicit guidance on evaluating the evidence for mechanism hypotheses is given in Parkkinen et al (2018)."
Brief rationale for update	Currently, there are 11 specific mechanism hypotheses

(max. 200 words)	that influence IARC classifications: • The ten key characteristics of carcinogenicity; • The 'mechanistic class' hypothesis. However, discussions at the recent evaluation of styrene and styrene-7,8-oxide showed that: • These 11 hypotheses should not be thought of as exhaustive; • It will be difficult to formulate an exhaustive list. In this recent evaluation, human studies were judged inadequate, but animal studies were sufficient. This leads to a preliminary overall classification of 2B. A further specific mechanism hypothesis was strongly supported by mechanistic studies and was accepted by the mechanistic working group: • SMH: Styrene only causes cancer, if it does at all, via the metabolic intermediary styrene-7,8-oxide. This yielded a problem: • Human and animal evidence led to a preliminary rating of 2A for styrene and 2B for styrene-7,8-oxide. That is, styrene is probably carcinogenic and styrene-7,8-oxide is possibly carcinogenic but *not* probably carcinogenic. • Yet, given SMH, the probability of styrene-7,8-oxide being carcinogenic must be at least that of styrene being carcinogenic. Therefore, the danger arose that the classifications for styrene and styrene-7,8-oxide would be inconsistent, in the context of SMH. In the end, some members of the working groups recognised this problem and the classification of styrene-7,8-oxide was upgraded to 2A. This prevented inconsistency of classifications, but it was clear that the current preamble did not fully capture this line of reasoning. There is nothing wrong with this line of reasoning and it would be advisable to update the preamble to accommodate the role of hypotheses such as SMH. There are two options for updating the preamble: a. Admit a twelfth kind of specific mechanism hypothesis, of which SMH is an instance; or b. Admit any specific mechanism hypothesis that is relevant to the classification of agents under consideration. We would suggest option (b), because it is future-proof. SMH reflects only one kind of connection between two agents. Other connections might be more complex, particularly when carcinogenicity proceeds along multiple metabolic pathways. More generally, it is good to be as explicit as possible about the methods employed. One way of doing this is

	to mention explicitly the reliance upon the ten key characteristics of carcinogenicity. Another way is to provide some guidance on how mechanism hypotheses are to be evaluated.
References, if any (max. 5)	Smith, M. T., Guyton, K. Z., Gibbons, C. F., Fritz, J. M., Portier, C. J., Rusyn, I., et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environmental Health Perspectives*, *124*, 713–21. Parkkinen, V. P., Wallmann, C., Wilde, M., Clarke, B., Illari, P., Kelly, M.P., Norrell, C., Russo, F., Shaw, B., Williamson, J. (2018) *Evaluating Evidence of Mechanisms in Medicine*. Springer.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 3 12 35-38
Current text	"Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6)."
Proposed update (revised text)	"Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Pert B, Section 6). Indeed, this practice has been defended as an instance of mechanism-based extrapolation (Wilde and Parkkinen 2017). Advice on how to evaluate evidence of mechanisms for the purposes of mechanism-based extrapolation is given in (Parkkinen et al 2018)."
Brief rationale for update (max. 200 words)	There is some debate about the relevance to humans of findings of carcinogenicity in animals (LaFolette and Shanks (1995) "Two models of models in biomedical research," *Philosophical Quarterly*, 45(179): 141-160). In addition, there has been debate about the extent to which evidence of mechanisms can provide evidence that findings in animals are relevant to humans (Howick et al (2013) "Problems with using mechanisms to solve the problem of extrapolation," *Theor Med Bioeth*, 34: 275-291). However, in response to these debates, some have provided a defence of the practices of IARC (Wilde and Parkkinen 2017). It might be helpful to cite this reference here, as a justification for the practice of using mechanisms to support the relevance of finding in animals to humans. It might also be a good idea to provide some explicit advice on how evidence of mechanisms should be evaluated for the purposes of mechanism-based extrapolation, by providing a reference to the advice given in Parkkinen et al (2018).

References, if any (max. 5)	Wilde, M. and Parkkinen, V.P (2017) "Extrapolation and the Russo-Williamson thesis," *Synthese*: https://doi.org/10.1007/s11229-017-1573-y. Parkkinen, V. P., Wallmann, C., Wilde, M., Clarke, B., Illari, P., Kelly, M.P., Norrell, C., Russo, F., Shaw, B., Williamson, J. (2018) *Evaluating Evidence of Mechanisms in Medicine*. Springer.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 4 15 12-14
Current text	"Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and humans."
Proposed update (revised text)	"Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and humans by a process of mechanism-based extrapolation (Wilde and Parkkinen 2017)."
Brief rationale for update (max. 200 words)	There is some debate about the relevance to humans of findings of carcinogenicity in animals (LaFolette and Shanks (1995) "Two models of models in biomedical research," *Philosophical Quarterly*, 45(179): 141-160). In addition, there has been debate about the extent to which evidence of mechanisms can provide evidence that findings in animals are relevant to humans (Howick et al (2013) "Problems with using mechanisms to solve the problem of extrapolation," *Theor Med Bioeth*, 34: 275-291). However, in response to these debates, some have provided a defence of the practices of IARC (Wilde and Parkkinen 2017). It might be helpful to cite this reference here, as a justification for the practice of using mechanisms to support the relevance of finding in animals to humans.
References, if any (max. 5)	Wilde, M. and Parkkinen, V.P (2017) "Extrapolation and the Russo-Williamson thesis," *Synthese*: https://doi.org/10.1007/s11229-017-1573-y.

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Sarah Lawley
Your principal affiliation	Government of Canada
If another party suggested that you submit this nomination, please identify	
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Attached

2. Proposed update to the Preamble to the *IARC Monographs*

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.1 1 26
Current text	its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.
Proposed update (revised text)	its present form, *IARC Monographs on the Identification of Human Carcinogens*.
Brief rationale for update (max. 200 words)	The Monograph program identifies human carcinogens – it is not a hazard assessment or risk assessment process. The title should reflect the content accurately to support the public in understanding the content.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.1 1 41
Current text	The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of

	each individual Working Group.
Proposed update (revised text)	The Preamble is a statement of scientific principles and working procedures to be used in Monograph meetings to ensure consistency across Monograph evaluations. [Delete remainder of paragraph.] [ADD: IARC needs to add, here or in the appropriate section of the document, what the working procedures are. This at minimum should include: the Working Group applies a set of pre-specified criteria to ensure that the scientific information on which the evaluation is based is robust and reliable, and that the working procedures of each sub-group follow a set of guidelines to ensure that it is objective, rigorous, and consistent. More detailed information could be in the Preamble or, if too lengthy, in a referenced and publicly available document.]
Brief rationale for update (max. 200 words)	The Preamble should contain working procedures. In turn, the working procedures must contain explicit, detailed instruction on the process that IARC follows. This is crucial for scientifically responsible advice and consistent practices across Monographs, particularly given IARC's efforts to include scientists who work in countries that have been under-represented in past Advisory Groups – as the makeup of the groups becomes more varied, it becomes more critical to ensure that everyone is working from the same baseline and has the same interpretation of scientific rigour. It may be necessary to have one broader level of guidance, which is always used, included in the preamble, along with a statement that any additional guidance provided to adapt to the agent under consideration must be made public for transparency. If detailed working procedures are too lengthy to include directly in the Preamble, it could reference another publicly available document (similar to the RoC handbook).
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.2 2 20-21
Current text	The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title.
Proposed update (revised text)	The *Monographs* are an exercise in [DEL: ~~evaluating~~] [ADD: identifying] cancer hazards [DEL: ~~despite the historical presence of the word 'risks' in the title~~].

Brief rationale for update (max. 200 words)	The title of the *Monographs* should be changed to reflect the nature of the exercise. Once accomplished, this sentence can be revised without the caveat.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.2 2 30-32
Current text	The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.
Proposed update (revised text)	The Preamble [DEL: ~~continues the previous usage of~~] [ADD: uses] the phrase 'strength of evidence' [DEL: ~~as a matter of historical continuity~~], although it should be understood that Monographs evaluations consider studies that support a finding of [DEL: ~~a cancer hazard~~] [ADD: carcinogenicity] as well as studies that do not.
Brief rationale for update (max. 200 words)	If 'strength of the evidence' is accurate, it should be used in the Preamble without the need for a historical justification. If it is not accurate, the appropriate term should be substituted. The Monograph program <u>identifies</u> human carcinogens and language should consistently reflect this.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	5 A.2 2 37-43
Current text	Information on mechanisms may, however, be used in making the overall evaluation. As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.
Proposed update (revised text)	[Insert text, as appropriate, that refers to the framework currently used by IARC.]
Brief rationale for update	IARC currently uses a framework with 10 key

(max. 200 words)	characteristics to identify and organize mechanistic data (see Goodman and Lynch 2017), but as the framework is not referenced in the preamble it is not available as context for users of the Monographs. We note that it is referenced in the Instructions to Authors (last public update March 2017) – however, if it is a standard tool of the Working Group, it should be referenced in the Preamble so that readers are aware of how the evidence is being organized and assessed. The framework was published by Smith et al in Environmental Health Perspectives (124 (6) (2016), pp. 713-721) as **Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis** (https://ehp.niehs.nih.gov/15-09912/).
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	6 A4 3 6-15
Current text	The Monographs are used by national and international authorities to make risks assessments, formulate decisions concerning preventive measures, provide effective cancer control programs and decided among alternative options for public health decisions.
Proposed update (revised text)	The Monographs [DEL: ~~are~~][ADD: could be] used by national and international authorities…
Brief rationale for update (max. 200 words)	National or international authorities could have different sources of information or procedures/processes to make their assessments or decisions. The Monographs is not the only one. The change proposed brings more congruence to the whole paragraph considering that in the second part it talks about the sovereignty of countries to make their own regulatory decisions.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A4 3 40-42
Current text	Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Proposed update (revised text)	The Preamble needs to be clearer about how this happens, what is pertinent, what are the criteria for inadequate or irrelevant – see further comments on section B below.
Brief rationale for update (max. 200 words)	
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A5 4 26-31
Current text	Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.
Proposed update (revised text)	Working Group Members generally have published significant research [DEL: ~~related to the carcinogenicity of the agents being reviewed, and~~] [ADD: investigating the sources, carcinogenic hazard, and toxicological mechanisms of the agent being evaluated. This could include, but may not be limited to, individuals who have published significant work investigating agent source(s), and/or carcinogenic hazards in human (i.e., epidemiologic studies), and/or carcinogenic effects in experimental animals, and/or mechanisms underlying carcinogenicity and any related toxicological properties (e.g., genetic toxicity).] IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views. [Appropriate additional text to be identified by meeting experts – necessary language could be included here or placed in another, referenced, document.]
Brief rationale for update (max. 200 words)	First addition more accurately captures the expertise of Working Group Members. For additional text request: It is critical that the Working Group members be adequately qualified and that the selection process addresses any potential unevenness in the strengths of the members. IARC should establish clear guidelines for baseline qualifications for participation in a

	Working Group, as well as specifications to ensure that each Working Group has adequate diversity of expertise to cover all issues that could arise in the assessment. IARC should also provide clarity on roles and responsibilities of the Chair and sub-chairs of the Working Group. This would include the role of the Chair in acclimating Working Group members to the IARC processes, and making clear rules, expectations, and baselines to support common understanding in areas where interpretations can widely differ (e.g. scientific process). The sub-group chairs should also outline the obligations of each of the sub-group members, clarifying responsibilities including any tasks to take place before the Working Group Meeting. Prior to the beginning of each session of a Working Group, the IARC Secretariat and the Working Group Chair should work with each other to facilitate a 'calibration' session that allows members to properly understand all of the above context. The Working Group should not begin their analysis until this session is complete and all members understand the IARC processes and their individual roles and responsibilities.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A6 5 30-31
Current text	…. and participants are selected by IARC staff in consultation with other experts.
Proposed update (revised text)	…. and participants are selected by IARC staff in consultation [ADD: and coordination] with [DEL: ~~other experts~~][ADD: the Working Group Chair].
Brief rationale for update (max. 200 words)	It is unclear who the "other" experts are. The selection of members is so critical that the Preamble has to be clear about who and how decisions are made on the composition of the working groups.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A6 5 31-35

Current text	Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.
Proposed update (revised text)	[Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on [DEL: ~~carcinogenesis~~] [ADD: agent sources and carcinogenic hazard, including, but not necessarily limited to, information pertaining to human carcinogenic hazard from epidemiologic studies, carcinogenicity information from experimental (i.e., animal) studies, and information pertaining to pathophysiologic mechanisms underlying observed hazard.] [ADD: IARC will identify publicly-available information using bibliographic] [DEL: ~~, including data storage and~~] retrieval systems such as PubMed [ADD: , Scopus and the Web of Knowledge]. [DEL: ~~Meeting participants who are~~] [ADD: Working Group Members will be] asked to [DEL:~~prepare preliminary working papers for specific sections are expected to~~] supplement the IARC literature searches [DEL: ~~with their own searches~~] [ADD: as required].
Brief rationale for update (max. 200 words)	The current text does not sufficiently outline how IARC or Working Group Members should collect data from recognized sources of information, or set expectations for any standard operations. While some instructions are available in the IARC Monographs Instructions to Authors (most recent public update March 2017), more detail is necessary, and the existence of these instructions should be noted in the Preamble. 1. It is important to ensure that no relevant data are missed – clear mechanisms and processes for data gathering should be outlined, similar to the methods for identifying relevant literature as outlined in the NTP's RoC Handbook (p. 9). The level of detail in the Instructions to Authors is not sufficient. IARC should also make use of the appropriate modern tools to optimize the processes – for example, systematic review processes. Pages 12-14 of the NTP's ROC Handbook are an example of excellent guidance for a literature search strategy. Given that collection of <u>all</u> pertinent information is a challenge (particularly for grey literature), IARC must provide some sort of guidance regarding an effective and complete search strategy. 2. It is important for the data gathering process to be transparent so that the public can understand how and why

	choices were made. If detailed instructions are too lengthy to include directly in the Preamble, it could reference another publicly available document (similar to the RoC handbook).
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 5 36-44
Current text	Industrial associations, labor unions and other knowledgeable organization may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade, market research publications and, in some cases, by direct contact with industries.
Proposed update (revised text)	Industrial associations, labor unions and other knowledgeable organization may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. [ADD: Relevant unsolicited input from industrial associations, labor unions and other knowledgeable organization may be considered]. Information on production and trade is obtained from governmental, trade, market research publications and, in some cases, by direct contact with industries.
Brief rationale for update (max. 200 words)	This would allow the public share input on the subject of production and use, and could enhance the information available to the Working Group.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 6 18-20
Current text	The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* program website soon after the meeting.
Proposed update (revised text)	
Brief rationale for update (max. 200 words)	We note that there is a concern about the length of time between the summary being posted (immediately after the conclusion of the Working Group meeting) and the Monograph being published. We wonder if some of this concern might be alleviated by publishing a slightly longer

	summary of the exercise (e.g. five pages rather than one) immediately after the conclusion of the Working Group Meeting, which could include a brief summary noting the key studies used as the basis for the evaluation. This might provide an early sense of how the decision was arrived at.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.2(b) 6 30-39
Current text	The scope of the IARC monographs has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Overtime the structure of a Monograph has evolved to include the following sections:
Proposed update (revised text)	The scope of the IARC monographs [DEL: ~~has expanded beyond chemicals to~~] includes complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. [DEL: ~~Overtime the~~] [ADD: The]structure of a Monograph [DEL: ~~has evolved to~~] includes the following sections:
Brief rationale for update (max. 200 words)	These changes will bring the Monograph to the present instead of evoking what it was before.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.2(b) 9-10 20-14
Current text	Entire section
Proposed update (revised text)	[Appropriate replacement text to be identified by meeting experts – necessary language could be included here or placed in another, referenced, document. May include: Working Group members will be expected to use expert judgment to evaluate the scientific quality and pertinence of publically-available information. Critical evaluations of available information should consider source reliability, study design and/or experimental approach, use of appropriate controls, data analysis and interpretation methodology, and any sources of potential bias or conflict of interest.]
Brief rationale for update	The current text does not sufficiently outline how Working

(max. 200 words)	Group Members should consider the quality of studies reviewed. 1. It is important to have agreement on the baseline criteria that underlay the quality of a study (e.g. risk of bias assessment). More specific instructions or specifications should be provided to ensure that each working group has a set of consistent principles to evaluate the pertinence and quality of the available literature, similar to methods extensively outlined in the NTP's RoC Handbook (pp. 23-40). Monograph Working Group Members currently undertake this process in an ad hoc manner without any explicit IARC guidance. 2. It is important for the process of evaluating the quality of studies to be transparent and consistent. Recognizing that some content-specific considerations will differ depending on the agent, each Working Group should utilize consistent principles to document any specific deviations used from the standard Monograph process. If detailed instructions are too lengthy to include directly in the Preamble, it could reference another publicly available document (similar to the RoC handbook).
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.3 12-13 45-2
Current text	Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted.
Proposed update (revised text)	This text needs to be clearer about how this happens, what is pertinent, what are the criteria for inadequate or irrelevant – see further comments on this section below.
Brief rationale for update (max. 200 words)	
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.3.a 13 30-38
Current text	
Proposed update (revised text)	[Appropriate replacement text to be identified by meeting experts – necessary language could be included here or

	placed in another, referenced, document. May include: Working Group members will be expected to use expert judgment to evaluate the scientific quality and pertinence of publically-available information. Critical evaluations of available information should consider source reliability, study design and/or experimental approach, use of appropriate controls, data analysis and interpretation methodology, and any sources of potential bias or conflict of interest.]
Brief rationale for update (max. 200 words)	The current text does not sufficiently outline how Working Group Members should consider the quality of studies considered. Section B.3 should include a section on this similar to Section B.2(b) for humans for the following reasons: 1. It is important to have agreement on the baseline criteria that underlay the quality of a study. More specific instructions or specifications should be provided to ensure that each working group has a set of consistent principles to evaluate the quality of the available literature, similar to methods outlined in the NTP's RoC Handbook (pp. 58-67). 2. It is important for the process of evaluating the quality of studies to be transparent. Recognizing that the process will differ depending on the agent, each Working Group should document and share the process that they use for each Monograph. If detailed instructions are too lengthy to include directly in the Preamble, it could reference another publicly available document (similar to the RoC handbook).
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.3 15 Before line 11
Current text	N/A
Proposed update (revised text)	[Appropriate additional text to be identified by meeting experts – necessary language could be included here or placed in another, referenced, document.]
Brief rationale for update (max. 200 words)	This section should include information on criteria for causality (similar to section B.2(f)), and all pertinent information pertaining to the mechanisms underlying human carcinogenic hazard. It may be appropriate to move text from section B.6.(b), lines 25-31, and to then expand on it. The example of the NTP's RoC Handbook (pp. 68-69) may be useful.

	It is important for the Working Group Members to have clear principles regarding criteria for causality to support their analysis and to ensure consistency within the Monograph Programme.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4 15 15-17
Current text	The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited.
Proposed update (revised text)	The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. [Insert appropriate additional text to be identified by meeting experts (or reference guidance) giving direction on how key studies will be identified and defining 'representative studies.']
Brief rationale for update (max. 200 words)	It is important for clarity, consistency, and transparency that the methods used to identify 'representative studies' are specified, and that the definition of 'representative studies' is agreed. If this needs to change based on the agent, a process should be identified by each Working Group and the process used should be public with the Monograph.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4(b) 15-17 (Full section)
Current text	(Full section)
Proposed update (revised text)	[Appropriate additional text to be identified by meeting experts – necessary language could be included here or placed in another, referenced, document.]
Brief rationale for update (max. 200 words)	IARC provides author instructions regarding the use of a framework for identifying and organizing mechanistic data around 10 specific characteristics of carcinogens. Within the preamble, this framework should be referenced, and language should be included or referenced that provides guidance on how Working Group Members can integrate both positive and negative findings on these characteristics into the overall assessment.

	It is important for both consistency and transparency that there be clear guidance so that Working Group Members can appropriately assess the relevance of information on these characteristics, and so that the public understands how the information is applied. If detailed guidance are too lengthy to include directly in the Preamble, it could reference another publicly available document (similar to the RoC handbook).
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.4 N/A N/A
Current text	N/A
Proposed update (revised text)	[Appropriate additional text to be identified by meeting experts – necessary language could be included here or placed in another, referenced, document. May include: Working Group members will be expected to use expert judgment to evaluate the scientific quality and pertinence of publically-available information. Critical evaluations of available information should consider source reliability, study design and/or experimental approach, use of appropriate controls, data analysis and interpretation methodology, and any sources of potential bias or conflict of interest.]
Brief rationale for update (max. 200 words)	The current text does not sufficiently outline how Working Group Members should consider the quality of the mechanistic data considered. Section B.4 should include a section on this for the following reasons: 1. It is important to have agreement on the baseline criteria that underlay the quality of a study. More specific instructions or specifications should be provided to ensure that each working group has a set of consistent principles to evaluate the quality of the available literature. 2. It is important for the process of evaluating the quality of studies to be transparent. Recognizing that the process will differ depending on the agent, each Working Group should document and share the process that they use for each Monograph. If detailed instructions are too lengthy to include directly in the Preamble, it could reference another publicly available document (similar to the RoC handbook).

References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 22 29-32
Current text	The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.
Proposed update (revised text)	[Would it be possible for the Advisory Group to consider ways to make this nuance in classification more clear, so that it could be better understood by the public?]
Brief rationale for update (max. 200 words)	
References, if any (max. 5)	

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Fraize-Frontier, S. Roth, C. Ormsby, J-N. Lasfargues, G.
Your principal affiliation	Anses
If another party suggested that you submit this nomination, please identify	
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A.6 5 31-33
Current text	Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed.
Proposed update (revised text)	Subsequently, relevant biological and epidemiological data are collected by IARC from at least two recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed.
Brief rationale for update	According to current international

(max. 200 words)	guidelines, the literature search has to be carried out in, at least, two recognized sources of information
References, if any (max. 5)	ANSES (2017). Illustrations et actualisation des recommandations pour l'évaluation du poids des preuves et l'analyse d'incertitude à l'Anses. Maisons-Alfort, Anses. CIHR (2010). A Knowledge Synthesis Chapter, Canadian Institutes of Health Research (CIHR). OHAT (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration Research Triangle Park, N.C., NIEHS.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B 6 22
Current text	
Proposed update (revised text)	The literature search process as well as the subsequent selection process of the retrieved studies on which the weight of the evidence is based, must both be detailed by IARC, then validated or revised by the working group.
Brief rationale for update (max. 200 words)	The literature search and study selection processes are key steps of any scientific review. As they are not conducted by the Working Group itself, they must be detailed and endorsed or, if necessary, revised by the Working Group.
References, if any (max. 5)	ANSES (2016). Évaluation du poids des preuves à l'Anses : revue critique de la littérature et recommandations à l'étape d'identification des dangers. Maisons-Alfort, Anses. OHAT (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration Research Triangle Park, N.C., NIEHS. EFSA (2017). Guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal. Parma, Italy, European Food Safety Authority (EFSA).

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B 6 34

Current text	1. Exposure data 2. Studies of cancer in humans 3. Studies of cancer in experimental animals 4. Mechanistic and other relevant data 5. Summary 6. Evaluation and rationale
Proposed update (revised text)	1. Literature search and selection of studies 2. Exposure data 3. Studies of cancer in humans 4. Studies of cancer in experimental animals 5. Mechanistic and other relevant data 6. Summary 7. Evaluation and rationale
Brief rationale for update (max. 200 words)	As the literature search and selection of studies is an essential step of a scientific review, it is important to specifically include it in the Preamble.
References, if any (max. 5)	ANSES (2016). Évaluation du poids des preuves à l'Anses : revue critique de la littérature et recommandations à l'étape d'identification des dangers. Maisons-Alfort, Anses. CIHR (2010). A Knowledge Synthesis Chapter, Canadian Institutes of Health Research (CIHR). EFSA (2017). Guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal. Parma, Italy, European Food Safety Authority (EFSA).

Location of text to be updated:	
Section (from A.1 to B.6(e))	B.1
Page number (1−25)	7
Line number (1−47)	1
Current text	
Proposed update (revised text)	1. Literature search and selection of studies Each Monograph describes the different steps and results of the process of literature search and study selection. In particular, the criteria for selecting studies are communicated. The results of the whole process (from literature search to study inclusion) are summarized in the form of a PRISMA figure.

	(a) Identification of studies This paragraph details the different data sources queried, the date and publication period covered of the queries and the search equations or, at least, the keywords used. It is important that the literature search is not too restrictive so as not to miss any important scientific contributions to the evaluation of the agent under investigation. This may however lead to retrieving studies that are not pertinent to the scope of the work. (b) Screening of retrieved studies This first step of the selection process of the studies retrieved via the literature search is based on the title, the abstract, the keywords and, if applicable, the table of contents of the scientific publications or reports detailing the study. The aim of the screening step is to identify and exclude those retrieved studies that are not pertinent to the scope of the work, eg they deal with the subject of interest, that the study period is appropriate, etc. The step is carried out through the use of specific exclusion criteria that are presented in the Monograph. (c) Eligibility of studies Once the non-pertinent studies have been excluded, this second step of study selection is based on a review of the full-text of the associated retrieved scientific publications or reports of the study. The aim of this step is to select those studies that do not have very major flaws regarding in particular the study design and data analysis including the definition of the studied population, the disease of interest, the considered exposure, the consideration of confounding factors ant possible temporal effects. These different elements will inform as well the causality relationship evaluation. This second selection step is carried out through the use of specified criteria that are presented in the Monograph.

	(d) Inclusion of studies Those studies that pass the above two-step selection process are used as input for the next steps of the appraisal that also takes account of the intrinsic quality of each study included.
Brief rationale for update (max. 200 words)	The above-proposed four-step process is widely recommended in the current internationally recognized methodological guidance documents. It transparently provides all the information needed to appreciate and evaluate the process used to the available evidence that will be assessed in the next steps. If this information is not clearly communicated in the Monograph, the credibility of the work could be questioned.
References, if any (max. 5)	ANSES (2016). Évaluation du poids des preuves à l'Anses : revue critique de la littérature et recommandations à l'étape d'identification des dangers. Maisons-Alfort, Anses. CIHR (2010). A Knowledge Synthesis Chapter, Canadian Institutes of Health Research (CIHR). OHAT (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration Research Triangle Park, N.C., NIEHS. Liberati, A., et al. (2009). "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration." PLoS medicine **6**(7).

1. Name and affiliation of commenter

Your name	Daniele Wikoff
Your principal affiliation	ToxStrategies
If another party suggested that you submit this nomination, please identify	American Beverage Association
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Submitted

2. Proposed update to the Preamble to the *IARC Monographs*

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.1 2 3 – first text addition
Current text	*Proposed update involves text/topics not currently addressed in the Preamble.*
Proposed update (revised text)	NEW TEXT TO BE INSERTED To ascertain consistency in approach, elevate transparency, and enhance credibility of IARC monographs, a formalized process for updating the Preamble will follow the WHO Handbook for Guideline Development (WHO, 2014).. *Subsequently, it is suggested that an entire new section be added to provide specific, formal guidance on how and when Preamble updates will be conducted*.
Brief rationale for update (max. 200 words)	Currently, the Preamble appears to be inconsistently and sporadically revised or updated. The current draft does not contain information regarding the specific method by which the Preamble itself should be updated. A transparent, specific methodology by which the Preamble would be modified and/or updated would provide consistency for future updates. IARC should consider following a formalized guideline process document such as the WHO (2014) document in developing the revised IARC Preamble. This guidance is intended for any WHO department, program or staff member wishing to produce a guideline; members of a WHO guideline steering group; members of a WHO guideline development group (GDG); members of a WHO guideline external review group; and anyone interested in understanding how WHO develops guidelines. Following a formalized process such as that suggested by the WHO (2014) would assist the IARC monograph program in ensuring the Preamble's consistency, transparency, and accountability as well as its credibility.

References, if any (max. 5)	WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.1 2 3 – second text addition
Current text	*Proposed update involves text/topics not currently addressed in the Preamble.*
Proposed update (revised text)	NEW TEXT TO BE INSERTED The process for updating the Preamble will include multiple opportunities for stakeholder and public comment.
Brief rationale for update (max. 200 words)	The current IARC preamble does not specifically address how and when public or stakeholder comments will be collected, considered, and reflected on in the monograph development process. The Preamble should specifically identify multiple points in the update process when public and stakeholder comments will be collected, how it will be collected, and subsequently how it will be disseminated, evaluated, and integrated into the process.
References, if any (max. 5)	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.1 2 3 – Third text addition
Current text	*Proposed update involves text/topics not currently addressed in the Preamble*
Proposed update (revised text)	NEW TEXT TO BE INSERTED During public comment periods, all public commenters will be provided equal opportunity to submit and/or present comment. All comments submitted to IARC will be made publicly available (including made available to the Advisory Group), and all comments will be formally considered by the Advisory Group as part of the update process.
Brief rationale for update (max. 200 words)	Available information from IARC suggest that only "pertinent" public comments and/or only selected individuals from the public will reach the Advisory Group; it is recommended that the process be updated to allow both the Advisory Group and the IARC to consider all public comments. Per the IARC Q&A (May 18, 2018), online comments can be submitted, but only "Pertinent comments will be made to the Advisory Group…" Thus, it is unclear which comments are "pertinent" or whether all public comments will be equally considered. Additionally, while the scientific webinar provides another mechanism by which comments can be made, the selection of participants appears to be at the discretion of IARC and will be based on experts solicited from IARC and from the public nominations of presenters (which suggests that not all of those interested in providing comment will have equal opportunity to do so). It is recommended that the process be updated to allow equal opportunity for all commenters, and that the Advisory Group formally consider all public comments and allow for these comments to be posted for viewing.
References, if any (max. 5)	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.1 2 3 – fourth text addition
Current text	*Proposed update involves text/topics not currently addressed in the Preamble*
Proposed update (revised text)	NEW TEXT TO BE INSERTED In updating the Preamble, IARC will include diverse group of individuals in the process, e.g., stakeholders, experts in systematic review, carcinogenicity, exposure assessment, metabolism, biochemistry, molecular biology, computational toxicology, epidemiology, and animal toxicology.
Brief rationale for update (max. 200 words)	The IARC appears to have only solicited experts in cancer evaluation for the Advisory Group experts and presenters for the scientific webinar for the Preamble update, despite the Preamble content's focus on the process, approach, and principles underlying such assessments. Such a narrow focus does not allow for a holistic review of the Preamble. Many entities have described the need for multidisciplinary experts in developing guidelines and similar documents. For example, the WHO (2014) Handbook for Guideline Development describes guideline development group members as relevant technical experts, end-users, and experts in assessing evidence and developing guidelines. Similarly, external review groups are described as needing technical experts, end-users, program managers, advocacy groups and individuals affected by the condition addressed in the guideline, among other stakeholders. It is recommended that the IARC monograph program ensure the Preamble is updated by a group that represents a diverse group of stakeholders, experts in systematic review and also experts in all aspects of the carcinogenicity evaluation, including mechanisms (metabolism, biochemistry, molecular biology, computational toxicology, etc.) epidemiology and experimental animal evaluations of carcinogenicity (i.e., the subjects of the monograph sections) as well as exposure assessment.
References, if any (max. 5)	WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC National Academies of Sciences, Engineering, and Medicine. 2017. Using 21st Century Science to Improve Risk-Related Evaluations. Washington, DC: The National Academies Press. doi: 10.17226/24635. National Academies of Sciences, Engineering, and Medicine. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. doi: 10.17226/18764.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.1 1 41
Current text	The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous Monograph meetings but remain, predominantly, the prerogative of each individual Working Group.
Proposed update (revised text)	NEW TEXT TO BE INSERTED In an effort to provide transparent, comprehensive, and consistent evaluations of potential human carcinogenicity, the Preamble has been updated to reflect both the scientific principles as well as the systematic procedures and decision criteria that are implemented to achieve the principles. *Additional, and substantial, text needs to be drafted to address descriptions of the procedures that will be followed to achieve the principles. Such text should be included throughout the Preamble (several specific aspects addressed in these comments). In particular, procedures for literature identification and selection, data extraction, critical appraisal, evaluation of evidence, integration of the totality of the evidence are needed.* *Each section should contain sufficient detail to describe both scientific principles as well as procedures such that they are transparent, rigorous, and reproducible. Descriptions should address procedures that occur prior to the monograph meeting, at the meeting, and subsequent to the meeting – and should address the role of the IARC Secretariat and Working group in carrying out the principles and procedures*
Brief rationale for update (max. 200 words)	The Preamble is commonly described by the IARC staff and IARC publications as being a means of providing a transparent and comprehensive document (e.g., Cogliano et al., 2003, 2005), despite the lack of detail on principles and procedures of the evaluation process.

	The information in the current Preamble does not sufficiently describe the scientific principles applied to evaluating the carcinogenicity of an agent. The scientific principles provided are vague, leading to ambiguous inclusion/exclusion of information, inconsistent interpretation of available evidence, and lack of transparency in the synthesis of the evidence in determining conclusions. Recognizing the need to be agnostic to any particular agent or type of agent, clarification and/or significantly more detailed descriptions of how evidence is identified, appraised, and integrated relative to overall conclusions are needed. As part of adding more detail regarding the principles, the procedures or process for implementing the principles should be explicitly laid out. Notably, there is no specification of working procedures outside of the preamble, which is a major issue related to lack of transparency – and undoubtedly leads to inconsistency in how the principles are interpreted and implemented by various working groups. Most significantly, substantial additions are needed to address the procedures for literature identification and selection, data extraction, critical appraisal, evaluation of evidence, integration of the totality of the evidence - as well as the role(s) of the IARC Secretariat and working groups in carrying out these procedures. Updates should reflect a more transparent and comprehensive statement of principles, decision criteria, and operating procedures.
References, if any (max. 5)	Cogliano V, R Baan, K Straif, Y Grosse, B. Secretan, F El Ghissassi,P Boyle, WHO IARC. 2005. Transparency in IARC Monographs. Lancet Oncol. 6:747. Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. Hoffmann, S., de Vries, R.B.M., Stephens, M.L., Beck, Dirven, H., Fowle, J.R., 3rd, Goodman, J.E., Hartung, T Kimber, I., Lalu, M.M., Thayer, K., Whaley, P., Wikoff Tsaioun, K., 2017. A primer on systematic reviews in toxicology. Arch Toxicol 91, 2551-2575.

	WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED Title [*and throughout the Preamble*] Title [*and throughout the Preamble*] Title [*and throughout the Preamble*]
Current text	Title: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Each instance of the use of the term "risk"
Proposed update (revised text)	NEW TEXT TO BE INSERTED *All monograph titles, including text within the Preamble, should be revised to reflect the replacement of the term "risk" with "hazard".* IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans • The term "risk" should be replaced with the term "hazard" throughout the Preamble. *Additionally, to ensure there is no confusion when interpreting the IARC monograph carcinogenicity classifications which reflect hazard assessments (not risk), the following text should also be included in the Preamble at the outset:* "Any IARC classification should not be viewed as a substitute for a regulatory review and/or risk assessment. The IARC classifications only address hazard –one of four components of risk assessment, and thus only a part of the information typically considered by regulatory bodies in risk characterization and decision-making. National regulatory agencies should conduct an appropriate risk assessment before decisions are made as to whether risk mitigation measures are warranted." *Other changes should include:* [INSERT on line 13, p.3] - "However, risk assessments are not conducted by IARC but left to regulatory authorities in the various nations"…
Brief rationale for update (max. 200 words)	Confusion regarding the use of the term "risk" continues to increase; this term should be replaced with "hazard" to more appropriately characterize the

	underlying scientific process and reduce public confusion. While the issue regarding the use of the term "risk" has been deliberated in the past, the IARC Monographs still retains the term "risk" in their title. The 2015 IARC Monographs Q&A points out their cancer classifications are hazards, not risks: *"IARC classifies carcinogens in five categories ... The classification indicates the weight of the evidence as to whether an agent is capable of causing cancer (technically called "hazard"), but it does not measure the likelihood that cancer will occur (technically called "risk") as a result of exposure to the agent."* The Preamble acknowledges "*The Monographs are used by national and international authorities to make risk assessments*…" and "*these evaluations represent only one part of the body of information on which public health decisions may be based*." It is important that authorities have clear definitions of what the output represents such that they can appropriately utilize the Monographs in evaluations of risk. It is critical the preamble reflect the underlying scientific process – which is only of hazard identification (not risk).
References, if any (max. 5)	2015 IARC Monographs Q&A document. http://monographs.iarc.fr/ENG/News/Q&A_ENG.pdf. Accessed 10 May 2018. International Programme on Chemical Safety (IPCS). 2004. IPCS Risk Assessment Terminology. World Health Organization. Boobis, A.R., S.M. Cohen, V.L. Dellarco, J.E. Doe, P.A. Fenner-Crisp, A. Moretto, T.P. Pastoor, R.S. Schoeny, J.G. Seed, and D.C. Wolf. 2016. Classification schemes for carcinogenicity based on hazard identification have become outmoded and serve neither science nor society. Reg. Tox. Pharmacol. 82:158-166.

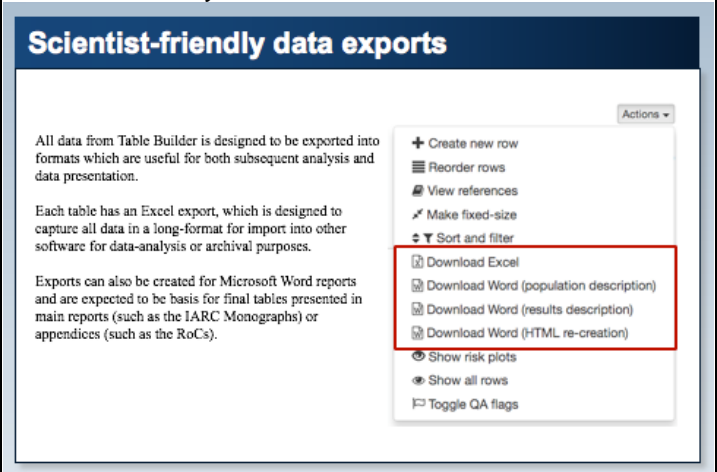
Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B. 6 21
Current text	*[Proposed update involves text/topics not currently addressed in the Preamble.]*
Proposed update (revised text)	Similar to procedures being implemented by public health agencies globally, the IARC Preamble scientific principles and procedures have been updated to integrate the practice of evidence-based reviews conducted systematically in order to provide evidence-based monographs produced with rigor, transparency, and reproducibility in the monograph process. Evidence-based practice involves systematic reviews, meta-analyses as well as other 'state-of-the-science' techniques, which utilize a predefined, multistep process to identify, select, critically assess, analyze and synthesize evidence from the totality of scientific studies to reach a conclusion. Evidence-based reviews based on high quality (i.e., valid and reliable), relevant studies will improve the consistency, transparency, and objectivity when conducting assessments on the overall strength of the totality of evidence.
Brief rationale for update (max. 200 words)	Evidence-based reviews (e.g., systematic reviews, meta-analyses) are the current "state-of-the-science" approach for conducting assessments, utilized by entities globally (including those that fund the IARC monograph program); the IARC Preamble should integrate the practice of systematic reviews to provide greater rigor, transparency, and reproducibility. Systematic reviews are methods by which to answer a specific research question that uses a predefined, multistep process to identify, select, critically assess, analyze and synthesize evidence from scientific studies to reach a conclusion. It is different from a systematic search as it uses a structured process to critically appraise individual studies and to develop conclusions. As an ever-evolving field, the standards for conducting literature-based evaluations have improved significantly since the last IARC Preamble update. Evidence-based systematic reviews have long-been used in the fields of medicine and other scientific disciplines and have now become the "state-of-the-science" method used by regulatory agencies

	worldwide - including the U.S. Environmental Protection Agency, European Food Safety Authority, National Toxicology Program's Office of Health Assessment and Translation OHAT, and the World Health Organization among others to conduct assessments.
References, if any (max. 5)	AMSTAR. 2017. https://amstar.ca/. Cochrane. 2018. https://www.cochrane.org/. Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. National Toxicology Program. 2015. Systematic Review. https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html. WCRF. 2007. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. AICR; Washington, DC.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	REVISED TEXT WITH INSERTIONS A.6 6 13
Current text	IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.
Proposed update (revised text)	REVISED TEXT WITH INSERTIONS IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. ~~The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent~~. When unanimity is not achieved by the Working Group Members, the chair will poll Working Group Members to determine the diversity and rationale of differing scientific opinion. The IARC Secretariat will document majority and minority views, including descriptions of key evidence upon which the Working Group Members rely on for such opinions. The IARC Secretariat will also document how consensus is reached when it is not readily apparent from the initial polling (this information will be recorded in the final Monograph for the given agent). Specific documentation of the position of each Working Group will also be provided when consensus is not readily apparent (i.e., opinions of the epidemiological working group vs. the exposure working group); while all Working Group members have an equal vote, the expertise of Working Group members relative to the differing scientific opinions is important context when weighing the totality of the evidence. The IARC Secretariat will ensure that no particular member(s) of the Working Group have undue influence on other members during the consensus evaluation. No consensus is achieved when dissenting

	views are significant based on the underpinning science and/or the minority view is strongly supported. [*Additionally, the term "consensus" needs to be defined, along with the process for achieving consensus as part of the weight of evidence analyses – particularly when there are majority and minority views. Text regarding documentation of working group opinions and votes (particularly dissenting opinions and rationale) should also be directed to be included in the Preamble.]*
Brief rationale for update (max. 200 words)	There is significant ambiguity regarding "consensus" – the Preamble should be refined to specifically define "consensus," the process used to determine consensus (including consideration of both qualitative and quantitative analyses), as well as to instruct reporting of working groups opinions (particularly dissenting opinions and rationale). Details are not provided on the process itself in the Preamble or what determines when a "consensus" has been reached, and how this relates to determining (and documenting) a majority or minority, or any dissenting views. The current Preamble acknowledges the possibility of diversity on scientific opinion; the procedures for documenting the differences and underlying issues, as well as subsequent discussions and decisions, should be included as part of the scientific principles of determining the weight of the evidence.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A6 5 26
Current text	*An entire section of new text should be added to address the principles and procedures for providing drafts of planning documents, literature search findings, analyses, and draft monographs for transparency and public comment.*
Proposed update (revised text)	NEW TEXT TO BE INSERTED Planning documents, literature search findings (including comprehensive lists of included/excluded articles with rationale), analyses conducted by IARC Secretariat or working group members (e.g., meta-analyses) and draft monographs will be made available for public comment. Final versions of such supporting documents and information will be included in the Monographs. All data considered by the IARC Secretariat and the Working Group members will be publicly available via Table Builder exports and open access to HAWC workspaces for each agent. Public comments on planning documents, literature search findings, analyses, and draft monographs shall be considered by the Working Group. Additionally, each Monograph Meeting will have a public call for data which will allow for submission of relevant information that may not be in the peer-review literature but would be relevant to a Working Group assessment.
Brief rationale for update (max. 200 words)	Due to the limited transparency in planning, conduct, and development of IARC monographs, it is recommended that a public review component be included in the principles of the Preamble such that planning documents, literature search findings, evidence tables, draft summaries, and draft monographs be subject to public comments and comments be considered by the working groups. With respect to the underlying evidence reviewed, the IARC could easily make this information publicly available with the toggle of a switch to make the HAWC workspace publicly available, and by making

	exports from Table Builder files publicly available (i.e., the IARC is already using collaborative platforms which organize the evidence and make it readily available to others). *Example from Shapiro et al., 2017 demonstrating the relative ease of making monograph evaluation materials readily available*:  Having a process similar to the National Toxicology Program's Report on Carcinogen process, or any other major public health entity (e.g., USEPA, USFDA, EFSA), would increase transparency and ultimately the clarity of work products issued by the Monograph Program.
References, if any (max. 5)	National Toxicology Program. 2015. Handbook for Preparing Report on Carcinogens Monograph. US Department of Health and Human Services. Shapiro A, Lunn R, Jahnke G, Schwing P, Guyton K, Loomis D, and Guha N. 2017 Table builder: A content management system for carcinogenicity health assessments for the IARC Monographs and the NTP Report on Carcinogens. Presented at: 4th International Symposium on Systematic Review and Meta-Analysis of Laboratory Animal Studies. Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC.

	U.S. Environmental Protection Agency. 2018. Strengthening Transparency in Regulatory Science. Proposed Rule. 83 FR 18768 Health Assessment Workspace Collaborative (HAWC). http://hawc.readthedocs.io/en/latest/index.html

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.4 3 40-44
Current text	Each Monograph reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. A Monograph does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.
Proposed update (revised text)	REVISED TEXT for lines 40-41 Each Monograph reviews all pertinent epidemiological studies, cancer bioassays in experimental animals, and other relevant data (including mechanistic evidence), and considers cursory exposure information. REVISED TEXT for lines 43-44 A Monograph does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4)~~. Only those data considered by the Working Group to be relevant to making the evaluation are included.~~; however, all data meeting inclusion/exclusion criteria will be identified and rationale for use be provided as part of the monograph. NEW TEXT TO BE INSERTED All data will be identified using a systematic approach. Pertinent epidemiological studies, cancer bioassays in experimental animals, other relevant data (including mechanistic data), and exposure studies, will be determined via implementation of processes developed *a priori* and documented in a protocol for each agent. As part of the protocol, a detailed search strategy will be developed, validated, and documented *a priori* by an Information Specialist. The search strategy will include syntax specific to each database (e.g., MeSH in PubMed), a list of databases (including grey literature sources if included), and dates of searching. The strategy will also detail the process for screening titles,

	titles and abstracts, as well as full text against inclusion/exclusion criteria. Such criteria will be developed to specifically characterize populations, exposures, comparators, and outcomes for inclusion/exclusion. These criteria will be developed *a priori* by the IARC Secretariat and reviewed and approved by working group members prior to implementation. [*Suggested text addresses systematic literature search methodology concepts such as: more detailed and transparent search strategy using an information specialist; inclusion of multiple literature databases (including grey literature); use of formal search strategy; documentation of literature search and strategy process; timing of search strategy prior to data call-in; utilization of the Health Assessment Workplace Collaborative (HAWC) or similar type of collaborative workspace*. *Additionally, the search and findings should be made public on the IARC website prior to and as part of the monograph assessment*]
Brief rationale for update (max. 200 words)	The Preamble is void of transparency principles and procedures related to systematic and objective identification of key studies. Consistent with the standards of conducing comprehensive reviews and identifying evidence in a systematic manner, the principles and procedures for identification of all studies considered in the monograph (not just epidemiological and animal studies) should be transparent and reproducible. The *a priori* approach documented in the protocol should include the literature search strategy as well as inclusion and exclusion criteria for each agent. The protocol should be informed by an information specialist, reviewed and approved by the working group, and made publicly available. The IARC would receive more useful information during the call for data if the search strategy and findings were published along with the call for data.

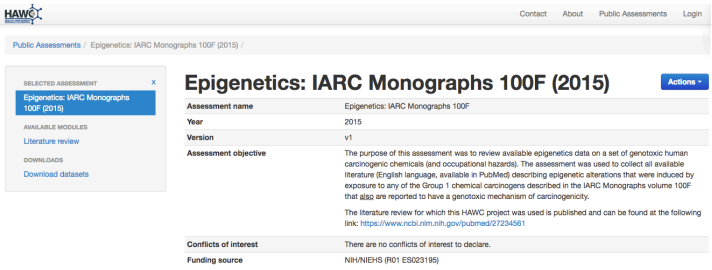
References, if any (max. 5)	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25086.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.4 4 1
Current text	Only those data considered by the Working Group to be relevant to making the evaluation are included.
Proposed update (revised text)	All data pertinent to the evaluation of "other relevant data" (as determined *via* inclusion/exclusion criteria applied during the identification of studies, and meeting data quality criteria requirements) will be considered by the Working Group. Those data pertaining to an adverse outcome pathway that is relevant to the specific outcome under evaluation will be given more weight. *Additionally, it is suggested to revise the scientific principles to reflect definitions and/or criteria for determining which mechanistic data are relevant.*
Brief rationale for update (max. 200 words)	The preamble is currently void of scientific principles related to what is "relevant"; clear descriptions of what should be considered relevant (or not) are required. Two key points of particular issue are: 1) All available data that are identified during the literature search (which by default should capture data relevant to the evaluation) must be considered by the working group. That is, data sets should not be "cherry-picked." 2) Data should be evaluated using the adverse outcome pathway approach. In doing so, the specific outcome (cancer type) should be considered in determining relevancy in the weight of evidence analysis. Providing scientific principles and criteria related to determination of which mechanistic data are "relevant" (e.g., inclusion/exclusion criteria, those that address relevant adverse outcomes) would improve the transparency and reproducibility of the identification and

	evaluation of mechanistic data used to down- or up-grade classifications.
References, if any (max. 5)	Fay, K.A., Villeneuve, D.L., LaLone, C.A., Song, Tollefsen, K.E., Ankley, G.T., 2017. Practical approaches to adverse outcome pathway developm and weight-of-evidence evaluation as illustrated b ecotoxicological case studies. Environ Toxicol Ch 1429-1449. LaLone, C.A., Ankley, G.T., Belanger, S.E., Embı M.R., Hodges, G., Knapen, D., Munn, S., Perkins, Rudd, M.A., Villeneuve, D.L., Whelan, M., Willet Zhang, X., Hecker, M., 2017. Advancing the adve outcome pathway framework-An international hor scanning approach. Environ Toxicol Chem 36, 14 1421. Fay, K.A., Villeneuve, D.L., Swintek, J., Edwards Nelms, M.D., Blackwell, B.R., Ankley, G.T., 201 Differentiating Pathway-Specific From Nonspecif Effects in High-Throughput Toxicity Data: A Fou for Prioritizing Adverse Outcome Pathway Develo Toxicol Sci 163, 500-515.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	REVISIONS TO EXISTING TEXT AND NEW TEXT TO BE INSERTED. A.4 4 4-7
Current text	Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.
Proposed update (revised text)	REVISE on line 4, p.4 – Data from government agency reports that can be made ~~are publicly~~ available should ~~are~~ also be considered. ~~Exceptionally, d~~ Additionally, doctoral theses and other material that are in their final form and publicly available may be reviewed. *Additional text is needed to identify sources of high-throughput data, such as ToxCast/Tox21, that may be utilized.*
Brief rationale for update (max. 200 words)	Clarification regarding criteria for inclusion based on peer-review or public availability are needed. For example, if doctoral theses are accepted, studies submitted for regulatory approval (e.g., GLP, guideline-based studies) and provided to IARC would presumably also be included. Clarification regarding the sources of, as well as the peer-review status (and similar considerations) of HTS data are also needed.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated:	NEW TEXT TO BE INSERTED
Section (from A.1 to B.6(e))	A.6
Page number (1−25)	7
Line number (1−47)	33
Current text	…relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed.
Proposed update (revised text)	NEW TEXT TO BE INSERTED IMMEDIATELY AFTER '… such as PubMed.' Identification of relevant biological, epidemiological, and other relevant data will be based on a search strategy. The syntax and databases queried, as well as the date of searches, will be documented and reported in the monograph. Screening and selection of studies will be based on the inclusion/exclusion criteria refined for the agent, also reported in the monograph. Subsequent collection, evaluation, and storage of pertinent epidemiological studies, cancer bioassays in experimental animals, other relevant data (including mechanistic data), and exposure studies will be transparently facilitated via the Health Assessment Workspace Collaborative (HAWC) (or similar documentation and auditing tool). Results of the search and screening (including lists of included/excluded studies, along with rationale) will be provided for public comment, working group consideration, and will be included in the final monograph.
Brief rationale for update (max. 200 words)	It is recommended that the Preamble be updated to direct the generation of a formal search strategy (including search syntax, databases, dates, etc) and that the resulting strategy be included in planning documents (via agent-specific protocols) provided to the public prior to conducting the search and assessment. The IARC Monograph Program would receive more useful information during the call for data if the search strategy and findings were published along with the call for data.

	Given that the IARC monograph program utilizes the Health Assessment Workplace Collaborative (HAWC), making the search strategy and findings of such public would be as simple as a toggle of a switch. Use of these tools can facilitate transparency and allow for materials to be displayed for viewing on the web. It is recommended that the IARC monograph program utilize this feature, similar to what was employed in monograph 100F (https://hawcproject.org/assessment/185/). 
References, if any (max. 5)	Health Assessment Workspace Collaborative (HAWC). http://hawc.readthedocs.io/en/latest/index.html.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.4 3 41, 43
Current text	Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.
Proposed update (revised text)	NEW TEXT TO BE INSERTED IMMEDIATELY AFTER CURRENT TEXT The relevancy of the study will be determined as part of the literature search process, and specifically each study will need to comply with all inclusion criteria per the protocol (i.e., meet criteria for relevancy). All included studies will subsequently be reviewed and appraised for study quality and validity using the criteria described [*REFERENCE SECTION FOR SPECIFIC STUDY QUALITY – SEE SUBSEQUENT COMMENT*]. Those judged to be inadequate will not be further reviewed; rationale for exclusion based on quality or inadequacy will be documented and included in the final monograph. *In addition, it is suggested that an entire section for new text be added to address the scientific principles – including the specific criteria - for determining and documenting adequacy and relevancy for all study types.*
Brief rationale for update (max. 200 words)	The Preamble is currently void of specific scientific criteria employed to determine relevancy and adequacy of studies. The scientific principles in the Preamble should include the generation, implementation, and reporting of inclusion/exclusion criteria for determining relevancy and well as criteria for determining adequacy (which are assumed to be based on study quality and validity). The scientific principles as well as the process that should be utilized to comply with such principles related to inclusion/exclusion of studies are not sufficiently addressed in the current preamble. Notably, it acknowledges that each working group

	selects what they find to be relevant (which is not consistent with a systematic or evidence-based approach). Additional criteria or descriptions are needed to provide sufficient detail and consistency to the IARC Secretariat(i.e., those initially identifying studies) and to inform working group determinations of what constitutes exclusion based on inadequacy and/or irrelevancy. This is especially of importance to evaluations of complex agents where exposure may not be well-identified or characterized, thus emphasizing the need for clear definitions of what is considered adequate or relevant. It is recommended that the scientific principles in the Preamble be updated to indicate the criteria and process used to transparently and consistently characterize adequacy and relevance as it relates to how each study is reviewed (or not reviewed), cited (or note cited), etc.
References, if any (max. 5)	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/25086.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.2.b 9 19 – First text addition
Current text	(b) Quality of studies considered
Proposed update (revised text)	*The Preamble should be revised to include formal, defined criteria for evaluation of internal and external validity of study quality. An entire new section (not drafted as part of these comments) is needed to describe these criteria.* *In addition to the definitions, the scientific principles for applying and integrating such data quality criteria should also be included. An entire section (not drafted as part of these comments) is needed to describe how to apply the data quality criteria*. *The additional NEW text may read as follows*: Study quality will be evaluated according to [INSERT REFERENCE TO NEW SECTION ON STUDY QUALITY CRITERIA]. It will be appraised by [INSERT REFERENCE TO NEW SECTION ON HOW TO IMPLEMENT STUDY QUALITY] In brief, each study will need to meet minimum criteria for inclusion: [INSERT DESCRIPTION]. All other studies will have clearly documented descriptions of the outcome of study quality appraisal. For example, epidemiological literature will only be considered to meet minimum criteria if exposure has been adequately measured using objective techniques, confounding (on a topic-specific basis) has also been accounted for, and outcome (cancer) was assessed using an objective and reliable technique. Subsequently, all included epidemiological studies would also be characterized for these quality domains, with descriptions and categorizations as to the adequacy for which exposure, confounding, and outcome assessment were evaluated in the original study. Appraisal of study quality on a study-specific basis will be conducted prior to the working group meetings, with documentation provided in the monograph. When a large volume of evidence is available, studies will be placed into study quality tiers

	and the weight-of-evidence shall be driven primarily by those studies in the top study quality tiers.
Brief rationale for update (max. 200 words)	While the preamble alludes to evaluation of study quality, it does not provide clear criteria or principles to do so. The preamble should provide structured criteria for evaluation of study quality via assessment of internal and external validity such as practiced by regulatory and health authorities globally. Because each set of evaluations is done by a different working group and staff within the IARC, the preamble should include additional specific criteria to evaluate study validity (internal), adequacy, and reliability of each study type. **The scientific principles for how bias domains (e.g., confounding, exposure, outcome, selection) are to be critically appraised <u>for every study</u> - as part of an evaluation of potential systematic error and consequently potential impact on direction and magnitude of results - need to be included along with how study quality will be integrated into the weight of evidence assessment when all data are considered in totality.** The IARC monograph program is encouraged to consider approaches being utilized by regulatory authorities across the globe for evaluating study quality, e.g., "assessment of adequacy" practiced by the European Chemicals Agency via REACH, or evaluation of study validity via risk of bias practiced by USEPA, EFSA, NTP and others.
References, if any (max. 5)	Schunemann, H.J., Cuello, C., Akl, E.A., Mustafa, R.A., Meerpohl, J.J., Thayer, K., Morgan, R.L., Gartlehner, G. R., Katikireddi, S.V., Sterne, J., Higgins, J.P., Guyatt, G. Group, G.W., 2018. GRADE guidelines: 18. How ROBI and other tools to assess risk of bias in nonrandomized st should be used to rate the certainty of a body of evidence Clin Epidemiol. Guyatt, G.H., Oxman, A.D., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., Montori, V., Akl, E.A., Djulbegovic, B., Falck-Ytter, Y., Norris, S.L., Williams, J.W., Jr., Atkins, D., Meerpohl, J., Schunemann, H.J., 2011. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 64, 407-415.

	Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect. 2014;122(7):711-71. Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. EFSA, 2015. Tools for critically appraising different stu designs, systematic review and literature searches.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.2.b 9 19 – Second text addition
Current text	(b) Quality of studies considered
Proposed update (revised text)	NEW TEXT TO BE INSERTED *The Preamble should be revised to include formal, defined criteria for evaluation of external validity and relevancy to the assessment of human carcinogenicity.* *In addition to the definitions, the scientific principles for applying and integrating consideration of external validity as part of inclusion/exclusion should likewise be inserted as text along with how such evaluations relate to the weight of evidence determinations in the context of the totality of the evidence*.
Brief rationale for update (max. 200 words)	Because each set of evaluations is done by a different working group, and different staff within the IARC Secretariat, the preamble, having clear criteria for evaluation and integration of external validity as part of inclusion/exclusion as well as the weight of the totality of the evidence would improve the quality and consistency of the IARC monographs. The text in the current preamble also alludes to aspects relevant to the external validity of a study, another common element to formalized evaluations of study quality – assessment of the directness (or indirectness) of evidence. That is, how generalizable, relevant, or how "fit for purpose" is the evidence for evaluating, in this case, the potential for human carcinogenicity. Revisions to the preamble should also include formal, systematic assessment of the external validity.
References, if any (max. 5)	Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Grade guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol. 2011;64(12):1303-1310. Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect. 2014;122(7):711-71.

	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.6 19 15
Current text	6. Evaluation and rationale
Proposed update (revised text)	*Revise Section 6 adding text to clearly include the principles, as well as how these principles will be evaluated and integrated in the assessment of the totality of the evidence.* *New text relative to elaboration of principles may read:* To improve transparency of the overall process as well as the workflow and consistency of evaluations by individual workgroups and to provide a reproducible reporting format for the monographs, a structured approach for evidence integration and assessments on weighing the totality of the evidence is utilized. The following aspects will be considered in evaluating the totality of the scientific evidence and determining the strength of that evidence: • Risk-of-bias; • Consistency (as well as unexplained inconsistency); • Dose-response; • Magnitude; • Study quality; • Etc.” *Additional text is required to describe the exhaustive list of appropriate principles and how each of these will specifically be defined, assessed, and integrated*.
Brief rationale for update (max. 200 words)	Having clear criteria and processes for integrating evidence and conducting the weight of evidence analysis would improve the quality and consistency of the IARC monographs. Currently, Section 6 primarily provides definitions of the categories of carcinogenicity, but it does not provide scientific principles related to how the findings from Section 5 should be interpreted relative to the categorical conclusions. That is, there is no guidance as to how aspects related to study quality, consistency, confounding, bias, or temporality (elements described as important in other sections of the Preamble) are integrated.

	It is recommended that Section 6 be expanded to include: • Criteria to be evaluated for each body of evidence (e.g., risk of bias, consistency, dose-response, magnitude and other appropriate criteria) as well as for the overall body of evidence; • descriptions of how evaluation criteria for a body of evidence relate to the "strength" of the totality of the evidence; • defined criteria as to when and how quantitative meta-analyses would be conducted and how these meta-analyses would be integrated in developing conclusions; and descriptions of how the accuracy of qualitative and quantitative analyses are confirmed. A structured approach to evidence integration would improve transparency of the overall process, improve the workflow and consistency of evaluations by individual workgroups, and provide a reproducible reporting structure for the monographs.
References, if any (max. 5)	Guyatt, G., Oxman, A.D., Akl, E.A., Kunz, R., Vist, G., B J., Norris, S., Falck-Ytter, Y., Glasziou, P., DeBeer, H., Jaeschke, R., Rind, D., Meerpohl, J., Dahm, P., Schunema H.J., 2011. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64, 383-394. Morgan, R.L., Thayer, K.A., Bero, L., Bruce, N., Falck-Y Y., Ghersi, D., Guyatt, G., Hooijmans, C., Langendam, M Mandrioli, D., Mustafa, R.A., Rehfuess, E.A., Rooney, A. Shea, B., Silbergeld, E.K., Sutton, P., Wolfe, M.S., Wood T.J., Verbeek, J.H., Holloway, A.C., Santesso, N., Schune H.J., 2016. GRADE: Assessing the quality of evidence in environmental and occupational health. Environ Int 92-93 616. EFSA., 2017. Guidance on the use of the weight of eviden approach in scientific assessments. EFSA Journal, p. 4971 Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science

	assessments. Environ Health Perspect. 2014;122(7):711-71.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.2.f. 11 28
Current text	After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965).
Proposed update (revised text)	After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results will be considered and excluded with reasonable certainty. In addition, all studies included in the weight of evidence analysis in the context of the totality of the evidence should (a) be consistent with an estimate of effect significantly and meaningfully greater than unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is significantly and meaningfully greater than unity, and (c) have a narrow confidence interval, due to sufficient population size. Applicability of available evidence of the potential for carcinogenicity based on several epidemiological studies may apply only to some type(s) of cancer, to the dose levels reported or evaluated by the original study authors, and to the intervals between first exposure and disease onset observed in these studies and cannot be extrapolated beyond. These elements – as well as the elements of study quality described above – will be specifically considered by the working group and documented in the monograph. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965).

Brief rationale for update (max. 200 words)	The preamble should direct that considerations of study quality as well as all considerations of causality be equally applied to all studies (regardless of outcome). For each element of causality, full descriptions of evidence as it relates to the element should be provided. For example, temporality should include descriptions of the evidence which supports or evaluates such, as well as evidence that does not support.
References, if any (max. 5)	EFSA., 2017. Guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal, p. 4971 Guyatt, G., et al., 2011. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64, 383-394 Weed, D.L., 2005. Weight of evidence: a review of con and methods. Risk Anal 25, 1545-1557. Lutter, R., Abbott, L., Becker, R., Borgert, C., Bradley, Charnley, G., Dudley, S., Felsot, A., Golden, N., Gray, Juberg, D., Mitchell, M., Rachman, N., Rhomberg, L., Solomon, K., Sundlof, S., Willett, K., 2015. Improving of evidence approaches to chemical evaluations. Risk A 186-192. Rhomberg, L., 2015. Hypothesis-Based Weight of Evid An Approach to Assessing Causation and its Applicatio Regulatory Toxicology. Risk Anal 35, 1114-1124.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.2 2 30
Current text	The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that Monographs evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.
Proposed update (revised text)	[*Additional text is needed to describe the scientific principles and process to integrate all of the available evidence.*]
Brief rationale for update (max. 200 words)	The IARC preamble indicates that evaluations consider studies that support a finding of cancer hazard as well as studies that do not; however, there is no description of the scientific principles that describe how this is defined or implemented in practice. Strength of evidence should consider elements of causality as well as confidence in the underlying evidence. Importantly, strength of evidence should include consideration of dose as it relates to interpretation of findings particularly from high-dose chronic bioassays in experimental animals and the relevance of modes of action to human exposure.
References, if any (max. 5)	Guyatt, G., et al., 2011. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summar findings tables. J Clin Epidemiol 64, 383-394. Gaylor, D.W., 1992. Relationship between the shape dose-response curves and background tumor rates. R Toxicol Pharmacol 16, 2-9. Slikker, W., et al, 2004. Dose-dependent transitions i mechanisms of toxicity. Toxicol Appl Pharmacol 20 225.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.3 3 18
Current text	Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity.
Proposed update (revised text)	*[Additional text should be provided to define these criteria and provide specific examples of the types of evidence required to fulfill these criteria.]*
Brief rationale for update (max. 200 words)	Regarding selection of agents, the preamble indicates that agents are selected for review based on "evidence of human exposure" and "some evidence or suspicion of carcinogenicity." This text should be defined as to what type of scientific evidence is used to determine "evidence of human exposure" and likewise "suspicion" of carcinogenicity within the context of the Bradford-Hill criteria. In addition to clear definitions, examples of the type of evidence required to fulfill these criteria for the various types of agents (including lifestyles or complex mixtures) should be provided.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.4 4 15
Current text	The reasons for not giving further consideration to an individual study are also indicated in the square brackets.
Proposed update (revised text)	*[Additional text is needed to define reasons studies may not be considered and direct the procedures for consistent reporting across agents evaluated.* *Standard criteria should be developed and reported (vs. examples), thus providing both clarity and reproducibility across working groups.]* To further provide clarity and reproducibility across working group determinations relative to dismissing any particular study from the evaluation. For studies not given further consideration, rationale will be provided in the monograph which addresses both: • Lack of relevance; • Lack of adequacy (e.g., aspects by which study quality criteria not met); • Others as appropriate. IARC working groups will consistently record how they made such a determination in their report.
Brief rationale for update (max. 200 words)	While the Preamble directs the Working Group to provide reasons for not giving consideration to a study in the "square brackets," in practice, the monographs often do not provide clear or concise information as to the reason. Providing more guidance in this area in the Preamble would result in greater transparency regarding which studies are not fully considered (as well as the rationale), which will also result in greater reproducibility across Working Groups among the Monographs.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.3 14-15 entire section
Current text	(b) Studies of cancer in experimental animals [ENTIRE SECTION]
Proposed update (revised text)	*[Suggest text be revised/added throughout section to reflect definitions and/or criteria for determining sufficiency and evaluation of experimental animal data such that they are transparent and reproducible.]*
Brief rationale for update (max. 200 words)	It is recommended that the scientific principles – as well as the process to carry out the principles – be updated to reflect definitions and/or criteria for evaluating evidence of cancer in experimental animals such that they are transparent and can be carried out across evaluations in a reproducible fashion. Examples of areas needing clarification include: (1) Criteria to combine tumor incidence in the absence of cell type of origin. (2) Documentation of when there are indications of restrictions in validity and reliability (e.g., animal populations with viruses) are needed, as well as descriptions of how studies were weighted. This is of particular need for "other studies" (p. 15 lines 3-8) not subject to OECD guidelines for long-term carcinogenicity. (3) Assessment of the relevance of evidence with respect to dose, toxicokinetic profile and/or comparisons to historical control data. (4) Inconsistencies in carcinogen determinations by Working Groups (which often *do not* include pathology experts) relative to NTP cancer bioassay reports (which include pathology experts). Data relevancy and adequacy should be evaluated using consistent criteria; such criteria should be provided in the preamble (addressed in separate comments). Examples include Klimish (1997), the ToxRTool, or domain-based assessments of validity.
References, if any (max. 5)	Slikker W, Anderson ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly RB, David RM, Doerrer HG, Dorman DC, Gaylor DW, Hattis D, Rogers JM, Setzer RW, Swenbery JA, Wallace K. 2004. Dose-dependent

	transitions in mechanisms of toxicity: case studies. *Toxicol Appl Pharmacol*. **201**(3): 226-94. National Toxicology Program. 2011. Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological, and Physical Agents in Laboratory Animals for the National Toxicology Program. Klimisch HJ, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul Toxicol Pharmacol*. **25**(1): 1-5. 10.1006/rtph.1996.1076. Schneider, K., Schwarz, M., Burkholder, I., Kopp-Schn A., Edler, L., Kinsner-Ovaskainen, A., Hartung, T., Hof S., 2009. "ToxRTool", a new tool to assess the reliabilit toxicological data. Toxicol Lett 189, 138-144. Office of Health Assessment and Translation. OHAT R Bias Tool for Human and Animal Studies. Office of He Assessment and Translation. Research Triangle Park, N Division of the National Toxicology Program, National Institute of Environmental Health Sciences; 2015. https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.h

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.3.a 15 22-29
Current text	An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.
Proposed update (revised text)	*[Suggest text be revised/added to clarify how data are evaluated and considered based on sex (e.g., one or two studies) and species.]*
Brief rationale for update (max. 200 words)	In determination of sufficiency of data for classification, clarifications regarding how observations in male and female rodents from the same species are considered (e.g., one or two studies), and, similarly, how inconsistent findings between sexes (e.g., tumors in one sex but not the other) would be considered and should be documented as to the relevance of these tumor responses in humans.
References, if any (max. 5)	National Toxicology Program. 2011. Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological, and Physical Agents in Laboratory Animals for the National Toxicology Program.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.4 15 11 – First insertion
Current text	Mechanistic and other relevant data [entire section]
Proposed update (revised text)	*[Add to this section to reflect the use of the "key characteristics of carcinogenesis" (KCC) approach for mechanistic data, as well as consideration of other possibly relevant data that are not considered KCC. Include descriptions of the principles and procedures as to what and how data organized by KCC (and 'other' possibly appropriate characteristic) should be evaluated relative to up- and down-grading classifications. Also include text regarding 'other' possibly appropriate characteristics under which as of yet unknown or unestablished characteristics of carcinogens may be identified and evaluated.]* *Text must also include specific details as to the strategic approach for organizing KCC data – as well as consideration of other data – relative to that provided in Instructions to Authors. This must address use of ToxCast/Tox21 data as well as the need for relevant expertise in data evaluation.* *Refined text needs to address the scientific principles related to study quality, reliability and relevance, as well as how these elements will be integrated when evaluating the totality of the evidence. Specific details on how consideration of all mechanistic data (vs. single studies that show activity) will be considered must be included. Translation of the evidence to up- or down-grading classifications should be clearly documented in IARC working group reports.*
Brief rationale for update (max. 200 words)	It is unclear how mechanistic data are identified, selected, evaluated and integrated into IARC assessments, particularly KCC data. The Preamble is currently void of reference to the "key characteristics of carcinogen" (KCC) organizational strategy for mechanistic data, an approach discussed in the Instructions to Authors and used in several recent monograph evaluations. It is recommended that the update include reference to this approach as well as descriptions of the principles relating to how the data are evaluated (including considerations of study quality,

	reliability and relevance) and utilized in up- or down-grading carcinogenesis classifications. Data from the ToxCast/Tox21 high-throughput screening program have also been organized by the KCCs and integrated into recent IARC monographs (e.g., volumes 110, 112, and 113). These data require specific expertise in identification, evaluation, and interpretation. It is recommended that the Preamble also includes an 'other possibly appropriate characteristics' category. There may be other as of yet unknown or unestablished characteristics of carcinogens. The Preamble should address how all such data will be identified (including syntax) and considered in the evaluation.
References, if any (max. 5)	Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124:713-721. Guyton, K. Z., Rusyn, I., Chiu, W. A., Corpet, D. E., van den Berg, M., Ross, M. K., Christiani, D. C., Beland, F. A., and Smith, M. T. (2018a). Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis* **39**(4), 614-622. Judson, R., Houck, K., Martin, M., Richard, A. M., Knudsen, T. B., Shah, I., Little, S., Wambaugh, J., Setzer, R. W., Kothiya, P., et al. (2016). Analysis of the effects of cell stress and cytotoxicity on in vitro assay activity across a diverse chemical and assay space. *Toxicol. Sci.* **153**(2), 409.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED. B.4 15 11 – Second insertion.
Current text	Mechanistic and other relevant data [entire section]
Proposed update (revised text)	*Add to this section text to reflect what factors need to be considered when evaluating information relevant to the KCC.* *Paramount to the inclusion of KCC (and other relevant data), the Preamble must address how the collective mechanistic evidence (which is likely to include data demonstrating both activity as well as lack of activity) will be evaluated in the context of (a) adverse outcome pathways pertinent to specific cancer type(s) under evaluation,* ***and*** *(b) evidence from other streams (human, animal, exposure). The principles and procedures for considering study quality and relevance should be included in this text.* *Refined text should also address interpretation of KCC (and other relevant) data relative to up- and down-grading classifications. Specific criteria are needed to determine when such data are sufficient for up- or down- grade (e.g., use of a single assay vs use of an entire body of evidence).* *Examples of types of relevance and integration information that need to be considered:* *(1) whether an individual KCC may influence a hazard classification;* *(2) whether information on a mechanistic event in the absence of a histopathological-level change in the same tissue should be provided;* *(3) determining human relevance in relation to mechanistic data from non-human species;* *(4) appropriate weighting of each line of evidence based on study quality, reliability and human relevance in the context of the totality of the evidence; and,*

	(5) determining how heterogenous data may be integrated into an overall conclusion regarding strength of activity for a specific mechanism or KCC.
Brief rationale for update (max. 200 words)	It is recommended that the update include descriptions of the principles relating to how KCC data (as well as other relevant data) are evaluated in context of adverse outcome pathways *that are pertinent to the specific cancer type under evaluation*. In addition to identifying the principles and procedures for evaluation of KCC (and other relevant data), the Preamble needs to address how such data will be integrated with other relevant information, as well as with data from other evidence streams (human, animal, exposure). The Preamble also needs to address how the totality of the evidence will be evaluated (i.e., consideration of all KCC data vs. just those with activity). The assessment of the totality of the mechanistic data needs to include quality and relevance. Previous versions of the *Instructions to Authors* contained information on which KCCs were commonly linked. These linkages have since then been removed, thus lending some confusion as to how the KCC data are being evaluated.
References, if any (max. 5)	Goodman, J., and Lynch, H. (2017). Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. *Toxicol. Appl. Pharmacol.* **319**, 39-46. Guyton, K. Z., Rusyn, I., Chiu, W. A., Corpet, D. E., van den Berg, M., Ross, M. K., Christiani, D. C., Beland, F. A., and Smith, M. T. (2018a). Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis* **39**(4), 614-622. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124:713-721

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.4 15 11 – Third insertion.
Current text	1. Mechanistic and other relevant data
Proposed update (revised text)	*[Add to this section text to reflect the identification, evaluation, and integration of high-throughput data (HTS) data.]* Per the search strategy employed (REFERENCE SEARCH STRATEGY, SEPARATE COMMENT), the IARC Secretariat will identify all pertinent HTS data, make appropriate adjustments for cytotoxicity or related factors, and provide these to the Working Group for consideration. Each working group will contain at least one member that is an expert in evaluating HTS data. HTS data will be assessed as part of the overall evaluation of KCC data, recognizing that HTS data (if available) are only a portion of the body of evidence for other relevant data. Working Group members that are not experts in assessment of HTS data will be advised to the limitations of such data (as well as other *in vitro* data), including, for example, the importance of accommodating cytotoxicity, and characterizing the endpoints for which HTS data are available (and not available) and which assay data are associated with respective adverse outcome pathways (and those that are not). Comparisons of activity from HTS assays relative to assays of similar endpoints reported in the peer-reviewed literature shall be conducted. Descriptions of how HTS assessments of the agent under review are relevant to and possibly inform (or not inform) cancer hazard characterizations shall be documented in the working group report.
Brief rationale for update (max. 200 words)	The preamble is currently void of discussion related to use of high-throughput (HTS) data as a source of information to be considered; the update should address identification and evaluation of these data types. It should be recognized however that HTS assays were intended to be leveraged as a screening tool, not specifically designed to assess pathways related to carcinogenesis *per se*. Thus use of such data

	to up-and down-grade classifications should be included. HTS data from the ToxCast/Tox21 programs have been considered in recent IARC monographs (e.g., volumes 110, 112, and 113) (Chui et al., 2017). These data are currently reported in the monographs as a relative measure compared to many other agents based on ranking for overall activity for each KCC. It is not clear how the qualitative assessment of the agent under review compared to all other chemicals in the database is used to inform cancer hazard characterization. The incorporation of HTS data and the basic application and limitations of such data in evaluations (e.g., as discussed in Chui et al., 2017, importance of cytotoxicity per Judson et al., 2016) should be included in the preamble. It should be noted that a level of expertise in understanding how data are developed and analyzed is also required when evaluating these data.
References, if any (max. 5)	Chiu WA, Guyton KZ, Martin MT, Reif DM, Rusyn I. 2017. Use of high-throughput in vitro toxicity screening data in cancer hazard evaluations by IARC monograph working groups. ALTEX. Guyton, K. Z., Rusyn, I., Chiu, W. A., Corpet, D. E., van den Berg, M., Ross, M. K., Christiani, D. C., Beland, F. A., and Smith, M. T. (2018a). Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis* **39**(4), 614-622. Judson, R., Houck, K., Martin, M., Richard, A. M., Knudsen, T. B., Shah, I., Little, S., Wambaugh, J., Setzer, R. W., Kothiya, P., et al. (2016). Analysis of the effects of cell stress and cytotoxicity on in vitro assay activity across a diverse chemical and assay space. *Toxicol. Sci.* **153**(2), 409.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED. B.1 (with carry over to other sections) 7 22
Current text	For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.
Proposed update (revised text)	For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given. This information will be utilized throughout the monograph evaluation process beginning with identification of information. The specific definitions for each complex agent, such as a mixture, lifestyle, or similar, will be used in the search syntax employed as well as when establishing inclusion and exclusion criteria to glean relevant information. The specific definitions will also be used to develop agent-specific criteria for the evaluation of epidemiological literature. That is, for complex agents such as mixtures or lifestyle factors, criteria to evaluate the sufficiency and adequacy of exposure (as a study quality domain) will be determined. *Additional text related to the evaluation of complex agents, including characterization of the agent, exposure to the agent, and how studies will be appraised considering the complex issues is recommended in this section as well as throughout the Preamble where appropriate.* *Examples of scientific principles in identification, characterization and evaluation of complex agents should include: (1) Define complex agent based on key attributes such as important physiochemical properties; (2) Outline process by which mechanistic data for complex agents - likely to be limited to its components - are to be identified and evaluated; (3) Specify criteria by which data quality and relevance for complex agents are to be evaluated and weighed, including how confounding and bias are considered; (4) Appropriate contextualization of analyses, evidence synthesis and interpretation of the totality of the scientific evidence for complex agent; and, (5) Specify criteria by which data adequacy and confidence in*

	evaluation of exposure to the complex agent is assessed.
Brief rationale for update (max. 200 words)	The current scientific principles related to evaluation of complex agents is too limited. Recognizing the complexity of agents such as mixtures or lifestyles, it is important that the Preamble address the scientific principles related to identification of the complex agent, as well as to directing that agent-specific definitions and characterizations be provided as part of the planning documents and announcement of evaluations. Particular emphasis should be placed on establishing clear definitions in early phases of the assessment, and subsequent use of definitions for identification and appraisal of individual studies. The confidence in exposure to complex agents, particularly for observational studies in humans, should be considered carefully and interpretation of findings should be measured in the context of the totality of evidence.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.5 5 10, 22 – First text insertions.
Current text	Line 10: Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, … Line 22: All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.
Proposed update (revised text)	*[Additional text is needed to include topics not sufficiently addressed in the Preamble – specifically, the current text should be refined to include both financial and non-financial aspects of COI such that it is consistent with the WHO Handbook for Guideline Development (WHO, 2014) to enhance the detail regarding IARC's Conflict of Interest process.]* Line 10: Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial **and non-financial** interests, employment and consulting, … Line 22: All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry. **To ensure balance in perspectives, conflicts of interests (COI) disclosures should include both financial and non-financial considerations and should be managed appropriately, following principles laid out in the WHO Handbook for Guideline Development (WHO, 2014).**
Brief rationale for update (max. 200 words)	The current approach for disclosure and management of conflict of interest is inconsistent with what is practiced globally (IOM 2011; NAS, 2003; WHO, 2014). Both

	financial and non-financial interests should be disclosed and managed. For example, the 2014 WHO Handbook states: "…[C]ertain individuals should not participate at all in the development of a guideline… those who have intellectual conflicts of interest that are severe and/or cannot be adequately managed at the group level … (such as) an author or co-author of one or more key studies within the body of evidence underpinning a recommendation, particularly if the body of evidence is limited… (see Section 6.10). (p.68)". **IARC should strongly consider supplementing its limited current text with a detailed, standardized process that encompasses both financial and non-financial conflicts.** It is confusing as to how the conflict of interest information is considered relative to the expectation currently described in the Preamble – that is, if the expectation is that each participant serves as an individual scientist versus a representative of a given entity, it is unclear how financial and nonfinancial conflicts are separated and considered for individuals vs. their position as a representative. IARC should strongly consider supplementing its limited current text with a detailed, standardized process that includes both financial and non-financial conflicts.
References, if any (max. 5)	National Academy of Sciences (NAS). The National Academies Conflicts of Interest Policy for Committees used in the Development of Reports. May 2003. (http://www.nationalacademies.org/coi/) Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC. WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED A.5 4, 5, 6 Multiple.
Current text	Lines 26-28, p. 4. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Line 22, page 5: All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry. Line 8, page 6: Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered.
Proposed update (revised text)	Line 22, page 5 (continued from prior Table insertions): **Conditions that might limit or preclude participation of an individual during IARC monograph development may include (WHO, 2014):** ▪ **The prospective IARC working group expert is an author or co-author of one or more key studies within the body of evidence that forms the basis of the draft recommendation, particularly if the body of evidence is limited; and/or,** ▪ **The prospective IARC working group expert is or has been involved in a major academic programme of work that concerns the intervention, approach or exposure under consideration in the guideline, including conducting trials or systematic reviews and publishing conclusions or opinions on the benefits and/or harms**. Line 8, page 6: Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered **and not from the institution where study was performed**.

	In addition to the text suggested, additional descriptions are needed to include topics not sufficiently addressed in the Preamble – specifically, text that would clarify, by use of examples, conditions when major conflicts exist that address not only financial but also non-financial conflicts. This text would need to specifically address the approach for managing conflict considering that the experts are identified based on the findings from the literature search.
Brief rationale for update (max. 200 words)	Currently, the Preamble is not clear on how non-financial interests of Working Group members are identified and managed. The principles (and process) for doing so are critical to include in the updated Preamble given that Working Group members are identified from the literature search. Thus, it is not clear how the interests of such members are managed given that they are selected from the authors of the studies being evaluated. The Preamble could include language to specifically describe conditions that might limit or preclude participation of an individual. For example, selected conditions that apply not currently addressed in the IARC preamble process may include (WHO, 2014): ▪ Is an author or co-author of one or more key studies within the body of evidence that forms the basis of the draft recommendation, particularly if the body of evidence is limited; and ▪ The prospective member of the working group is or has been involved in a major academic programme of work that concerns the intervention, approach or exposure under consideration in the guideline, including conducting trials or systematic reviews and publishing conclusions or opinions on the benefits and/or harms.”
References, if any (max. 5)	National Academy of Sciences (NAS). The National Academies Conflicts of Interest Policy for Committees used in the Development of Reports. May 2003. (http://www.nationalacademies.org/coi/) WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

	Institute of Medicine (IOM). 2011. Finding What Works in Health Care: Standards for Systematic Reviews. J. Eden et al. eds. NAS; Washington, DC.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED. A.5 5 22 – Third text insertions.
Current text	All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.
Proposed update (revised text)	*Text should be added to the Preamble [following both of the above insertions in the prior two tables] to include detailed descriptions of <u>how</u> COI (financial and non-financial) <u>are to be evaluated and managed</u> (vs. being simply identified).*
Brief rationale for update (max. 200 words)	Criticisms received regarding unbalanced working groups could be addressed by revising the principles related to selection of working groups, including a more formalized plan for disclosure and management of financial and non-financial COI consistent with globally accepted standard practice (NAS, 2013; WHO, 2014). The current Preamble briefly addresses disclosure of only financial conflicts (non-financial conflicts are not addressed). It provides no guidance as to how disclosures are to be evaluated and managed. Criticism has been raised that some Working Groups are unbalanced and possibly prone to bias. It is well-recognized that both financial and non-financial bias need to be declared and appropriately managed. It is recommended that IARC's revised Preamble include a mechanism that parallels *WHO's Handbook for Guideline Development* by which both financial and non-financial conflicts of Interests for prospective IARC working group experts can be evaluated and managed in a systematic manner. In addition, others have addressed the need for balance and management of conflicts (e.g., IOM, 2009). IARC is strongly encouraged to align its COI process relative to how COI will be evaluated and managed for full transparency in selection of working group members, especially as it relates to invited experts, to the *2014 WHO Handbook for Guideline Development*.

References, if any (max. 5)	National Academy of Sciences (NAS). The National Academies Conflicts of Interest Policy for Committees used in the Development of Reports. May 2003. (http://www.nationalacademies.org/coi/) McLaughlin, J.K., P. Buffett, C. La Vecchia, L. Lipworth, W.J. Blot, and R. E. Tarone. Problems with IARC's 'expert' working groups. Int. J. Epidemiol. 40:1728-1729. NAS. 2018. Our Study Process. http://nationalacademies.org/studyprocess/index.html. Accessed 17 May 2018. Cope, M.B., and D.B. Allison. White hat bias: a threat to the integrity of scientific reporting. Acta Pædiatrica 2010. 99: 1615-1617. DOI:10.1111/j.1651-2227.2010.02006.x WHO. 2014. WHO Handbook for Guideline Development. 2nd Edition. WHO; Geneva.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.1.d 8 3, 9-18
Current text	(d) Occurrence and exposure Data that indicate the extent of past and present human exposure … the epidemiology of infection is described.
Proposed update (revised text)	*[Text on lines 9-18 in this section should be deleted and replaced with below text (or similar) as exposure information for agents and mixtures is not necessary since it is not used in the assessment of carcinogenicity.]* **A summary of the range of potential exposures is documented in working group reports and IARC monographs. Available exposure information should be used solely to better understand context around exposure to the agent (e.g., route of exposure), not as a surrogate for agent identification and presumed risk characterization**.
Brief rationale for update (max. 200 words)	One of the sections involved in an evaluation of an agent is "exposure." It is unclear why a section on exposure would be included in the Preamble when exposure information is not part of the evaluation of potential for hazard. Rather, exposure is primarily used for setting priorities for review. This information is not necessary and not used in the assessment of carcinogenicity, and thus it is unclear how or why this section is included – particularly considering that the IARC evaluations focus on hazard vs. risk (as risk would include consideration of exposure).
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	NEW TEXT TO BE INSERTED B.6 19 *Entire section*
Current text	*Section does not contain text pertinent to the comment*
Proposed update (revised text)	*The role of the exposure working group, as well as the appropriateness of their expertise relative to hazard classifications, needs to be addressed as it pertains to the overall evaluation.* *The principles of evaluation provided in the Preamble should specifically address the appropriateness of the exposure working group participating in the determination of consensus evaluations given that IARC classifications are hazard based (and do not account for exposure).*
Brief rationale for update (max. 200 words)	Exposure information is not part of the evaluation of potential for hazard. The exposure working group's role in developing and voting on overall classifications is unclear. Rationale regarding the appropriateness of having exposure workgroup members vote on overall classifications based on hazard data in epidemiological, animal, and mechanistic studies needs to be provided. Further clarification on the scientific principles associated with the evidence reviewed by the exposure group is needed given that this information is not necessary and not used in the assessment of carcinogenicity.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	SUGGESTED TEXT DELETION. B.4.e 18 24-27
Current text	Effects on reproduction, embryonic, and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.
Proposed update (revised text)	*Delete above text, as not relevant to a carcinogenic evaluation; or provide clarification and rationale as to the study types and specific information from such study type that is relevant to carcinogenicity.*
Brief rationale for update (max. 200 words)	Little guidance is provided in this section on the type of information required to be provided on the endpoints mentioned in this section and their relevance to assessing carcinogenicity *per se*. Clarifications and rationale are needed regarding the specific study types, as well as the endpoints from each study, that are relevant to the evaluation of carcinogenicity. Such information should be addressed early in the monograph process as part of the search strategy and identification of information to ensure that all pertinent other relevant information are identified and evaluated in a consistent and systematic manner.
References, if any (max. 5)	Click here to enter text.

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Prof. Dr. Hans Verhagen
Your principal affiliation	EFSA (European Food Safety Authority), Parma, IT
If another party suggested that you submit this nomination, please identify	-
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Form is attached to the email and e-signed by Hans Verhagen

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A1 1 26-27
Current text	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
Proposed update (revised text)	IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans
Brief rationale for update (max. 200 words)	We suggest that the title of the monographs is amended to better reflect its intended scope (as described on page 2, lines 20-24). We believe this is important due to the potential confusion that the difference between hazard and risk can generate. The definitions of hazard and risk are already included in the document on page 2, lines 18-20.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A2 2 18-20
Current text	A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard.
Proposed update (revised text)	A 'hazard' is the inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent. A 'risk' is the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.
Brief rationale for update (max. 200 words)	Use WHO terminology. In particular the definition of 'risk' would benefit from mentioning the 'probability of an adverse effect'.
References, if any (max. 5)	http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf?ua=1 "IPCS Risk Assessment Terminology Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment"

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A2 2 20-24
Current text	The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.
Proposed update (revised text)	-
Brief rationale for update (max. 200 words)	This is very clearly explained and could be reflected in the title.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A2 2 30-32
Current text	The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that Monographs evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.
Proposed update (revised text)	The Preamble continues the previous usage of the phrase 'weight of evidence' as a matter of historical continuity, although it should be understood that Monographs evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.
Brief rationale for update (max. 200 words)	'Weight of evidence' is the terminology mostly used in the context of risk assessment, including by WHO (ICPS 2009). Recently, EFSA published guidance documents on Weight of Evidence, Biological Relevance, Uncertainty, and principles for dealing with data and evidence in scientific assessments. EFSA would be pleased to share its approach and current thinking on the above with IARC colleagues.
References, if any (max. 5)	IPCS (2009): Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food http://www.inchem.org/documents/ehc/ehc/ehc240_chapter5.pdf EFSA 2017 - Guidance on the use of the weight of evidence approach in scientific assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4971 EFSA 2017 - Guidance on the assessment of the biological relevance of data in scientific assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4970 EFSA 2018 - Guidance on Uncertainty Analysis in Scientific Assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5123 EFSA 2015 - Principles and process for dealing with data and evidence in scientific assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4121

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25)	 A2 2-3

Line number (1–47)	44-5
Current text	Although the *Monographs* have emphasized hazard identification, important issues may also involve dose-response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose-response relationship. A *Monograph* may undertake to estimate dose-response relationships within the range of the available epidemiological data, or it may compare the dose-response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose-response assessment.
Proposed update (revised text)	Although the *Monographs* have emphasized hazard identification, important issues may also involve dose-response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose-response relationship. A *Monograph* may undertake to estimate dose-response relationships within the range of the available epidemiological data, or it may compare the dose-response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose-response assessment. In order to inform the cancer risk, the mode of action should be identified focusing on stochastic (non-thresholded) or non-stochastic (thresholded) modes of action.
Brief rationale for update (max. 200 words)	Depending on the mode of action, exposure estimates can inform the estimate of public health risks.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A4 3 41-42
Current text	Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.
Proposed update (revised text)	Those judged inadequate or irrelevant to the evaluation may be cited but not summarized, and the reasons for this, including data quality evaluation criteria applied, are indicated. If a group of similar studies is not reviewed, the reasons are indicated.
Brief rationale for update (max. 200 words)	For transparency, the reasons for concluding that studies are inadequate or irrelevant should be indicated. Having clear quality criteria made explicit and why they lead to selection or discarding of individual studies is also important.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 A4 4 3-9
Current text	With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered.
Proposed update (revised text)	With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including

	meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. For regulated chemicals and chemical mixtures, mandatory guidelines studies conducted by the applicants and reviewed by regulatory agencies constitute a very relevant source of data. All information publically available or available to any party under request can then be considered.
Brief rationale for update (max. 200 words)	A scientific evaluation should be based on the "totality of the pertinent scientific data and weighing of the evidence" and clearly defined criteria should be used to assess their quality in a systematic way. In many an instance industry studies are available in addition to published work. In contrast to many published studies, industry studies are typically conducted under GLP and according the (e.g. OECD) test guidelines and their study reports always contain all the raw data. These additional data could also be used. IARC can then rely on, or at least make use of, the evaluation as conducted by e.g. EFSA or ECHA. In addition, consistency with the use of unpublished data on 'chemical and physical properties, on analysis, on production and use and on occurrence' (A4, lines 11-12; A6, lines 36-44) can be assured. New transparency and access to data rules have been developed in the EU, US and many other jurisdictions that allow this information to be requested. If the information made publicly available is insufficient, IARC can consider to contact the study owners and regulatory agencies to provide additional information on these studies, including the raw data.
References, if any (max. 5)	http://www.unece.org/fileadmin/DAM/env/pp/documents/cep43e.pdf (CONVENTION ON ACCESS TO INFORMATION, PUBLIC PARTICIPATION IN DECISION-MAKING AND ACCESS TO JUSTICE IN ENVIRONMENTAL MATTERS) https://www.efsa.europa.eu/en/press/news/161209

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B 6 37
Current text	Mechanistic and other relevant data
Proposed update (revised text)	Mechanistic and other relevant data, in particular information on genetic toxicology
Brief rationale for update (max. 200 words)	Genetic toxicity distinguishes between stochastic and non-stochastic modes of action, viz if the effect has a threshold for the effects to occur or not.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B1 7 7-25
Current text	**(a) General information on the agent** For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the

	ingredients. For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented. For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated. For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given. Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.
Proposed update (revised text)	[More specific information can be included at the discretion of the Advisory Group]
Brief rationale for update (max. 200 words)	Recently EFSA has updated its requirements for specification of novel foods, which included rounds of public consultation. Some of these requirements could be relevant to the IARC work and the Advisory Group.
References, if any (max. 5)	EFSA 2016 - Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4594 EFSA 2016 - Guidance on the preparation and presentation of the notification and application for authorisation of traditional foods from third countries in the context of Regulation (EU) 2015/2283. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4590

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B1 7 19-23
Current text	For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated. For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.
Proposed update (revised text)	For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and ~~respirable~~ particles, size range and relative dimensions are indicated. For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.
Brief rationale for update (max. 200 words)	1. Exposure to particles through the oral route can be equally important, hence the proposal to delete the reference 'respirable' only. 2. The word 'drugs' should be qualified, e.g. narcotic drugs or recreational drugs as opposed to medicinal drugs (which should benefit from a complete description (cf lines 8-15).
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B1 8 6-8
Current text	When available, data on the generation, persistence and

	bioaccumulation of the agent are also included. Such data may be available from national databases.
Proposed update (revised text)	When available, data on the generation, persistence and bioaccumulation of the agent and of known metabolites and breakdown products are also included. Such data may be available from national databases.
Brief rationale for update (max. 200 words)	The information should include metabolites and breakdown products as exposure may not be to the parent compound.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B 6 33-35
Current text	Over time, the structure of a Monograph has evolved to include the following sections: 1. Exposure data 2. Studies on cancer in humans 3…
Proposed update (revised text)	The structure of a Monograph should include the following sections: 1. Identity of the agent or agents 2. Exposure data 3. Studies on cancer in humans 4… For chemicals, the identity could clarify if the agent is a substance or a mixture and the identity could be reported according to UN GHS principles (UN, 2017).
Brief rationale for update (max. 200 words)	The identity of the agent is a key element and should not be part of the exposure section. In the evaluation of the studies, the WG should consider if the study has been conducted directly with the agent under evaluation (including impurities) or with mixtures containing other chemicals. Recent updates by EFSA on the identity of a substance have been referred to above.
References, if any (max. 5)	UN, 2017 "Globally harmonized system of classification and lebbeling of chemicals (GHS)". https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev07/English/ST_SG_AC10_30_Rev7e.pdf

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B-1(a) 7 7-25
Current text	For chemical agents, sections on chemical…
Proposed update (revised text)	For chemical agents, the identity should clarify if the agent is a substance or a mixture and the identity should be reported according to UN GHS principles (UN, 2017). When studies on technical products containing other ingredients are included in the assessment, the full composition should be reported if available. If the full composition is not available, the information available to the WG for assessing that the study results are linked to the agent under evaluation and not to other ingredients should be reported, including the WG evaluation of this information.
Brief rationale for update (max. 200 words)	*NOTE: see also previous comment: The identity would be better in a separate section, not a subsection under exposure data.* It is critical to clarify the agent under evaluation and to harmonize with other UN bodies regarding the identification of

	chemical substances and mixtures.
References, if any (max. 5)	https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev07/English/ST_SG_AC10_30_Rev7e.pdf

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	14 B2b 10 14
Current text	[No current text, the proposal is to add new sentences]
Proposed update (revised text)	Recommendations on how to report exposure in epidemiological studies are available for some areas such as pesticides (EFSA PPR Panel, 2017)
Brief rationale for update (max. 200 words)	New recommendations to be added
References, if any (max. 5)	EFSA PPR Panel 2017. Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'. EFSA Journal 2017;15(10):5007, 101 pp. https://doi.org/10.2903/j.efsa.2017.5007

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	15 B2e 11 4-23
Current text	Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio et al., 1992; Toniolo et al., 1997; Vineis et al., 1999; Buffler et al., 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies. Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.
Proposed update (revised text)	Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio et al., 1992; Toniolo et al., 1997; Vineis et al., 1999; Buffler et al., 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

	Biomarkers require standardisation and harmonisation, as well as analytical and physiological validation. (WHO 2001; Verhagen et al. 2018). Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.
Brief rationale for update (max. 200 words)	There are many new developments on biomarkers such as via the EU projects Human Biomonitoring for EU (https://www.hbm4eu.eu/) and Foodball (http://foodmetabolome.org/)
References, if any (max. 5)	World Health Organization (2001). Biomarkers in risk assessment: validity and validation. http://bit/ly/2rO6byw Verhagen H., Merten C., Chiusolo A. Arcella D. and Binaglia M. (2018). Human biomonitoring requires validation. https://theanalyticalscientist.com/issues/0318

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B3 12 30-38
Current text	Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is sufficient evidence of carcinogenicity in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. ~~Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans.~~ Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).
Proposed update (revised text)	Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically ~~plausible~~ possible that agents for which there is sufficient evidence of carcinogenicity in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Whereas these agents are considered to pose a possible carcinogenic hazard to humans, their risk for humans remains to be established. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans

	(see Part B, Section 6).
Brief rationale for update (max. 200 words)	The mechanism (genotoxic or not) is important to inform the absence or presence of a threshold for the effect, as well as the dose to which humans are exposed and consequently the absence or presence of a risk to public health.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B3 12-13 45-2
Current text	Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).
Proposed update (revised text)	Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted, with the rationale for this being provided. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, ~~2002~~2018).
Brief rationale for update (max. 200 words)	1. As above – transparency for decision to exclude studies. 2. OECD Test Guidelines TG 451 and 452 were updated in 2018.
References, if any (max. 5)	http://www.oecd.org/env/test-no-451-carcinogenicity-studies-9789264071186-en.htm http://www.oecd.org/env/test-no-452-chronic-toxicity-studies-9789264071209-en.htm

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B3 13 9-11
Current text	For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery.
Proposed update (revised text)	For studies of mixtures, as is the case for single compounds, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery.
Brief rationale for update (max. 200 words)	This reflection applies equally to single compounds and could be added.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B3b 14 2-17
Current text	[the current text is adequate but needs additional considerations]
Proposed update (revised text)	[the current text is adequate but may need additional considerations which are beyond the purpose of this consultation]
Brief rationale for update	[Additional considerations could include:

(max. 200 words)	• Role of genetic toxicity • Stochastic versus non-stochastic modes of action • Presence or absence of a threshold for the effects • Dose / exposure
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 B3biii 16-17 19-36
Current text	[entire text, almost 2 pages long]
Proposed update (revised text)	Click here to enter text.
Brief rationale for update (max. 200 words)	Additional considerations could be included: • Role of genetic toxicity • Stochastic versus non-stochastic modes of action • Presence or absence of a threshold for the effects • Dose / exposure Recently EFSA issued guidance on the evaluation of genotoxicity (including an update), which we consider relevant and we would be pleased to discuss with IARC colleagues.
References, if any (max. 5)	EFSA 2011 - Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2379 EFSA 2017 - Clarification of some aspects related to genotoxicity assessment. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5113

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 6 19 16
Current text	Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.
Proposed update (revised text)	Evaluations of the ~~strength~~ weight of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.
Brief rationale for update (max. 200 words)	'Weight of evidence' is the terminology mostly used in the context of risk assessment, including by WHO (ICPS 2009). Recently, EFSA published guidance documents on Weight of Evidence, Biological Relevance, Uncertainty, and principles for dealing with data and evidence in scientific assessments. EFSA would be pleased to share its approach and current thinking on the above with IARC colleagues.
References, if any (max. 5)	IPCS (2009): Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food http://www.inchem.org/documents/ehc/ehc/ehc240_chapter5.pdf EFSA 2017 - Guidance on the use of the weight of evidence approach in scientific assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4971 EFSA 2017 - Guidance on the assessment of the biological relevance of data in scientific assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4970

	EFSA 2018 - Guidance on Uncertainty Analysis in Scientific Assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5123 EFSA 2015 - Principles and process for dealing with data and evidence in scientific assessments. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4121

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 6d 22 4-15
Current text	Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenic~~ity~~ of the agent to humans.
Proposed update (revised text)	Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenic hazard of the agent to humans.
Brief rationale for update (max. 200 words)	IARC may wish to distinguish more clearly between hazard and risk; carcinogenicity is more linked to risk than to the hazard concept
References, if any (max. 5)	

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	David Forman
Your principal affiliation	IARC
If another party suggested that you submit this nomination, please identify	N/A
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Forthcoming

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	Section B, Subsection 6(d) Overall evaluation 22-23
Current text	
Proposed update (revised text)	Page 22 line 33 delete "The agent is probably carcinogenic to humans" Page 23 line 1 delete "The agent is possibly carcinogenic to humans" Page 22 line 33, insert new paragraph 6 in bold: **"Agents assigned to Group 2 (A or B) will be summarily categorised as having limited (or inadequate) evidence for carcinogenicity in humans together with a statement regarding the animal and mechanistic evidence"**

Brief rationale for update (max. 200 words)	To obtain a Group 1 evaluation, there usually has to be sufficient evidence of carcinogenicity in humans derived from consideration of epidemiological studies while the Group 2 evaluations (A or B) are given when there is insufficient (or inadequate) evidence of carcinogenicity in humans but positive evidence from animal and/or mechanistic studies. The fundamental distinction between Groups 1 and 2 is whether the evidence for human carcinogenicity is sufficient or not. There is a contradiction between calling an agent a probable or possible carcinogen (the current definition of Group 2), with the implication of causal effect, with there also being lack of sufficient evidence for human carcinogenicity. The underlying causal model of cancer is probabilistic in nature and it is self evident that not all those exposed to a Group 1 agent, will develop cancer. The distinction between agent X being “probably” or “possibly” carcinogenic (Group 2A/2B) and agent Y being “definitely” carcinogenic (Group 1) but only causing cancer with a certain probability can be confusing especially to a lay audience and more so when translated through popular media. The fundamental criteria for Group 1 “sufficient evidence of human carcinogenicity” can appear to become compromised by confusion with the Group 2A label of probable carcinogen (and, to a lesser extent, the 2B label of possible carcinogen). Not only does this undermine the careful science leading to the respective evaluations but it can also mask the important conclusion that, for any Group 2 evaluation, evidence falls short in demonstrating that the agent can cause human cancer.
References, if any (max. 5)	

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Hans Kromhout
Your principal affiliation	Institute for Risk Assessment Sciences, Utrecht University
If another party suggested that you submit this nomination, please identify	
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	IARC has recent WHO Declaration of Interest forms of me

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1–25) Line number (1–47)	 Section 1 C 7-8 39-43 and 1-2
Current text	See preamble
Proposed update (revised text)	
Brief rationale for update (max. 200 words)	The current text is non-binding. It should be stressed that also production data in non-western countries should be unearthed. For a lot of chemicals production is no longer happening in the old-industrialized countries in Europe and North America. It should be considered to have the preparatory work done at the secretariat and collect this information in a more standardized way. At present it depends too much on

	the interest, knowledge and language skills of the scientist making up a particular working group.
References, if any (max. 5)	See for a good example the recent Monograph on Acrylates Mono Vol 122

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section 1D 8 3-18
Current text	See preamble
Proposed update (revised text)	
Brief rationale for update (max. 200 words)	The current text is non-binding. It should be more explicitly stated that current estimates of the number of individuals exposed worldwide should be looked for. A good example of such an approach is present in the Monograph on Welding Volume 118, where actually worldwide estimates of the number of people welding were presented. Also (trends in) occupational exposure levels could be collected from nationwide databases. Again it would be best if this approach would be institutionalized through collaboration of IARC with database owners like for instance DGUV in Germany and INRS in France. This would take away the burden of collecting this information from the working group members, who could then concentrate on bringing all this information together and get a better and more systematic picture. In its current form this section is a mish mash when monographs are compared and the quality and completeness of this information too much depending on the researchers within this section.

	It should be stressed that also production data in non-western countries should be unearthed. For a lot of chemicals production is no longer happening in the old-industrialized countries in Europe and North America. It should be considered to have the preparatory work done at the secretariat and collect this information in a more standardized way. At present it depends too much on the interest, knowledge and language skills of the scientist making up a particular working group.
References, if any (max. 5)	See for a good example the recent Monograph on Welding Mono Vol 118

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section 2 B 9 36-37
Current text	See preamble
Proposed update (revised text)	
Brief rationale for update (max. 200 words)	This section should be extended with at least a detailed paragraph describing that the quality of the exposure assessment should be incorporated from the start when evaluating the epidemiological evidence. Basically nothing is written about this in the current preamble. It the most recent volumes of the Monograph the quality of the exposure assessment in the epidemiological evidence was described and taken into account when weighing the evidence at hand. It is essential that this very important aspect will get a formal place in the preamble and in the procedures through which the Studies of Cancer in Humans section evaluates the evidence at hand.

References, if any (max. 5)	The most recent monographs

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	David Williams
Your principal affiliation	International Governmental Organization (IGO) Watch
If another party suggested that you submit this nomination, please identify	N/A
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	N/A

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.5 4 26-31
Current text	"Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts." Working Group Members must also have expertise, and "an absence of real or apparent conflicts of interest...Consideration is also given to demographic diversity and balance of scientific findings and views."
Proposed update (revised text)	General comments: While it is reasonable for IARC to use literature searches and identify real or apparent conflicts of interest to gather working group members, it is also important for IARC to follow the lead of regulatory agencies in balancing different perspectives, including

	that of industry. The U.S. Environmental Protection agency and the European Food Safety Authority have been able to deliver effective regulation precisely because of industry involvement in the rule-making process, not in spite of it. Best practices call for IARC to adopt the procedures of the National Academy of Sciences (2003), which require a balance of different perspectives.
Brief rationale for update (max. 200 words)	Rationale above.
References, if any (max. 5)	European Food Safety Authority (EFSA). 2018. "Independent science." https://www.efsa.europa.eu/en/howwework/independentscience National Academies. 2003. " Policy on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports." 3-5p. http://www.nationalacademies.org/coi/bicoi_form-0.pdf United States Environmental Protection Agency. 2002. "Overview of the Panel Formation Process at the Environmental Protection Agency Science Advisory Board." Science Advisory Board, EPA-SAB-EC-02-010, 10p., September. https://yosemite.epa.gov/sab/sabproduct.nsf/WebFiles/OverviewPanelForm/$File/ec02010.pdf

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.4;B.2(f) 3; 11 40-42; 28-37
Current text	From A.4: "Each Monograph reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized." From B.2(f): “A strong association (e.g. a

	large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound."
Proposed update (revised text)	General comments: How IARC determines what is "inadequate" or "irrelevant," or which studies are "judged to be of high quality" is explained in section B.2 (b) to include well-defined variables, clearly-presented statistical methods, and consideration of other explanations, but IARC does not discuss external and internal validity, the justification of including and excluding different variables, significance-level benchmarks, and publication bias. Studies can come to drastically different results based on subtle differences in variables included in regression equations, and definitions of "statistical significance" have been stretched beyond the commonly-accepted "p<.05" to fit a certain conclusion. (see, for instance, Wood et al, 2014). IARC must consciously incorporate these considerations into their quality-determination processes.
Brief rationale for update (max. 200 words)	Rationale above.
References, if any (max. 5)	Wood, J., Freemantle, N., King, M. and Nazareth, I., 2014. "Trap of trends to statistical significance: likelihood of near significant P value becoming more significant with extra data."*The BMJ*, 348, p.g. 2215.

IGOWATCH

September 7, 2018

Dr. Kurt Straif
Section Head
Monographs Group
International Agency for Research on Cancer (IARC)
150 Cours Albert Thomas
69372 Lyon CEDEX 08
France

Dr. Straif:

On behalf of citizens of more than one hundred countries around the globe, International Governmental Organization (IGO) Watch urges IARC to make sensible changes to the *Monographs* Preamble. Problems in the wording of the Preamble have led to faulty evaluation procedures by IARC, resulting in unnecessary product restrictions and undue concerns by governments and consumer groups.

Substances such as aloe vera, d-limonene, and aniline are all considered at least "possibly carcinogenic" by the organization, despite insufficient evidence and a presumption of danger. Additionally, IARC refused to drop coffee's "possible carcinogen" status for more than two decades, even after the weight of evidence suggested that coffee had important protective effects against heart disease and various cancers.

Even after retracting the "possible carcinogen" status, IARC refused to reclassify to "unlikely to cause cancer in humans." Despite sharing ample empirical evidence that there are inverse relationships between coffee and different types of cancers, IARC concluded simply that coffee is "unclassifiable as to its carcinogenicity in humans."

Undergirding these harmful decisions is vague determination criteria found in the Preamble, which IGO Watch describes in greater detail in the enclosed public comments form. Studies deemed to be "inadequate" are not considered by IARC, despite little clarification on what constitutes an adequate or high-quality study. While IARC does list some legitimate criteria for included studies, the agency fails to explain their thresholds for statistical significance and consideration of variable inclusion.

These shortcomings are concerning, given the real-world consequences of IARC classifications. IARC classifications lie at the center of some American states' consumer protection laws, with rulings triggering regulatory actions by governments and growing costs for taxpayers. In California, for instance, IARC designations trigger warning labels, which add additional costs onto products that are often passed onto consumers. For farm production, warning labels on the end product often force farmers to inefficiently keep different produce far apart for liability purposes.

IARC should use these comments and other submissions to change course and consider all evidence from all perspectives when evaluating different substances.

Regards,

David Williams
President

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Gina Hilton, Ph.D.
Your principal affiliation	PETA International Science Consortium Ltd.
If another party suggested that you submit this nomination, please identify	None
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Completed for submitted- Gina Hilton

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.2 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.2 Page 2 Lines 35-37
Current text	The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms.
Proposed update (revised text)	The aim of the *Monographs* is to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, including underlying mechanisms.
Brief rationale for update (max. 200 words)	The underlying mechanistic information that can be collected by in vitro and in chemico methods are critical for the consideration of potential carcinogenicity relevant to humans.
References, if any (max. 5)	None

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.2 Page 2 Lines 44-45
Current text	Although the *Monographs* have emphasized hazard identification, important issues may also involve dose-response assessment.
Proposed update (revised text)	Although the *Monographs* have emphasized hazard identification, important issues may also involve dose-response and human-relevant exposure assessment.
Brief rationale for update (max. 200 words)	Human risk to a carcinogenic agent must include both hazard and exposure assessment in order to more fully protect human health. Potentially useful chemicals could unduly be considered carcinogenic to humans in the absence of considering the realistic exposure scenario and risk assessment.
References, if any (max. 5)	None

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.3 Page 3 Lines 17-18
Current text	(a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity.
Proposed update (revised text)	(a) there is evidence of human exposure and (b) there is scientifically-sound evidence of carcinogenicity.
Brief rationale for update (max. 200 words)	The selection of agents for review should be scientifically based on objective information indicating an agent is potentially carcinogenic.
References, if any (max. 5)	None

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.4 Page 3 Lines 43-44
Current text	A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated.
Proposed update (revised text)	A *Monograph* will cite relevant mechanistic literature concerning the agent being evaluated.
Brief rationale for update	Increasing use of *in vitro* and *in chemico*

(max. 200 words)	assays are being used to generate mechanistic information relevant to carcinogenicity assessment. These data should be reviewed and cited in *Monographs (Corvi, Madia et al. 2017).*
References, if any (max. 5)	Corvi, R., F. Madia, et al. (2017). "Moving forward in carcinogenicity assessment: Report of an EURL ECVAM/ESTIV workshop." Toxicol In Vitro 45(Pt 3): 278-286.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.4 Page 4 Lines 1-2
Current text	Only those data considered by the Working Group to be relevant to making the evaluation are included.
Proposed update (revised text)	All mechanistic data will be considered by the Working Group and relevant information to making the evaluation are included.
Brief rationale for update (max. 200 words)	All mechanistic data should be considered during the Working Group review.
References, if any (max. 5)	None

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.4 Page 4 Lines 3-5
Current text	With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed.
Proposed update (revised text)	With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, reports that have been published or accepted for publication in the openly available scientific literature as well as regulatory documents are reviewed.
Brief rationale for update (max. 200 words)	The consideration of regulatory documents will provide thorough study information that might not be reported in the literature, but that are generally conducted according to internally-accepted test guidelines and are important to consider during review. Such regulatory information might be already publically available, or can be requested

	through a freedom of information act (FOIA) to government agencies.
References, if any (max. 5)	None

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section A.5 Page 4 Lines 26-28
Current text	Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts.
Proposed update (revised text)	Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts, as well as a call for nominations.
Brief rationale for update (max. 200 words)	To ensure the best experts are identified, there should be an opportunity for nominations from outside of IARC Working Group Members.
References, if any (max. 5)	None

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section B.3 Page 12 Lines 30-33
Current text	Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans.
Proposed update (revised text)	However, this association cannot establish that all agents that cause cancer in animals also cause cancer in humans (Goodman 2018).
Brief rationale for update (max. 200 words)	Several studies have presented issues concerning the application of the two-year rodent cancer bioassay data to predict human cancer risk (Ames and Gold 1990; Alison, Capen et al. 1994; Carmichael, Enzmann et al. 1997; Ward 2007; Billington, Lewis et al. 2010; Sistare, Morton et al. 2011; Gori 2013;

	Osimitz, Droege et al. 2013; Corvi, Madia et al. 2017; Paparella, Colacci et al. 2017; Goodman 2018). Reviews of the two-year rodent carcinogenicity bioassay have demonstrated that assumptions have been made for the carcinogenicity bioassay are incorrect. For example, (1) rodent carcinogens are not always human carcinogens and (2) results obtained at high doses are not necessarily indicative of results that will occur at lower, environmentally-relevant, doses (Goodman 2018). The rodent bioassay is known to have limited prediction to human outcome only for genotoxic DNA reactive chemicals, which can be screened through mechanistic type studies, thus alleviating the need to conduct the two-year rodent bioassay.
References, if any (max. 5)	Alison, R. H., C. C. Capen, et al. (1994). "Neoplastic lesions of questionable significance to humans." Toxicol Pathol **22**(2): 179-186. Ames, B. N. and L. S. Gold (1990). "Chemical carcinogenesis: too many rodent carcinogens." Proc. Natl. Acad. Sci. **87**(19): 7772-7776. Goodman, J. I. (2018). "Goodbye to the bioassay." Toxicol Res (Camb) **7**(4): 558-564. Gori, G. B. (2013). "Regulatory forum opinion piece: long-term animal bioassays: is the end near?" Toxicol Pathol **41**(5): 805-807. Ward, J. M. (2007). "The Two-Year Rodent Carcinogenesis Bioassay — Will It Survive?" Journal of Toxicologic Pathology **20**(1): 13-19

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 Section B.4 Page 16 Lines 27-28
Current text	Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.
Proposed update (revised text)	Genotoxicity data are discussed here to illustrate an evaluation of mechanistic data.
Brief rationale for update	Genotoxicity data are discussed here to

(max. 200 words)	illustrate an evaluation of mechanistic data.
References, if any (max. 5)	Mechanistic data provide important information about cancer potential and should be considered.

Public Comments Form
To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Gabrielle Lamourelle
Your principal affiliation	U.S. Department of Health and Human Services (HHS), Office of Global Affairs
If another party suggested that you submit this nomination, please identify	Includes contributions from: • National Cancer Institute, National Institutes of Health, HHS • U.S. Food and Drug Administration, HHS • U.S. Department of Agriculture
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.2 2 18-27
Current text	"A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The Monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the Monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher. In the Monographs, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity."
Proposed update (revised text)	Recommend moving the explanation of hazard assessment to the top of the Preamble and expanding its content. The importance of emphasizing hazard assessment is distinct from risk exposure; the Preamble should be further explain and emphasize both concepts. In this regard, consider also updating the Monograph title, for example "IARC Monographs Evaluating Hazards related to

	Carcinogenic Risks in Humans" to further clarify the objective of IARC Monographs.
Brief rationale for update (max. 200 words)	This update provides an important opportunity to clarify the scope and objective of the monographs and to structure the Preamble in a way that communicates its task of evaluating cancer hazards. The opening of the Preamble should clearly explain hazard assessments (e.g., IARC monographs) and differentiate these from risk assessments that evaluate exposure to estimate the likelihood of carcinogenic effect.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 22-23 P22, line 22-P23, line10
Current text	(description of Group 2A, Group 2B)
Proposed update (revised text)	Combine the two sub-categories Group 2A and Group 2B into a single "Group 2" and re-title it. Two alternative designations for a single Class 2 are as follows: "Agent is suspect but further studies required" or "Partial evidence to be declared carcinogenic".
Brief rationale for update (max. 200 words)	The last stage of the review process is an overall evaluation of the carcinogenicity of the agent to humans and a group classification depending on the conclusiveness of reviewed evidence: 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 in humans); or Group 4 (not carcinogenic to humans). Recent classification controversies have centered on a single categorization group – the use of "probably" in the title for exposures in Group 2A ("The agent is probably carcinogenic to humans"). Use of this term appears to make a partial indictment, when there is not sufficient data to support such a claim. While almost everyone interprets 'probably' as indicating a probability between 51% and 99%, studies (e.g., in of accounting) suggest that estimates of what "probably" means varies widely among (and potentially within) different countries. An alternative descriptor is needed conveying that there is a class of exposures for which there is some evidence of potential carcinogenicity, but this evidence is not complete or conclusive. This then implies that more studies focused in these areas should be encouraged in order to clarify the question. Two alternative designations for a single Class 2 are as follows: "Agent is suspect but further studies required" or "Partial evidence to be declared carcinogenic". IARC does not view its role guiding as telling countries whether to and how they should regulate various exposures. The monograph series does not attempt to do this, but

	instead suggests where more research might be profitably focused. Historically, and currently, the review and criteria for classifying an exposure to Group 1 (is carcinogenic in humans) has been robust and stood the test of time (e.g., only one downgraded over many decades). Similarly, there are many exposures that have no data for carcinogenicity and do not need to be studied. The Monograph series focuses on exposures with enough evidence to warrant careful review. There is certainly also a need to point out concerns about and opportunities for studies of the very large category of "possibly" carcinogenic and so it is appropriate to consider not using the metric of "probably" carcinogenic. Instead future monographs should highlight the existence of suggestions from laboratory studies or descriptive epidemiology, preliminary human studies, case-reports, or widespread human exposures. These, and other metrics have been reasonable rationales for prioritizing studies in the past without having to invoke "probably" carcinogenic as well as its legal implications of its use in different places in the world.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.3 3 31-38
Current text	"As significant new data become available on an agent for which a Monograph exists, a re- evaluation may be made at a subsequent meeting, and a new Monograph published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review."
Proposed update (revised text)	The U.S. National Cancer Institute believes the preamble should describe a process for petition and redress of questionable decisions of prior monographs for the uncommon circumstance when new information casts doubt on a prior monograph or indicates re-evaluation is warranted.
Brief rationale for update (max. 200 words)	While developing a single Class 2, as recommended above, could largely ameliorate this concern going forward, instances may still arise where a prior monograph should be reconsidered. For example, what if following an agent's classification as Group 2 (or even 3), convincing data were later identified indicating the compound is a potent carcinogen? What if a compound were classified as Group 2 but later evidence showed it to be of minimal

	carcinogenic risk? What if it were later discovered that a member of the monograph committee had an undisclosed conflict (e.g., financial conflict of interest)? Currently, it appears that the agent would have to be re-selected for another review through the process described in section A.3. If so, that could lead to a lengthy period before such evidence is reviewed and a misclassification could be corrected or reclassification considered.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	(General comment on document structure)
Current text	
Proposed update (revised text)	Please see the bottom of comment document for suggestions on concepts that could be grouped together in the Preamble introduction, or otherwise highlighted in the text.
Brief rationale for update (max. 200 words)	The preamble currently intersperses information key to understanding monographs' purpose and the process for preparing throughout the text. The Preamble would benefit from restructuring its content to provide an overview clearly conveying this information to a range of audiences, before providing historical background on the monographs.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.2 3 6-8
Current text	"The Monographs are used by national and international authorities to [make] risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions.'
Proposed update (revised text)	"The Monographs are used by national and international authorities to [help inform] risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions.'
Brief rationale for update (max. 200 words)	Suggest using "to help inform risk assessments", as a more accurate reflection of the content and purpose of the monographs. As written, could imply to some readers that the monographs themselves are sufficient to provide a risk assessment.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.3 3 17-23
Current text	Agents are selected for review based on two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity.
Proposed update (revised text)	Click here to enter text.
Brief rationale for update (max. 200 words)	This section could include a brief explanation that there are many exposures that have no data for carcinogenicity and do not need to be studied. The Monograph series focuses on exposures with enough evidence to warrant careful review. In addition, because there must be some evidence of exposure and carcinogenicity, few of the agents analyzed would be expected to be classified in Group 4.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.4 4 3-5
Current text	"With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed."
Proposed update (revised text)	Consider moving text up to top of this section and further explaining the exclusive use of openly available data from the scientific literature.
Brief rationale for update (max. 200 words)	While the scientific community understands the purpose and importance of relying on peer-reviewed literature, this process may differ from other evaluations of the same agents/exposures, for example by regulatory agencies, resulting in differing conclusions. Noting that IARC is <u>not</u> a regulatory agency, it would be helpful to clarify this point for diverse audiences.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.5 5 10-16
Current text	"Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some

	limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume."
Proposed update (revised text)	Recommend moving this explanation of conflict of interest (COI) before the categories of participants (e.g., before Section A.5 page 4 line 19). The description should be revised for consistency, as "real or apparent COI" appears within each category.
Brief rationale for update (max. 200 words)	The reader should understand this general point, which in part determines an individual's category for potential inclusion, before being presented with the discrete categories.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 5-6 Pg 5, line 33-35 and Pg 6., line 1-3
Current text	"Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches." "Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review."
Proposed update (revised text)	Working papers are mentioned in two places, but with very little related explanation. Recommend providing brief information, for example, on who prepares the papers, whether the Secretariat has a review role, and how the papers are used during the meeting.
Brief rationale for update (max. 200 words)	
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.6 6 17-20
Current text	"After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the Monographs programme website soon after the meeting."
Proposed update (revised text)	"After the meeting, the Secretariat completes the final monograph by verifying the material reviewed against the original literature, editing the monograph text, and preparing it for publication. IARC aims to publish the volume within six months of the Working Group

	meeting. IARC posts an advance summary, including the agent's classification, on the Monographs programme website soon after the meeting.""
Brief rationale for update (max. 200 words)	Preparation of the "master copy" and the posting of a summary/outcome in advance of the full Monograph could be more clearly explained to readers.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 19 23-24
Current text	"These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency)."
Proposed update (revised text)	Consider providing more explanation of this important concept in the Preamble, and in IARC communications on monograph findings.
Brief rationale for update (max. 200 words)	Without further explanation, readers may easily miss this important concept.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.2(c) 10 30-31
Current text	"IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular Monograph (see Part A, Section 4)."
Proposed update (revised text)	IARC should conduct or commission a systematic review and, when appropriate, a meta-analysis or pooled analysis of relevant epidemiological and animal studies. If possible, a dose-response analysis and formal estimation of publication bias should be performed.
Brief rationale for update (max. 200 words)	A systematic review, with all search terms and databases described, followed by meta-analysis is the current standard of practice in analyzing a series of studies, especially for epidemiology. The current practice of staff searching literature and then allowing working group members to add references is a "black box" that invites skepticism.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.5 5 26-30
Current text	"Working Group Members generally have published significant

	research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests.”
Proposed update (revised text)	[General question]
Brief rationale for update (max. 200 words)	Noting the literature search approach described in lines 26-30 of Preamble Section A.5, could IARC provide information on other means they commonly consider/use to transparently and systematically identify individuals with the requisite knowledge and expertise to contribute to these working groups?
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	References section 23
Current text	
Brief rationale for update (max. 200 words)	Recommend updating the references, as most are 10 to 20 years old and the science has changed considerably in that time period.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	General Comment
Current text	
Proposed update (revised text)	
Brief rationale for update (max. 200 words)	We note that IARC is an agency of the World Health Organization. However, the Preamble makes no mention of how the Monograph work may relate to, intersect, or interact with other WHO-related work with a role in identifying potential carcinogenic hazards to humans (e.g., JECFA).
References, if any (max. 5)	

Additional comments - Monographs introductory overview

Monograph Structure. As noted above, the preamble currently intersperses throughout the text information key to understanding monographs' purpose and the preparatory process. The Preamble would benefit from restructuring its content to provide an overview clearly conveying this information to a range of audiences, before providing historical background on the monographs. Consider grouping the following concepts together for greater clarity. This could be accomplished as a chapeau under "General Principles and Procedures".

Section A.1, Page 1, line 28-29:

Through the Monographs programme, IARC seeks to identify the causes of human cancer.

Section A.2, Page 2, lines 18-28:

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

In the Monographs, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic.

Section A.2, Page 2, lines 35-37

The aim of the Monographs has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms.

Section A.2, Page 2, lines 6-11:

The Monographs represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The Monographs may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

Section A.2, Page 3, lines 8-15:

The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

Section A.4, Page 4, lines 4-5:

only reports that have been published or accepted for publication in the openly available scientific literature are reviewed.

Section A.6, Page 6, lines 13-14:

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity.

Section A.6, Page 6, line 5-6:

The objectives of the meeting are peer review and consensus.

Section B.1, Page 6,lines 30-42:

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

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

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

Dr. Kurt Straif
Section Head
Monographs Group
International Agency for Research on Cancer
150 Cours Albert Thomas
69372 Lyon CEDEX 08
France

Dear Dr. Straif:

On behalf of National Cattlemen's Beef Association we appreciate the opportunity to participate in the public comment period for the proposed update of the Preamble to the IARC Monographs. Our specific comments are in the attached public comments form. Additions to existing text are in bold font, and deletions indicated by strikethrough. In addition, we also support recommendations put forward by the American Chemistry Council and Center for Advancing Risk Assessment Science and Policy for revising the Preamble.

Thank you for your consideration.

Sincerely,

Shalene McNeill, PhD, RD
Executive Director, Human Nutrition Research
National Cattlemen's Beef Association
smcneill@beef.org
Office: 830-569-0046
Cell: 830-570-1240

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Shalene McNeill
Your principal affiliation	National Cattlemen's Beef Association
If another party suggested that you submit this nomination, please identify	
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	See email attachment

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.1. Background Page 1 and 2 Lines 41-43 and 1-2
Current text	"The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominately, the prerogative of each individual Working Group."
Proposed update (revised text)	"…established as being effective during previous *Monograph* meetings ~~but remain, predominately, the prerogative of each individual Working Group~~."
Brief rationale for update (max. 200 words)	While it is suggested that the Preamble serves only as guidance rather than defining specific procedures and operations, Working Groups, in fact, often use the Preamble as a procedural guide. In an effort to maintain consistency in application of judgements discontinuing the allowance for individual Working Groups to operate via prerogative and, instead codifying the Preamble as a procedural guide or establishing a stand-alone procedural manual would increase operational consistency while promoting objectivity and transparency.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	A.2. Objectives and Scope Page 2 Lines 35-37
Current text	"The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms."
Proposed update (revised text)	"The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process~~, independently of the underlying mechanisms~~."
Brief rationale for update (max. 200 words)	Evaluation of mechanistic evidence as an integral, rather than independent aspect, of evaluating evidence is critical to ensuring that the totality of evidence is considered and a comprehensive weight of evidence assessment is completed.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	A.3 Selection of Agents for review Page 3 Lines 17-18
Current text	"Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity."
Proposed update (revised text)	"Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence ~~or suspicion~~ of carcinogenicity."
Brief rationale for update	Science is based on evidence not

(max. 200 words)	suspicions. Development of a formal process for screening and prioritizing agents for review could streamline the evaluation of critical agents and more effectively reduce the burden of cancer compared to expending valuable scientific resources to evaluate suspected carcinogens lacking any scientific evidence to support their evaluation.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 A.4. Data for Monographs Page 3 Lines 40-42
Current text	"Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized."
Proposed update (revised text)	See rationale below
Brief rationale for update (max. 200 words)	It would be useful to define "pertinent" and "inadequate" by providing clear inclusion/exclusion criteria along general guidelines on how to assign these determinations to epidemiological studies and cancer bioassays. Otherwise it is often confusing to determine why some studies are included in IARC's evaluations and others are not. While it is understood that criteria will vary depending on the agent being evaluated some general guiding principles would be useful.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25)	 A.6 Working Procedures Page 6

Line number (1−47)	Lines 13-16
Current text	"IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent."
Proposed update (revised text)	"IARC Working Groups strive to achieve a ~~consensus~~ **unanimous** evaluation. ~~Consensus reflects broad~~ **majority** ~~agreement among Working Group Members, but not necessarily unanimity.~~ **Voting procedures will allow sufficient time for each Working Group Member to state their opinion for classification. When unanimity is not readily apparent,** ~~T~~the chair ~~may elect to~~ **will** poll Working Group Members to determine the diversity of scientific opinion on issues ~~where consensus is not readily apparent~~ **and the diversity of scientific opinions will be quantified and summarized in the Overall Evaluation**. **Group 2A is the highest assignable category in absence of unanimity.**
Brief rationale for update (max. 200 words)	It is important that stakeholders and risk assessors understand when evaluations were arrived via unanimous support. As indicated below, Group 1 assignment should be reserved for Working Group unanimity. When decisions are not unanimous, quantification and summarization of the dissenting opinions can be useful in guiding further deliberations and public policy. It is also appropriate in this situation to assign a less definitive

	category such as that offered by Group 2A categorization.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 Evaluation and Rationale Page 19 Lines 16-18
Current text	“Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.”
Proposed update (revised text)	“Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data **including mechanistic evidence** are made, using standard terms. ~~The strength of the mechanistic evidence is also characterized.~~”
Brief rationale for update (max. 200 words)	Evaluation of mechanistic evidence as an integral, rather than independent aspect, of evaluating evidence is critical to ensuring that the totality of evidence is considered and a comprehensive weight of evidence assessment is completed.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 Evaluation and Rationale Page 19 Lines 20-22
Current text	“In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.”
Proposed update (revised text)	“In considering all of the relevant scientific data, the Working Group may

	assign the agent to a higher or lower category ~~than a strict interpretation of these criteria would indicate~~.”
Brief rationale for update (max. 200 words)	Current wording implies the opportunity for arbitrary or biased assessments. The sentence is best reworded and accompanied by guiding principles for the assignment of higher or lower categories so that objectivity and transparency is better assured.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 Evaluation and Rationale Page 21 Lines 22-23
Current text	“The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated using terms such as ‘weak’, ‘moderate’, or ‘strong’.
Proposed update (revised text)	“The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated using terms ~~such as~~ ‘weak’, ‘moderate’, or ‘strong’.
Brief rationale for update (max. 200 words)	The terms ‘weak’, ‘moderate’, and ‘strong’ should be standardized and defined for the purposes of the IARC Monographs. Guidance from other agencies may be useful in informing IARC’s definition and application of these terms as they relate to mechanistic evidence.
References, if any (max. 5)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6 (d) Overall Evaluation Page 22 Line 7-11
Current text	“In addition, when supporting data

	indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.
Proposed update (revised text)	~~"In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.~~
Brief rationale for update (max. 200 words)	This text amounts to the use of suspicion, rather than evidence, to make conclusions regarding cancer risk and causality.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	B.6. (d) Overall Evaluation – Group 1 Page 22 Lines 61-21
Current text	"This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity."

Proposed update (revised text)	"This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity." **This category is assigned only with Working Group unanimity.**
Brief rationale for update (max. 200 words)	

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	 B.6. (d) Overall Evaluation – Group 2A Page 22 Lines 40-42
Current text	"An agent may be assigned to this category if it 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."
Proposed update (revised text)	"An agent may be assigned to this category if it 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."
Brief rationale for update (max. 200 words)	Categorizations should be based on the totality of evidence. Mechanistic evidence should be considered an integral part, not an independent aspect, of a strength/weight of the evidence assessment.
References, if any (max. 5)	Click here to enter text.

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	Section B.6 (d) Overall Evidence – Group 2B Page 23 Lines 9-10
Current text	"An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data"
Proposed update (revised text)	~~"An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data"~~
Brief rationale for update (max. 200 words)	Totality of evidence from a strength of evidence assessment of all data, including but not limited to mechanistic data, should drive agent categorization.
References, if any (max. 5)	Click here to enter text.

Comments on the IARC Monographs Preamble

Ronald L. Melnick

1. Studies of cancer in experimental animals is certainly a mainstay of the IARC monographs program. This is largely because all known human carcinogens that have been studied adequately in experimental animals produce positive carcinogenic results and because several agents that were considered to be possible human carcinogens based on animal data were later confirmed as human carcinogens when reliable epidemiology data became available. However, conflicting views on the interpretation of animal carcinogenicity data have arisen largely because of factors related to the design and evaluation of experimental carcinogenicity studies. While the preamble clearly notes that IARC evaluations are based on "reports that have been published or accepted for publication in the openly available scientific literature," it is also important to recognize that the peer-review process for scientific publications is not perfect. Thus, IARC working groups must thoroughly review all animal carcinogenicity studies for their adequacy in design, conduct, and data analyses; this is particularly important because conclusions from each study reviewed in an IARC monograph are those of the working group and therefore may differ from those of the study authors. The current IARC preamble does a good job in describing how experimental cancer studies should be summarized and evaluated in the monograph, what aspects in the design and conduct of the studies that should be considered, additional factors that may be useful for data analyses, and encourages working group members to provide notations of any limitations in the design and conduct of the study as well as in the analysis and interpretation of the results. Because working groups may vary substantially on how thoroughly they note such limitations, it would be helpful if the IARC

preamble provided additional guidance on how working groups should judge the adequacy and validity of experimental animal studies. For example, the following questions and comments should always be considered and addressed in either the text (if addressed in the relevant publications) or in boxed notations in the write-up of each animal cancer study:

a) Study design:

i. What was the basis for the selection of doses? Were doses adequately challenging to identify a cancer hazard (if one exists) and to characterize dose-response relationships?

ii. Was the study of sufficient duration to detect late-developing tumors?

iii. Was the number of animals per group large enough to detect a change in incidence of tumors, especially rare or common tumors, in controls versus exposure groups

b) Conduct of the studies:

i. Was chemical purity, stability during storage and in the exposure medium (including frequency of reformulations if needed), and exposure uniformity (for inhalation studies) demonstrated to be adequate for the agent being studied?

ii. Was the study conducted in compliance with GLP requirements? While this will not overcome a poor design, it does ensure that the study was conducted according to protocol specified methods, that study data were fully recorded, and that calculations based on those data were performed accurately. GLPs were introduced in the early 1980s for animal carcinogenicity studies and are not always applicable to short-term studies (e.g., initiation/promotion, precancerous lesions, transformation assays). Non

GLP studies should not be ignored, especially if the working group has sufficient information on the design and conduct of the study to consider the data to be adequate for evaluation of potential carcinogenicity.

ii. Was a necropsy and complete histopathology conducted on all study animals, and were diagnoses of lesions reviewed by more than one qualified pathologist?

c) Evaluation of experimental data:

i. Were malignant and non-malignant lesions reported separately and combined for tumor types that have the potential to progress? The incidence of preneoplastic lesions (e.g., focal hyperplasias) in the same organ should also be reported because these lesions add to the weight-of-evidence of a cancer-causing effect.

ii. Were appropriate statistical tests used for pairwise and trend analyses? Were survival-adjustment methods used, especially in situations where there were differences in survival between controls and treatment groups? (if not, and individual animal data are available, the working group should conduct such analyses). Working groups should not always expect linear dose-response relationships; non-linear or non-monotonic relationships may also exist for certain agents. Consultation between the experimental animal subgroup and the mechanistic subgroup may shed light on potential dose-response relationships.

iii. Comparisons of tumor rates in treatment groups to the concurrent control group is most appropriate for evaluating an agent-induced effect. Comparisons of tumor rates in a given study to historical control rates with low variability are particularly useful for

evaluating rare or uncommon tumors, this is because the limited number of animals per group typically used in an experimental cancer study may not provide sufficient power to achieve statistical significance between controls and treatment groups. Some tumor types have highly variable incidences in controls among studies; in such instances comparisons to historical control rates should be done with caution. For example, it would not be appropriate to simply ignore increases in tumors rates in treated animals that fall within the range of the historical control; instead of excluding potentially important data, statistical comparisons should be made to historical control rates by methods that account for variability in tumor rates in the historical control database (for example, Peddada et al., 2007; Incorporating historical control data when comparing tumor incidence rates. J Amer Stat Assoc., 102:1212–20).

Draft reports on an agent must not be made public since all interpretations of the experimental data reflect the consensus opinion of the working group and not of the individual who wrote the first draft. Release of draft reports to the public can result in misleading opinions about the IARC review process.

2. For the overall evaluations of carcinogenicity, the Preamble allows placement of an agent in the category *carcinogenic to humans* "when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity." With increasing knowledge of mechanisms of carcinogenicity at the molecular and cellular levels, it is time for the preamble to include strong mechanistic evidence from exposed human cells or tissues rather than only from exposed humans when judging the overall

cancer classification for agents in which evidence of carcinogenicity from epidemiology studies is less than sufficient. As the Monographs program was established under the principle of primary prevention, the criteria for evaluating carcinogenicity should be able to rely on strong mechanistic evidence from human tissue and other sources (e.g., animal data, information on analogous agents, etc.) rather than requiring additional human exposures. A method is needed to ensure that all relevant mechanistic data are included in the evaluations.

Overall evaluations by IARC include the category *not classifiable as to its carcinogenicity to humans* (Group 3) when there is sufficient evidence of carcinogenicity in experimental animals and "strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans." This conditional statement needs clarification! The Preamble should explicitly note that sufficient evidence of carcinogenicity in experimental animals must never be dismissed based on inadequately tested mechanistic hypotheses of carcinogenicity that have been promoted to affect this classification downgrade.

3. In evaluating whether studies of cancer in humans show *sufficient evidence of carcinogenicity* or *evidence suggesting lack of carcinogenicity*, the working group is charged with ruling out chance, bias and confounding with reasonable confidence. In addition, for *evidence suggesting lack of carcinogenicity*, it is expected that studies had an adequate length of follow-up. The Preamble notes that "latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity". Unfortunately, it is not always clear to the reader of the monographs that these criteria were adequately met in the working group evaluations, especially when reaching the conclusion of *evidence suggesting lack of carcinogenicity*. Therefore, I recommend that working groups be charged with providing a detailed description

on how bias, latency, and all potential confounding factors were evaluated that led to the working group's decision on the classification of the agent.

Public Comments Form

To Propose an Update to the Preamble to the *IARC Monographs*

1. Name and affiliation of commenter

Your name	Bernard W. Stewart
Your principal affiliation	Faculty of Medicine, University of New South Wales/
If another party suggested that you submit this nomination, please identify	No other party involved.
WHO Declaration of Interests form (to sign and submit via preamble@iarc.fr)	Previously submitted in relation to the webinar.

2. Proposed update to the Preamble to the *IARC Monographs*

(for reference, see the current Preamble, full text available as PDF at: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf)

Location of text to be updated: Section (from A.1 to B.6(e)) Page number (1−25) Line number (1−47)	15 different locations, as specified in the following pages. Section 1 of this form (above)applies to all 15 updates. Each update has an explanatory heading
Current text	
Proposed update (revised text)	
Brief rationale for update (max. 200 words)	
References, if any (max. 5)	

Proposals for updating the *Monograph* Preamble

Discontinue use of the term 'agent' to encompass all matters subject to *Monograph* evaluation

Location of text to be updated

Section	A2
Page	2
Line Number	12-17

Current text

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

Proposed update (revised text)

Text above to be deleted and replaced with

In this Preamble, the term 'matter' refers to any agent or circumstance of exposure that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agent subject to evaluation have expanded from specific chemicals and classes of chemicals, to now include complex mixtures, biological organisms, physical agents and types of electromagnetic radiation. In parallel to that development, circumstances of exposure evaluated have expanded from occupational and work-related exposures to now include exposure to environmental pollutants and cultural or behavioural practices. These categories of agents and circumstances of exposure, as encompassing the scope of *Monographs*, may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A *Monograph* may concern (by title) particular circumstances of exposure to an agent already recognized to cause cancer in humans. The hazard presented by such particular circumstances of exposure may be the subject of a *Monograph* without requiring a re-evaluation of the agent as such.

> *Upon adoption of this proposed update, consequential editorial change to the Preamble would involve replacement of the word 'agent' or 'agents' where these words occur subsequent to the text above, with 'matter' or with 'agent or circumstance of exposure' as context indicates. Thus, at page 2, line 25 the amended text would read*:
>
> In the *Monographs*, an agent or circumstance of exposure is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that a matter subject to evaluation is carcinogenic.

Brief rationale for update (max. 200 words)
The early extension of the *Monograph* program to involve particular circumstances of exposure has comprehensively expanded the public health impact of the *Monographs*. However, to use the term ‘agent’ to refer to circumstances of exposure may be characterized as inappropriate or erroneous. It is inappropriate because circumstances of exposure such as shift work are not amenable to discussion with reference to what constitutes hazard identification and how this provides a basis for risk assessment. Use of ‘agent’ to mean ‘agent’ in the conventional sense and also circumstances of exposure is not in keeping with scientific practice. Statements such as ‘work as a painter is implicated as a carcinogenic agent in case-control studies’ are not found in the scientific literature.

Crucially, making distinction between agents on the one hand and circumstances of exposure on the other provides the basis for explaining appropriate application of the term ‘carcinogen’. Or more specifically, restricting the term ‘agent’ to its normal usage is background to explaining why describing ‘processed meat’ as ‘a carcinogen’ is wrong despite the fact that (eating) processed meat is carcinogenic.

Establishing the difference between ‘is carcinogenic’ and ‘is a carcinogen’

Location of text to be updated

Section	A2
Page	2
Line Number	28

Current text
No current text to be modified or deleted. New text proposed following the sentence
The terms ‘neoplasm’ and ‘tumour are used interchangeably.

Proposed update (revised text)
In *Monographs* prior to 1988, when only chemical agents were subject to evaluation, the expressions ‘is carcinogenic’ and ‘is a carcinogen’ could be used interchangeably. This is no longer the case. In respect of all classes of agent – chemical, physical or biological – these terms are interchangeable. However, though circumstances of exposure may be described as ‘carcinogenic’, scientific practice precludes use of the term ‘carcinogen’ in this context. The term ‘carcinogen’ indicates an agent which causes cancer and for which there is ‘no threshold’ when public health issues are addressed. In most countries, there are regulations to prevent exposure to specified carcinogens. To describe, for example, a exposures occurring in the course of a certain occupation as ‘a carcinogen’ is inappropriate and confusing despite the fact that workers so employed are at increased risk of cancer.

Brief rationale for update (max. 200 words)
The statement ‘IARC have categorized red meat as a probable carcinogen’ creates problems because this use of ‘carcinogen’ is contrary to scientific convention. Among the hundreds of research papers addressing carcinogenic risk associated with

consuming red meat, the impression is that none describe red meat as a carcinogen or a possible carcinogen. In most countries, regulations or public health policy concerning carcinogens involve the requirement for warning labels, statutory limits on exposure and the use of personal protective equipment. At the other extreme, there is nothing in the Preamble at present explaining why describing shift work as a probable carcinogen is not right.

Update and affirmation of reliance on 'peer reviewed publications'

Location of text to be updated

Section A4
Page 4
Line Number 3-6

Current text

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC….

Proposed update (revised text)

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have published or accepted for publication in the openly available scientific literature are reviewed. In particular, data/reports typically provided to national statutory authorities on the basis of 'Commercial – in confidence' and otherwise unpublished, are not taken into account. Availability of information on the web is not equated with 'published' which, in the present context refers specifically to publication in the peer-reviewed literature The same publication requirement applies to studies originating from IARC….

Brief rationale for update (max. 200 words)

Originally, reference to 'publication' in the specification of data to be addressed as the basis of a *Monograph* evaluation involved two separate considerations: accessibility and veracity, and these were inter-related. Today, data may be accessible via the web, but there can be no undertaking that all such data will be taken into account in an evaluation both because the credibility of information available on the web is not to be equated with peer review publication and in any event all such data may not be reasonably located and considered. Specific reference to 'Commercial – in confidence' informs the reader that different data concerning the same agent may be considered by the Working Group in comparison with data addressed by national statutory authorities in the context, for example, of licencing a pesticide or registering a pharmaceutical drug.

Update and affirmation of reliance on Working Groups involving 'experts'

Location of text to be updated

Section A5(a)
Page 4
Line Number 29

Current text:
Working Group Members are selected on the basis of (a) knowledge and experience and (b…

Proposed update (revised text)
Working Group Members are selected on the basis of (a) knowledge and experience specifically concerning the matters being evaluated in the *Monograph(s)* to be developed and (b…

Brief rationale for update (max. 200 words)
Amongst criticisms that has been made of the *Monograph* procedure is the suggestion that Working Group members who have directly contributed to the research literature in relation to the matter under evaluation have a vested interest in evaluations likely to increase concern. This criticism is offset by the singular insight which Working Group members invariably bring to respective evaluations. The proposed text enables the current Advisory Group specify and affirm practice that has operated since 1972.

Updated procedures prior the Working Group meeting

Location of text to be updated

Section A6
Page 6
Line Number 1-3

Current text
Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and invited specialists for review.

Proposed update (revised text)
Six months before the meeting, advice concerning relevant publications is sent to Working Group members together with a request to draft particular sections of the anticipated *Monograph*. These texts, designated 'First Drafts', are referred to other individual Working Group members for review, and modified accordingly. The First Drafts are then compiled and access is provided to Working Group Members and Invited Specialists prior to the meeting. From the commencement of the meeting, individual accountability for the wording of texts ceases, as Second Drafts, representing a consensus, are prepared by subgroups as described below.

Brief rationale for update (max. 200 words)
Primarily, the proposed update is necessary to account for current practice. Additionally, the proposed update makes clear that *Monographs* are not developed by the endorsement of individualcontributions, but involve scientific consensus reached and expressed, in the first instance, through subgroups.

Updated procedures after the Working Group meeting

Location of text to be updated

Section	A6
Page	6
Line Number	17-20

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

Proposed update (revised text)
Immediately following the meeting, typically within two weeks, IARC staff in collaboration with the Overall Chair will develop a summary report concerning evaluation(s) made for the purpose of journal publication, currently in *Lancet Oncology*. The final draft of this summary is circulated to all members of the Working Group for approval and, pending any changes, submitted by IARC to the journal. All members of the Working Group are required to observe an embargo, and to not communicate any aspect of the evaluation(s) made, until journal publication occurs. Where possible, the Overall Evaluation statements will be included in the journal publication, as well as being available from the *Monograph* website coinciding with the summary publication. IARC may issue a Press Release to correspond with journal publication of the summary statement.

Publication of the corresponding Volume of IARC *Monographs* is the responsibility of IARC, and includes verification of all citations made. Typically, online publication of the full Volume occurs between one and two years after the *Monograph* meeting.

Brief rationale for update (max. 200 words)
Provision of reasonable information and transparency

Monograph title is determined by the Working Group

Location of text to be updated

Section	B
Page	6
Line Number	22

Current text
No relevant current text: the matter addressed here is not presently included in the Preamble. The text below is proposed to be incorporated as a new paragraph immediately under the Section heading 'B. Scientific Review and Evaluation'

Proposed update (new text)
As structured and developed in accordance with this Preamble, all aspects of any volume of *Monographs* are the prerogative of the relevant Working Group. Such responsibility includes the title of the Volume and the title of individual *Monographs*. Most commonly, the Volume title and *Monograph* titles adopted by the Working Group are those which have been used by IARC staff for planning purposes. However, for the purpose of scientific clarity or for some other reason, the Working Group may identify a different unifying aspect in respect of the *Monographs* being developed, and adopt a new volume title. Likewise, the Working Group may change the title of individual *Monographs,* including when such change as is necessary to merge or split *Monographs* as those *Monographs* were originally envisaged for planning purposes.

Brief rationale for update (max. 200 words)
Though not addressed in the Preamble, the text now proposed describes procedures that have been operational for decades. Examples given here are not exhaustive. For Vol 32 (1983), the anticipated single *Monograph* on 'Polynuclear Aromatic Compounds' was abandoned by the Working Group in favour of about 15 separate *Monographs*, each devoted to a single polynuclear nuclear compound. More recently, a *Monograph* title of 'Red meat and processed meat' proposed for Vol 114 (2018) was altered by the Working Group to 'Consumption of red meat and processed meat'. The title originally envisaged for Vol 119, namely 'Some Chemicals in Food and Consumer Products' was changed by the Working Group to 'Some chemicals that cause tumours of the urinary tract in rodents'. Specification in the Preamble of the responsibility of the Working Group for the Volume title and for the title of individual *Monographs* is appropriate because of transparency, and also to further exclude any notion of 'IARC intervention' as accounting for any aspect of *Monograph* evaluation.

Confidence in cohort studies ahead of case-control studies as establishing an association

Location of text to be updated
Section B2(f)
Page 11
Line Number 38

Current text
No relevant current text: the matter addressed here is not presently included in the Preamble. The text below is proposed to be incorporated as a new paragraph immediately following the paragraph that concludes with the sentence 'If there are inconsistent results among investigations..'

Proposed update (revised text)
Consistent professional practice dictates that when studies otherwise comparable in quality of execution and reporting differ in outcome, greater confidence is vested in cohort studies than in case-control studies as indicating an association. This widely accepted principle was specifically affirmed by the 'Human evidence' subgroup participating in the *Monograph* on 'Consumption of red meat and processed meat' (Volume 114). This ranking of confidence is not a basis for discouraging the design, funding and execution of case-control studies. Studies of risk factors involving a low incidence of cancer, particularly in respect of rare tumour types, may not be amenable to assessment through cohort studies. Well-designed and executed case-control studies may contribute critical insight.

Brief rationale for update (max. 200 words)
The relative ranking of data from cohort studies and from case-control studies respectively as described in the update above is universally recognized. Without knowledge of this principle, a determination by a particular Working Group may appear inexplicable to *Monograph* readers. The vesting of greater confidence in cohort studies should not discourage the initiation and completion of case-control studies in appropriate circumstances, as is specified in the proposed new text.

Concordance between human and animal tumour sites

Location of text to be updated

Section	B3(d)
Page	15
Line Number	10 (*end of present text, staring a new line*)

Current text
No current text; update involves insertion of new heading and new material

Proposed update (revised text)

(d) Concordance between human and animal tumour sites

The anatomical site of tumour development, or the type of malignancy seen in carcinogen-treated experimental animals does not necessarily indicate the most likely site of tumour development in humans exposed to the same carcinogen. However, depending, among other things, on the type and class of carcinogen involved, there is a degree of concordance between human findings and animal evidence. IARC initiated, and recently concluded, a comprehensive and systematic appraisal of the degree of concordance between human and animal data in respect of all, but the most recent IARC evaluations resulting in recognition of agents carcinogenic to humans [1]. In some situations, site of carcinogen-induced tumours in experimental animals may provide an inference in relation to a possible site of tumour development in humans exposed to the same carcinogen.

Reference
[1] Baan R, Stewart BW and Straif K, Eds. (2018) Tumour site concordance and mechanisms of carcinogenesis. IARC Scientific Publications No. 165 IARC Lyon (in press).

Brief rationale for update (max. 200 words)
The proposed update reflects the results of a comprehensive IARC investigation which is to be reported in an IARC Scientific Publication (number 165), presently 'in press'. This assessment of carcinogen-induced cancer in experimental animals presents the context in which animal data may provide inferences concerning the likely site(s) of tumour development in humans. Some indication of this principle is appropriately included in *Monograph* coverage of data from experimental animals.

Mechanisms relevant to tumour site

Location of text to be updated

Section	B4(b)(iv)
Page	17
Line Number	37 (*end of present text, staring a new line*)

Current text
No current text; update involves insertion of new heading and new material

Proposed update (revised text)

The following text presumes that '4. Mechanistic and other relevant data' will be upgraded to describe how mechanistic data is presented with reference to the 'key characteristics' of carcinogens', these characteristics having been developed through an IARC Advisory Group, subsequently subject to journal publication and now regularly used in the course of Monograph evaluations. Despite such anticipated change, the update is shown below with reference to '(iv) which would be relevant were this text inserted into an unchanged '4. Mechanistic and other relevant data'

(iv) Mechanisms relevant to tumour site
The 'key characteristics' concerning carcinogens include recognition that many chemical carcinogens are metabolised to generate electrophilic intermediates capable of binding to DNA to generate pro-mutagenic lesions or, in respective of agents termed non-genotoxic, are able to bind to certain receptors and hence mediate malignant transformation. Apart from indicating that particular chemicals have the capacity to be carcinogenic, findings of this type, and other findings, may be relevant to the site in which tumours develop in carcinogen-treated animals and possibly in humans [1]. Data concerning carcinogen activation or other reaction pathways that is particular to an organ(s) may explain, at least in part, why tumours develop in particular organs following relevant treatment of experimental animals. Conversely, knowledge that an agent is associated with increased risk of a particular tumour type in humans may warrant particular scrutiny of studies using that the corresponding

tissue: studies which because of their small number may have otherwise received little attention. Accordingly, data from experimental systems may be used to predict, confirm or explain so-called target organs for particular carcinogens.

Reference
[1] Baan R, Stewart BW and Straif K, Eds. (2018) Tumour site concordance and mechanisms of carcinogenesis. IARC Scientific Publications No. 165 IARC Lyon (in press).

Brief rationale for update (max. 200 words)
The update above variously reflects practice which is both sound and operational. which has come to the fore during evaluation of PCBs (when the few studies on skin metabolism warranted scrutiny given the target organ) and DDT (where a huge literature on receptor studies warranted appraisal from the perspective that immunosuppression may be relevant to increased risk of non-Hodgkin lymphoma and a hazard in respect of breast cancer was not identified.

Criteria for reporting 'target organ' under 'Carcinogenicity in humans'

Location of text to be updated

Section	B6(a)
Page	19
Line Numbers	9-11

And

Line	17

Current text
At line 9:
A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans.

At line 17, no relevant text.

Proposed update (revised text)
At line 9
A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans in terms of the organ(s) for which there is *sufficient* evidence, and, if there are relevant data, the organ(s) for which there is *limited* evidence

At line 17:
The Working Group, if relevant data are available, identify the target organs for which there is *limited* evidence.

Brief rationale for update (max. 200 words)
This update makes provision for specifying different levels of evidence in respect of target organs, both in the context of both *sufficient* evidence for carcinogenicity in

humans and *limited* evidence of carcinogenicity in humans. That need is currently met by specifying organs by reference to ‘cause’ and/or to ‘a positive association’: terminology which is not defined in the present Preamble for this specific purpose, and which, in the case of ‘cause’, is inappropriate since only epidemiological data are involved.

Editorial matter: Modifying part ‘6’ heading to allow ‘Overall evaluation’ to be ‘7’

Location of text to be updated

Section	B6
Page	19
Line Number	15

And

Section	B6(d)
Page	22
Line	3

Current text
At page 19, line 15
6. Evaluation and rationale
At page 22. Line 3
(d) Overall evaluation

Proposed update (revised text)
6. Evaluation of specific data sets
7. Overall evaluation

Brief rationale for update (max. 200 words)
This update is editorial and would follow if a separate update, elevating the present subsubheading ‘(d) Overall evaluation’ to the subheading ‘7. Overall evaluation and rationale’ is adopted. The justification for an expanded ‘Overall evaluation’ is explained with reference to the proposal to make that change specifically. The term ‘specific data sets’ as used above refers to ‘Carcinogenicity in humans’ ‘Carcinogenicity in animals’ and ‘Mechanistic data’ to be evaluated as the present Preamble describes. But the updated subheading will then not include the present ‘(d) Overall evaluation’ allowing this matter to be designated ‘7.’ in the Preamble.

Specifying ‘Strength of Evidence’ in Group names and discontinuing Group 4

Location of text to be updated

Section	B6(d) and proposed to be new B7
Page	22

Line Number 12

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

Proposed update (revised text)
The 2018 Advisory Group adopted a new approach to the Overall Evaluation: one which made no change to scientific basis of the Overall Evaluation, but which provided clearer communication and more comprehensive information. Though Overall Evaluation of agents and circumstances of exposure is determined by strength of evidence, this key understanding is often not communicated. In particular, the Advisory Group noted that media comment in the last 5 years often equated matters listed in the same 'Group' as indicating equivalence in potency rather than strength of evidence. Apart being confusing, such descriptions of perceived equivalence between widely-damaging hazards and, for example, readily available foods, have the potential to trivialize *Monograph* evaluations.

Consequently the 2018 Advisory Group specified that the various Groups should, in all future *Monographs*, be identified not as 'Group 1' but as 'Strength of Evidence, Group 1' and so on for presently-designated Group 2A, 2B and 3. This change was calculated to markedly reduce the description of inappropriate equivalence. Adoption of these comprehensive names does not alter, or establish a case for re-evaluation, in respect of any *Monograph*.

In relation to 'Strength of Evidence' in the Overall Evaluation, the 2018 Advisory Group recommended no longer including 'Group 4: The agent *is probably not carcinogenic to humans*'. Allocation to Group 4 had required 'Evidence suggesting lack of carcinogenicity' in relation to human and animal data. After 120 volumes of *Monographs*, one agent is currently designated Group 4, with no prospect of that situation ever changing specifically because matters proposed to be evaluated in *Monographs* must, among other things, exhibit 'some evidence or suspicion of carcinogenicity' (see 'A3 Selection of matters for review'). The compelling reason for abolishing Group 4 is that the remaining Strength of Evidence Groups 1-3, now frame the *Monographs* as determine the strength of evidence that an agent or circumstance of exposure is carcinogenic rather than any possible perception that *Monographs* determine whether an agent or circumstance of exposure is carcinogenic or not. The one agent now in Group 4 fulfils all criteria for Strength of Evidence Group 3 where it may be listed from when Group 4 is discontinued.

Brief rationale for update (max. 200 words)
The reasons for adopting 'Strength of Evidence Group 1' and related terminology are adequately indicated in the proposed update and therefore not discussed further here.

Deletion of Group 4 is warranted because Group 4 is unnecessary and a distraction. Group 4 is unnecessary because there has never been a nomination received by IARC for an agent proposed to be categorized Group 4. The prospect of a particular agent

being categorized Group 4 has not been seen in the scientific literature. There is no toxicological recognition of agents lacking carcinogenicity and no review or commentary on such agents exists. Group 4 is a distraction because its inclusion indicates that *Monographs* are about distinguishing between agents that do or don't cause cancer. Untrue. The *Monographs* are about the strength of evidence regarding agents or circumstances of exposure that may cause cancer.

If Group 4 is to be retained, a range of updates are required:

- At A3 , the criterion '(b) there is some evidence or suspicion of carcinogenicity', should be expanded to include 'or evidence of a lack of carcinogenicity'
- Under B. Scientific Review and Evaluation should include specification of studies indicating lack of carcinogenicity. Granted this, the relevant subheadings should be 'Studies of cancer in humans, or lack of it'
- Section B4: In the current 'Mechanistic and other relevant data', no provision is made for 'Data indicating non-operation of mechanisms associated with carcinogenesis'. Relevant mechanisms should be specified.

Information that may be provided in the Overall Evaluation

Location of text to be updated

Section	B6 which is now proposed to be new B7(a)
Page	22
Line Number	13

Current text

No relevant current text; the proposed update is new text rather than amendment or deletion of current text. The proposed text is formatted according to adoption of an earlier update providing for a new 7. Overall evaluation and Rationale.

Proposed update (revised text)

(a) Features of the Overall Evaluation

Criteria for the Overall Evaluation of all matters subject to *Monograph* evaluation are specified in (b) below as the last element in this Preamble. Determinations on the bases of these criteria represent the 'bottom line' and are specified at the end of every *Monograph*. At the discretion of each Working Group, additional information may be included in the Overall Evaluation including:

- More specific information as to particular health authorities for which the evaluation may be relevant. The Overall Evaluation begins with contextual information applicable to all *Monographs* and recognizing their purpose as described in Section A of this Preamble. Namely

- In accordance with resolution of IARC Governing Council, this Overall Evaluation of [insert title of *Monograph*] is provided to health authorities of WHO members states and comparable authorities.

Particular Working Groups may indicate appropriate specific authorities by noting immediate relevance to departments or statutory authorities having national or comparable responsibility for occupational health and workplace hygiene, dietary and nutritional guidelines, pesticide or drug registration, food safety standards, consumer safety and so on.

- The Working Group may provide information concerning specific mechanistic data had which had influenced categorization according to strength of evidence.

- Explaining why the matter evaluated is not the title of the *Monograph*. Almost invariably, the matter identified in the title of the *Monograph* is the matter which is subject to Overall Evaluation. Where this is not the case, the Working Group may provide brief information. Evaluations may also be made of matters apart from or in addition to the matter specified in the Monograph title. Matters so addressed may include the specific components of complex mixtures, or a particular type or category comonly recognized as being an aspect of the *Monograph* title.

- The Working Group may indicate that relevant data were assessed with a view to making a particular evaluation(s), but in the event information available did not justify such an evaluation(s). Where earlier *Monographs* on the same title included an evaluation which has not been addressed in the updating *Monograph*, relevant information may be provided.

- Finally, without engaging in risk-benefit analysis, the Working Group may refer to benefits accruing through the agent or circumstance of exposure under evaluation.

Brief rationale for update (max. 200 words)
Currently, these is no description of what may be addressed in the Overall Evaluation apart from an explanation of mechanism(s) of action influencing categorization on the basis of strength of evidence. Currently, there is variation between *Monographs* in the information provided in Overall Evaluations.

Monograph evaluations have been interpreted by the media and other parties to be personal health advice or personal warnings about risk of cancer. The Preamble has always specified (in Section A) that *Monographs* constitute advice to health authorities. This context is now to be made clear in the Overall Evaluation.

All the issues specified by the bullet points in the updated text can be illustrated by reference to particular *Monographs*, with one exception. Namely, an indication of evaluations not made. This is novel, but readily justified by one anecdote. Having assessed hundreds of epidemiological studies, subgroup 2 (Cancer in humans) for Vol 114 (Consumption of red meat and processed meat) advised a plenary session that the available data were not adequate to make distinction (through separate evaluations)

between beef, lamb and pork or indeed, to distinguish between particular classes of processed meat. Neither did the data justify specific evaluations with reference to well-cooked or burnt meat. The likelihood of a more authoritative assessment of these considerations being made in future than that which was made was made by the particular subgroup is very small, if not zero. Yet there is nothing concerning these specific conclusions regarding type of red meat or different outcomes from cooking in the *Monograph*.

Update of the criteria for Overall Evaluation

Location of text to be updated

Section	B6(d) proposed to be the new B7(b)			
Page	21	to	Page	22
Line Number	27		Line	31

Current text

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

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

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

Group 2:

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

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

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it 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: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient*

evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

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

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

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

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

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

Proposed update (revised text)

(b) Criteria for Overall Evaluation

In the first instance, the matter to be evaluated is described according to the wording of one of the following categories, and the designated group is given. This categorization is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data. A two stage determination process is involved. An initial specification of the Strength of Evidence is made of the basis of evidence (specified as *sufficient*, *limited*, or *inadequate*, as described earlier in this Preamble) from studies in humans and experimental animals as shown in Fig. 1. Then account is taken of mechanistic data, and the Strength of Evidence may be revised as provided for in Figure 2. However, automatic or legalistic reliance on these guides is not possible; every agent or circumstance of exposure involves unique considerations, and hence all constraints described below are guidelines.

Strength of Evidence Group 1: The matter is *known to be carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, a matter may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent or circumstance of exposure acts through a relevant mechanism of carcinogenicity.

Strength of Evidence Group 2:

This category includes matters for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Strength of Evidence Group 2A (*probably carcinogenic to humans*) or Strength of Evidence Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly*

carcinogenic have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Strength of Evidence Group 2A: The matter is *probably carcinogenic to humans*.

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

Strength of Evidence Group 2B: The matter is *possibly carcinogenic to humans*.

This category is used for agents or circumstances of exposure for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent or circumstance of exposure for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. A matter may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Strength of Evidence Group 3: The matter is *not classifiable as to itscarcinogenicity to humans*.

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

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

Agents or circumstances of exposure that do not fall into any other group are also placed in this category.

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

If an evaluation of Strength of Evidence Group 3 is made, the Overall Evaluation ceases at this point, apart from any provision of information or a rationale.

In respect of all other evaluations, designation of the matter using the term 'carcinogen' is given by adopting one of the following statements according to the situations described.

The agent is appropriately described as *a known carcinogen*.

Designation as a carcinogen, regardless of how the term is further qualified, is restricted by current scientific practice and informed communication to agents and not applicable to circumstances of exposure. Designation as a 'known carcinogen' requires, and is limited to, agents, as distinct from circumstances of exposure, categorized Strength of Evidence Group 1.

The agent is appropriately described as *a probable carcinogen*.

Designation as a 'probable carcinogen' requires, and is limited to agents categorized Strength of Evidence Group 2A, and does not apply to circumstances of exposure.

The agent is appropriately described as *a possible carcinogen*.

Designation as a 'possible carcinogen' requires, and is limited to, agents and not circumstances of exposure, categorized Strength of Evidence Group 2B.

This circumstance of exposure is *not appropriately described as a carcinogen*.

The term 'carcinogen' is not established by any universally agreed scientific definition, but is indicative of an agent properly subject to public health action predicated on the understanding that any level of exposure may increase risk of cancer. Such agents are therefore appropriately subject to regulation or control. Common scientific practice does not apply the term 'carcinogen' to circumstances of exposure.

For agents and circumstances of exposure subject to evaluation and categorized as Strength of Evidence Group 1 or 2A the final determination addressed in an Overall Evaluation involves causation and identification of target organ(s). These determinations are made with reference to all available data: cancer in humans, cancer in animals and mechanism of action. The following evaluations may be made in relation to available evidence:

The agent or circumstance of exposure causes cancer of the [insert target organ(s)] in humans and (if warranted by the data, add) probably causes cancer of the [insert target organ(s)] in humans

The evaluation above is restricted to matters evaluated as Strength of Evidence Group 1.

In respect of matters evaluated as Strength of Evidence Group 2A, the evaluation shown below may be adopted.

The agent or circumstance of exposure probably causes cancer of the [insert target organ(s)].

Brief rationale for update (max. 200 words)

The updated Overall Evaluation presented above involves updates of a number of words and presently-used terminology in a different contexts. Rationale for certain of these changes has been presented earlier where the relevant terms are first used in the Preamble, and the relevant rationale are not repeated here. Otherwise, rationales for other specific updates are as follows.

Publication of the Overall Evaluation diagrams provided to Working Group members

These diagrams, and the two-stage procedure they indicate, are key to any comprehensive understanding of *Monograph* evaluations. These diagrams do not establish binding, automatic outcomes as is specified in the relevant updated Preamble text. Although the diagrams are totally consistent with the text explaining respective 'Strength of Evidence' categories, they provide for far clearer understanding.

Adoption of 'known to be carcinogenic' and 'known carcinogen'

Failure to adopt an adjectival qualification for 'carcinogenic' as the definition for Group 1 (in contrast to 'probably' and 'possibly' for 2A and 2B respectively) has resulted in IARC evaluations being 'interpreted', rather than quoted, in scientific and lay publications. The reason for this is obvious. Currently, relying on the 2006 Preamble, it may be said: '*Monographs* address agents suspected to be carcinogenic and categorize them according to whether they are carcinogenic, probably carcinogenic or possibly carcinogenic. The situation is worse when IARC evaluations are interpreted as identifying a 'carcinogen' (a word not currently used in the Overall Evaluation). In the scientific literature, statements like 'Benzene is a carcinogen according to IARC' are never seen; rather authors feel impelled to indicate that a definitive evaluation has been made by stating 'Benzene is a known carcinogen according to IARC'. Other comparable terms may be used as IARC evaluations are interpreted. Adoption of 'known', as proposed, will contribute toward IARC reclaiming control of its own evaluation terminology.

Specification of 'cause' in the Overall Evaluation rather than this terminology being used in respect of epidemiological data alone.

All commentaries on recognition of causation from epidemiological data concerning chronic, non-infectious risk factors, initially discuss necessary aspects of epidemiological investigations required, and then anticipate reference to all available data before specifying causation. Hill (1965) refers to the necessity to take account of 'biological plausibility' and Vineis (2018) to 'mechanism of action'. *Monograph* evaluations are ultimately based on all relevant human, animal and experimental data. The current *Monograph* practice, of asserting 'cause' wholly on the basis of epidemiological data, is inconsistent with scientific principles and with the systematic taking account of different data sets upon which the *Monographs* are based.

Concerning 'Carcinogenicity in humans', and for *sufficient evidence*, the Preamble specifies 'The Working Group considers that a causal relationship has been established…..and chance, bias and confounding could be ruled out with reasonable confidence'. Such determination of a 'causal relationship' from epidemiological data does not preclude later specification of 'causes' in reference to a particular tumour type in the Overall Evaluation. The Preamble goes on 'A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) where an increased risk of cancer was observed….' Again, providing a statement

specifying ‘increased risk’ from epidemiological data does not preclude, or trivialize, final specification of ‘target organ’ after all data are considered.

In short, specification of causation at the end of the Overall Evaluation is appropriate if the preceding evaluation of ‘Carcinogenicity in humans’ is set down using the words indicated for that purpose in the Preamble, rather than the words currently used.

Reporting likely target organ(s) for Strength of Evidence Group 2A evaluations

Scientific and media reporting the Volume 114 evaluations typically stated ‘IARC has found that eating red meat probably causes bowel/colorectal cancer’. There is no such statement in the *Monograph*, but is it wrong? Arguably the statement is not only correct; it brings together key information that otherwise is only available by integration of information provided in different parts of the Summary and Evaluation section. *Limited evidence of carcinogenicity* in humans is typically based on multiple studies concerning the same tumour type, amongst the totality of epidemiological data variously including a relatively small number of studies on each of multiple tumour types, the outcome from which for each tumour type is inconsistent. Specification of the tumour type primarily determining *limited evidence of carcinogenicity* in humans is reasonable and serves to make *Monograph* determinations more accessible.

Adoption of ‘probably causes’ in specifying the likely target organ(s) in the context of Strength of Evidence Group 2A.

Consideration of the assessment mentioned above, namely ‘IARC has found that eating red meat probably causes bowel/colorectal cancer’ also serves to indicate that the words ‘probably causes’ are entirely reasonable in the context under discussion. Use of this terminology in the relevant Overall Evaluation serves to make the outcome of a particular category of *Monograph* evaluation immediately accessible, without relying on conflation of various statements in the *Monograph* in question by third parties.

Specification of causation as the bottom line in Overall Evaluations

A confusing aspect of *Monograph* evaluations is that, for agents or circumstances of exposure specified to cause cancer, this most crucial information is not to be found at the end of the Overall Evaluation. Indeed, currently, that information is not found in the Overall Evaluation at all!

Compare the statement ‘Diesel engine exhaust causes cancer of the lung’ with ‘Diesel engine exhaust is carcinogenic to humans’ (Vol 105). The statement referring to causation of lung cancer is more concise; more informative; more memorable; less reliant on technical language and carries a clearer inference of possible prevention than the statement referring to carcinogenicity.

In current Monographs (where relevant), the relationship between the two such statements under consideration is counter intuitive. Logically, having established that diesel exhaust is carcinogenic to humans, reference to other data might allow specification that diesel exhaust causes cancer of the lung. Yet the *Monograph* is presently constrained to proceeding in the opposite direction: having established that diesel exhaust causes lung cancer, consideration of additional information permits assertion that diesel engine exhaust is carcinogenic.

Finally, counter to what any reader might take for granted, Working Group members never deliberated on specification of lung cancer as the target organ for diesel exhaust, or any such comparable determination: the naming of target organ(s) is included in a required corollary once *sufficient evidence* in humans is agreed.

The above considerations contribute to establishing why the *Monographs* are generally viewed as inaccessible and requiring specialist skill to enable correction interpretation.

This discussion is primarily concerned with problems of communication which increase the likelihood of extrapolation or interpretation of *Monograph* evaluations occurring rather than *Monograph* evaluations being quoted directly. The proposed updated Overall Evaluation will eliminate or reduce all problems consequent upon Monograph evaluations being 'explained' or interpreted.

Annex 3.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Advisory Group to Recommend an Update to the Preamble

Scientific Webinar, 15:00 – 18:00 (CEST), 17 September 2018

Agenda

15:00 – 15:05	Introduction from IARC Secretariat
15:05 – 15:15	Bice Fubini, University of Turin, Italy
15:15 – 15:25	Sabine Francke, U.S. Food and Drug Administration, USA
15:25 – 15:35	Nathaniel Rothman, National Cancer Institute (NCI), USA
15:35 – 15:45	Bernard Stewart, School of Women's & Children's Health, UNSW Australia
15:45 – 15:55	Julie Goodman, Gradient, USA
15:55 –16:05	Daniele Wikoff, ToxStrategies, USA
16:05 – 16:15	Jen Sass, Natural Resources Defence Council (NDRC), USA
16:15 – 16:25	Tracey Woodruff, University of California, USA
16:25 – 16:35	Martyn Smith, University of California, Berkeley School of Public Health, USA
16:35 – 16:45	Elaine Faustman, Department of Environmental and Occupational Health Sciences, University of Washington, USA
16:45 – 16:55	David Christiani, Harvard Chan School of Public Health, United States [pre-recorded presentation]
16:55 – 17:05	Ron Melnick, NIEHS, USA
17:05 – 17:15	Jef French, UNC Gillings School of Global Public Health, University of North Carolina, USA
17:15 – 17:25	Paul Lambert, University of Wisconsin, USA
17:25 – 17:35	John Cherrie, Heriot-Watt University, United Kingdom
17:35 – 17:45	Paul Demers, Occupational Cancer Research Centre Toronto, Canada
17:45 – 17:50	Dana Loomis, University of Nevada, USA
17:50 – 18:00	Q & A and Wrap up

List of speakers and participants

IARC requests that you do not contact or lobby participants, send them written materials, or offer favours that could appear to be linked to their participation. (You may send pertinent written materials to IARC.) IARC will ask participants to report all such contacts and will publicly reveal any attempt to influence the meeting. Thank you for your cooperation.

Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

Speakers

John Cherrie, Heriot-Watt University, United Kingdom[1]
David Christiani, Harvard Chan School of Public Health, United States[2] [pre-recorded presentation]
Paul Demers, Occupational Cancer Research Centre Toronto, Canada
Elaine Faustman, Department of Environmental and Occupational Health Sciences, University of Washington, United States
Sabine Francke, U.S. Food and Drug Administration, United States
Jef French, UNC Gillings School of Global Public Health, University of North Carolina, United States
Bice Fubini, University of Turin, Italy
Julie Goodman, Gradient
Paul Lambert, University of Wisconsin, Unites States
Dana Loomis, University of Nevada, United States
Ron Melnick, NIEHS, United States
Nathaniel Rothman, National Cancer Institute (NCI), United States
Jen Sass, Natural Resources Defence Council (NDRC), United States
Martyn Smith, University of California, Berkeley School of Public Health, United States
Bernard Stewart, School of Women's & Children's Health, UNSW Australia
Daniele Wikoff, ToxStrategies[3]
Tracey Woodruff, University of California, United States[4]

Webinar Participants

Frederick Beland, U.S. Food and Drug Administration, USA
Patience Browne, France
Weihsueh A. Chiu, Texas A&M University, USA
Vincent Cogliano, U.S. Environmental Protection Agency, USA
Neeraja Erraguntla, American Chemistry Council, USA[5]
Lin Fritschi, Curtin University, Australia

[1] John Cherrie, is a co-investigator of the IMPRESS project funded by the European Crop Protection Association, and a co-investigator of a study on hardmetal workers funded by the International Tungsten Industry Association.
[2] David Christiani , has provided expert testimony for various law firms for victims of tobacco use and for victims of asbestos exposure.
[3] Daniele Wikoff, is employed by ToxStrategies, a consulting firm that has provided research services to the American Beverage Association. ToxStrategies received financial support from the American Beverage Association for preparing written and oral comments, as well as travel support for Dr. Wikoff to participate as an observer.
[4] Tracey Woodruff, has received research support from various foundations for projects on systematic review methodology and decision making in public health.
[5] Neeraja Erraguntla, is Director, Chemical Products & Technology Division, American Chemistry Council. Her employer will support her travel to attend the Preamble AG meeting.

An Jamers, European Commission
Jennifer Jinot, US Environmental Protection Agency, USA [retired]
Jun Kanno, Japan Organization of Occupational Health and Safety, Japan
Andrew Kraft, U.S. EPA Integrated Risk Information System (IRIS) Program, USA
David Kriebel, University of Massachusetts Lowell, USA
Dirk W. Lachenmeier, Chemical and Veterinary Investigation Agency Karlsruhe, Germany
Qing Lan, National Cancer Institute, USA
Gérard Lasfargues, Director General, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), France
Frank Le Curieux, European Chemicals Agency (ECHA), Finland
Ruth M. Lunn, National Institute of Environmental Health Sciences, USA
Karlyn Middleton, U.S. Food and Drug Administration, USA
Rachel Owen, U.S. Department of State, USA
Susan Peters, Utrecht University, The Netherlands
Jonathan M. Samet, University of Colorado, USA
Jack Siemiatycki, University of Montreal, Canada
Hideko Sone, National Institute for Environmental Studies, Japan
Katya Tsaioun, Johns Hopkins Bloomberg School of Public Health, USA[6]
Jon Williamson, University of Kent, United Kingdom
Marianna Yakubovskaya, Ministry of Health, Russian Federation

IARC Secretariat

Lamia Benbrahim-Tallaa, IARC Monographs Group
Véronique Bouvard, IARC Monographs Group
Fatiha El Ghissassi, IARC Monographs Group
Yann Grosse, IARC Monographs Group
Kathryn Guyton, IARC Monographs Group
Amy Hall, IARC Monographs Group
Tamas Landesz, Administration and Finance
Heidi Mattock, IARC Monographs Group (Editor)
Mary Schubauer-Berigan, IARC Monographs Group
Kurt Straif, Head, Section of Evidence Synthesis and Classification

Posted on 09 November 2018

[6] Katya Tsaioun, is employed by the Johns Hopkins Bloomberg School of Public Health. Her employer will support her travel to attend the Preamble AG meeting.

Annex 4.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Advisory Group to Recommend an Update to the Preamble
Scientific Webinar, 15:00 – 18:00 (CEST), 17 September 2018

Compilation of presenters' slides

Agenda

15:00 – 15:05	Introduction from IARC Secretariat
15:05 – 15:15	Bice Fubini, University of Turin, Italy
15:15 – 15:25	Sabine Francke, U.S. Food and Drug Administration, USA
15:25 – 15:35	Nathaniel Rothman, National Cancer Institute (NCI), USA
15:35 – 15:45	Bernard Stewart, School of Women's & Children's Health, UNSW Australia Julie Goodman,
15:45 – 15:55	Gradient, USA
15:55 –16:05	Daniele Wikoff, ToxStrategies, USA
16:05 – 16:15	Jen Sass, Natural Resources Defence Council (NDRC), USA (oral presentation)
16:15 – 16:25	Tracey Woodruff, University of California, USA
16:25 – 16:35	Martyn Smith, University of California, Berkeley School of Public Health, USA
16:35 – 16:45	Elaine Faustman, Department of Environmental and Occupational Health Sciences, University of Washington, USA
16:45 – 16:55	David Christiani, Harvard Chan School of Public Health, United States [pre-recorded presentation]
16:55 – 17:05	Ron Melnick, NIEHS, USA
17:05 – 17:15	John E. French, UNC Gillings School of Global Public Health, University of North Carolina, USA
17:15 – 17:25	Paul Lambert, University of Wisconsin, USA
17:25 – 17:35	John Cherrie, Heriot-Watt University, United Kingdom
17:35 – 17:45	Paul Demers, Occupational Cancer Research Centre Toronto, Canada
17:45 – 17:50	Dana Loomis, University of Nevada, USA
17:50 – 18:00	Q & A and Wrap up

Please click on the name of the presenter to access the corresponding presentation

1 - Bice Fubini

IARC Preamble update

outline

Particles , fibers and foreign bodies

1 Peculiarity of agents acting in the solid state, particularly particles and fibers

⇐ Several chemical and physical properties to be indicated in section B1

2 Choice of the appropriate metric when comparing exposures in human data and doses in animal and in vitro cellular tests when comparing results obtained with different sources of the agent

⇐ The answer comes from mechanisms

3 Particles, dusts, fibers and foreign matter are not simple physical agents

4 Several physico chemical features and different reactive surface site involved in the carcinogenic mecchanism

⇐ Expected variability of hazard because of variability of all these features in different sources of the agent

Particles , fibers and foreign bodies

Preamble section B1

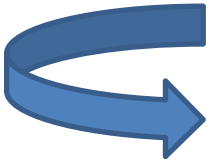
Agents acting at the **solid state** – particles, fibers, foreign bodies - are different from chemical , physical or biological agents, and should be mentioned separately in the list of agents (section B 1(a).

They act through their **exposed surface**, their **form/shape** end their **dimensions** Often all these factors contribute, at different stages of the pathogenic process, to the toxic response of cells and tissues.

Form, relative dimensions and, for particles and fibers, also **size distribution** and **specific surface** (extension of surface per unit mass), allow a precise definition of the agent. **Chemical composition** (s), whether mineral or material, mixture or single compound should be indicated

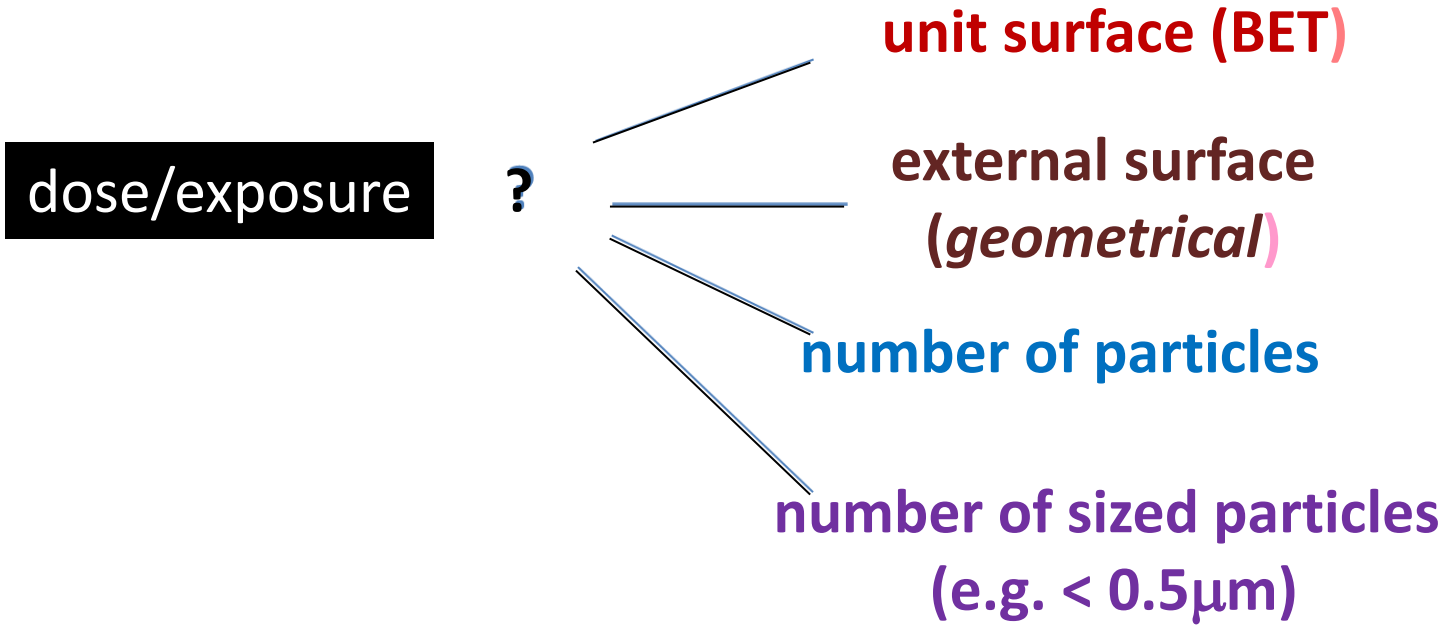
Particles and fibers mainly act as human carcinogens when inhaled, however when in the **nanosize range** penetrate through several body barriers, thus attaining various organs. The term *inhaled* in (section B 1(a) is thus presently too restrictive

Feedback from mechanisms for dose evaluation in animal studies and exposures in human studies



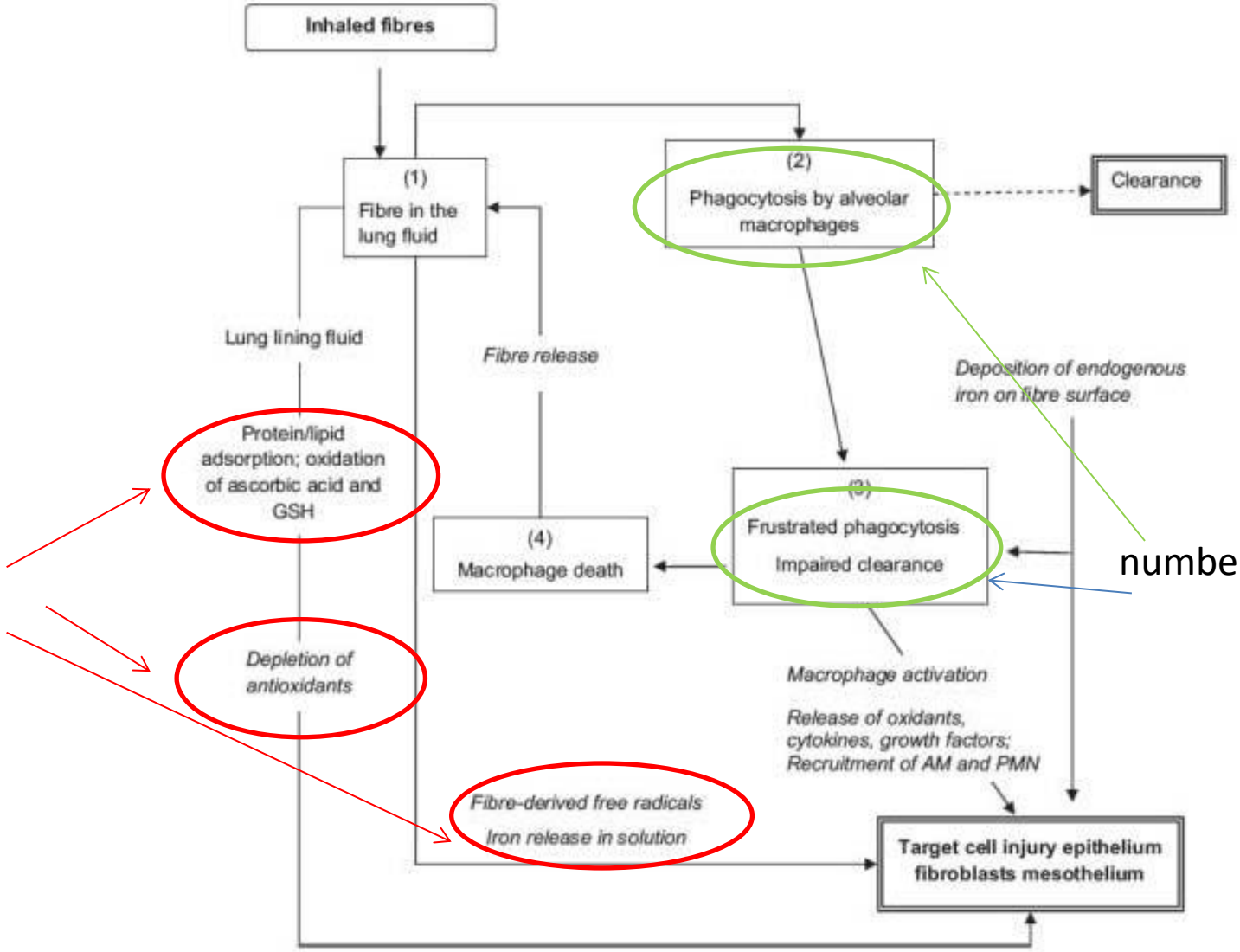
Particularly relevant with nanomaterials

Metrics: which is the best unit to use when comparing **doses** (animal o in vitro cellular tests) or **exposures** (human data) of different sources of the agent? Mass?



The mass is sufficient for"molecular" toxic agents but not for "particulate" toxic agents

asbestos



surface

number of fibers

IARC monograph 100c

A solid particle may comprise several characteristics – some chemical, some physical- which may act independently in different steps of the carcinogenic mechanism

From mechanisms the choice of the appropriate metric
for fibers and particles, often more than one has to be considered

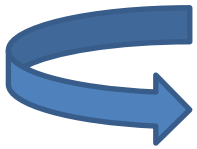
3 Particles, dusts, fibers and foreign matter are not simple physical agents

The scientific community agrees that with particles and fibers three factors determine pathogenicity

Size and shape

Surface reactivity

Biopersistence



Section 4, point (iii) " changes at the molecular level" page 25

… Physical agents may also be considered to comprise foreign bodies …poorly soluble particles dust and particles….

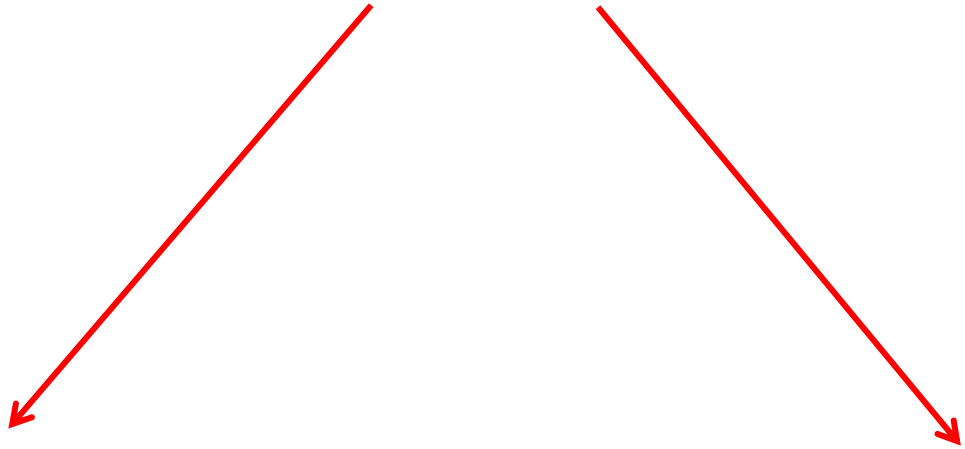
This limits the action to size and shape, without mentioning the chemical aspects linked to surface reactivity and biopersistence

4 Hazard variability

adverse reactions originate at the **interface** between the surface of the agent and body fluids, cell membranes or tissues

The surface

The surface, two independent aspects: extention (physical feature) and surface reactivity, (chemical feature)

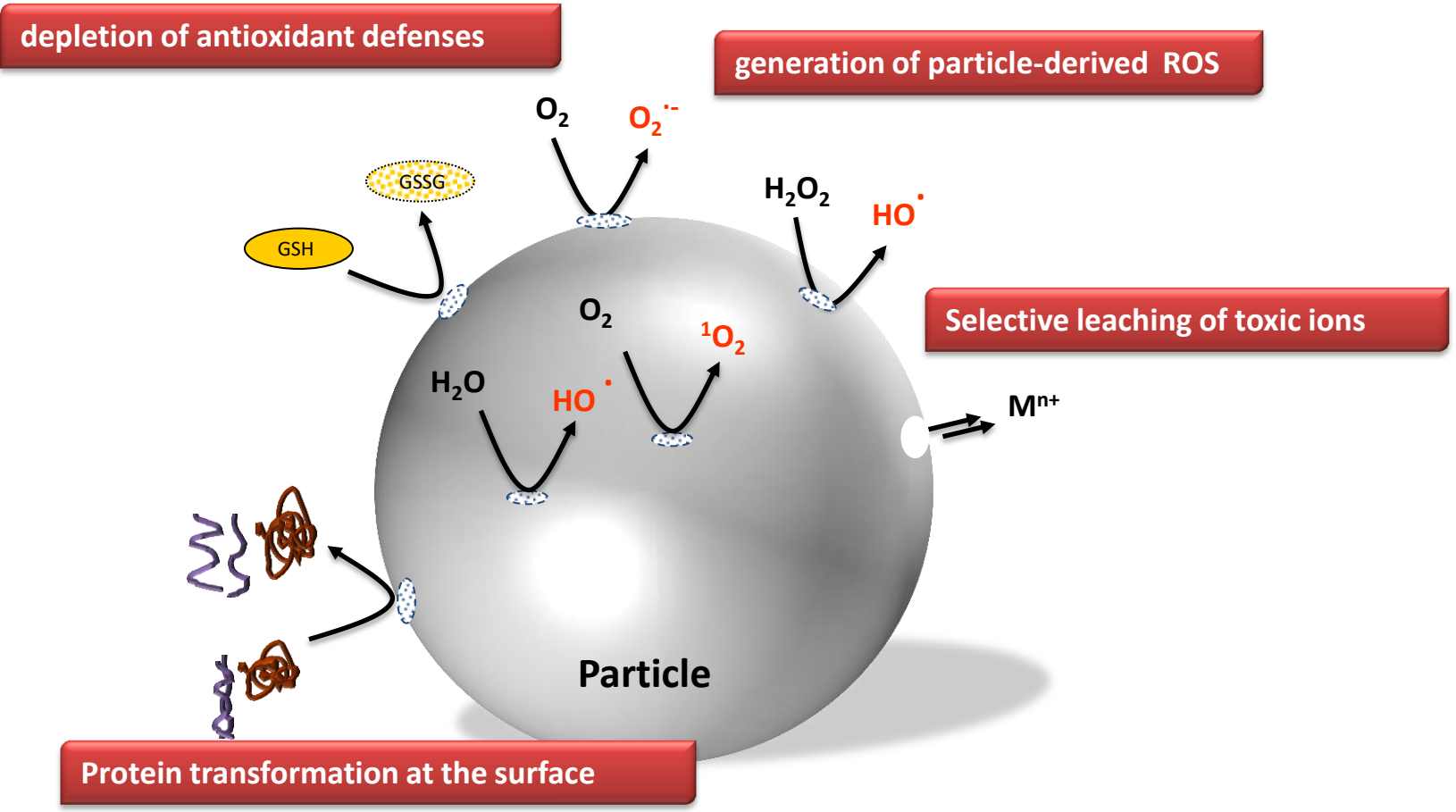


Specific surface: metric

Surface reactivity: generation of biochemical reaction upon contact with living matter

On a single particle various kinds of reactive surface sites

Different surface sites give rise to different potentially adverse reactions



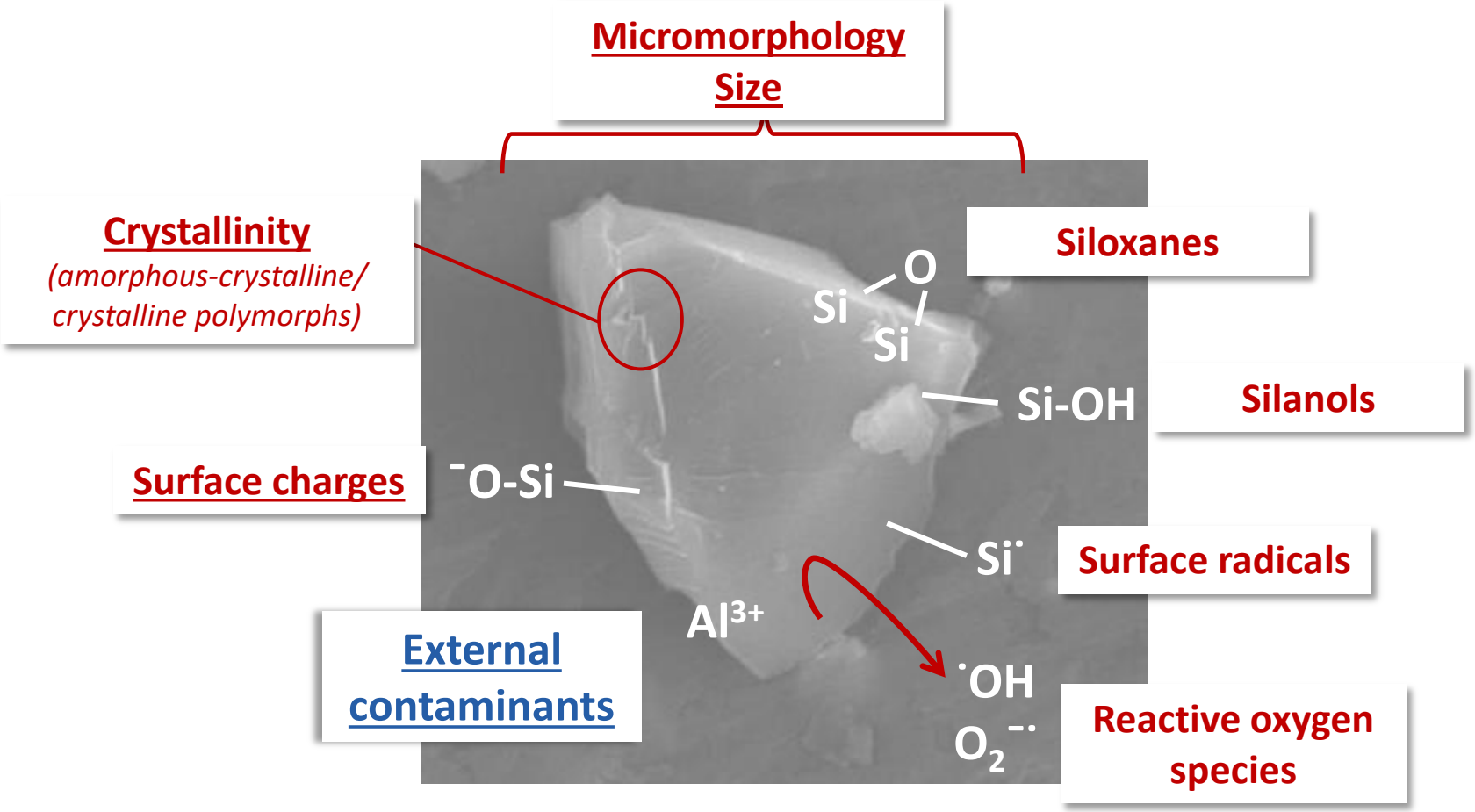
The relative abundance of surface sites may vary from one to another source

Great variability in the hazard related to solid agents

Take into account such possible differences when comparing studies

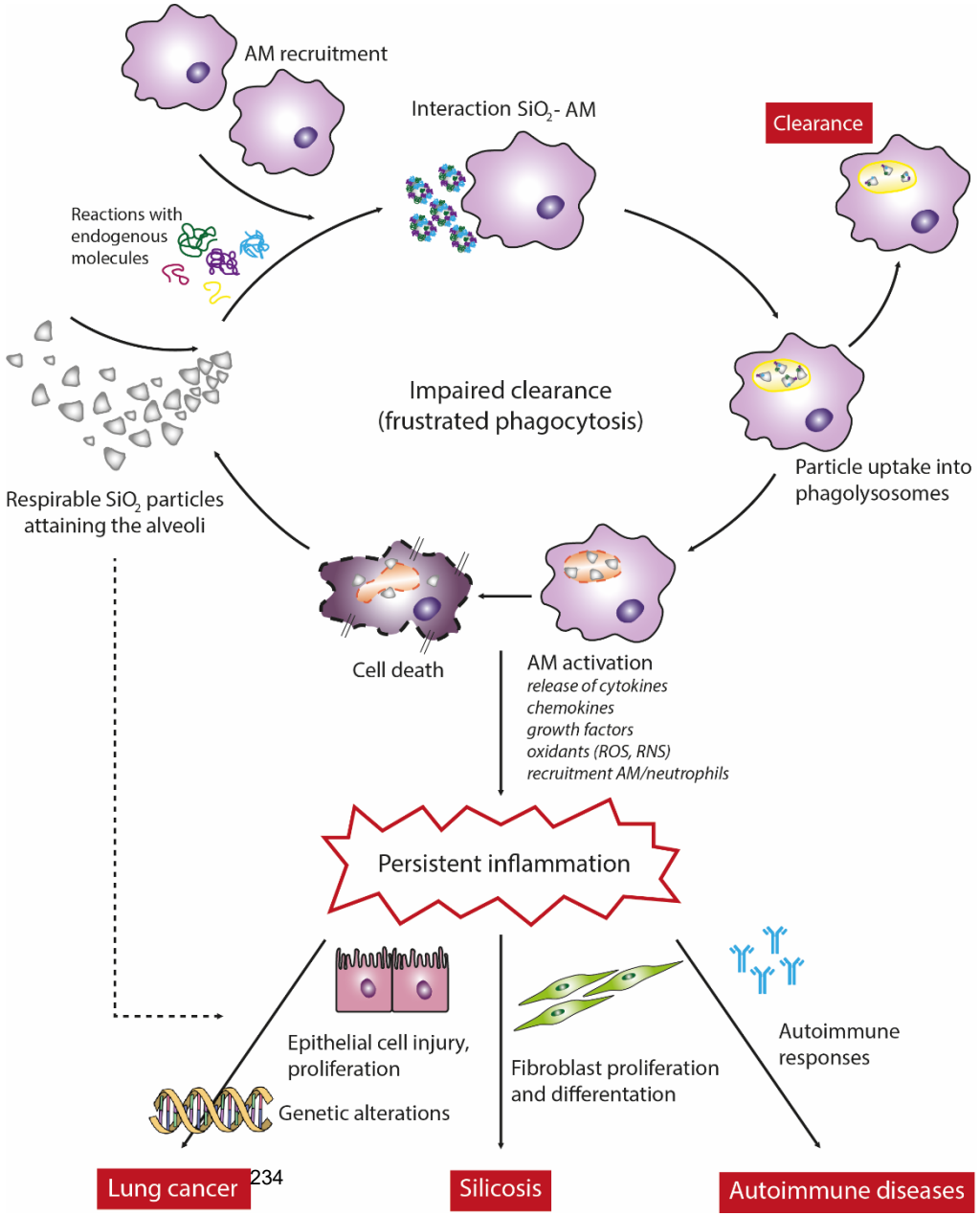
The physico-chemical bases of silica intrinsic variability

Large variety of physico-chemical features involved in the pathogenic process



Variety of particles with different surface properties → reactivity → pathogenicity

Silica particles interact with living matter in several subsequent steps



Redrawn from scheme in IARC monograph (*Vol. 100C,* ***2012***)
C. Pavan & B. Fubini, *Chem. Res. Toxicol. (2017)*

2 - Sabine Francke

Recommendations for an IARC Preamble Update from a regulatory pathology perspective

Sabine Francke, DVM, Dr.vetmed., PhD, DABT, Fellow IATP
Expert Toxicologic Veterinary Regulatory Review Pathologist

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Senior Science and Policy Staff
CFSAN Pathology
sabine.francke@fda.hhs.gov

IARC Preamble

- Thank you for the opportunity to speak
- We appreciate IARC's important work and its value to global regulatory decision making
- Specifically, the preamble contains many valuable considerations – still true despite rapidly changing science pertaining to carcinogenicity

US FDA CFSAN Pathology's Role in Cancer Risk assessment

=

Hazard identification

Reference: Bredfeldt and Arrieta, Hazard Identification in Toxicological Risk Assessment for Beginners; EditorsTorres and Bobst, Springer 2015, 19-41.

Hazard Identification

Its role within the Risk assessment process

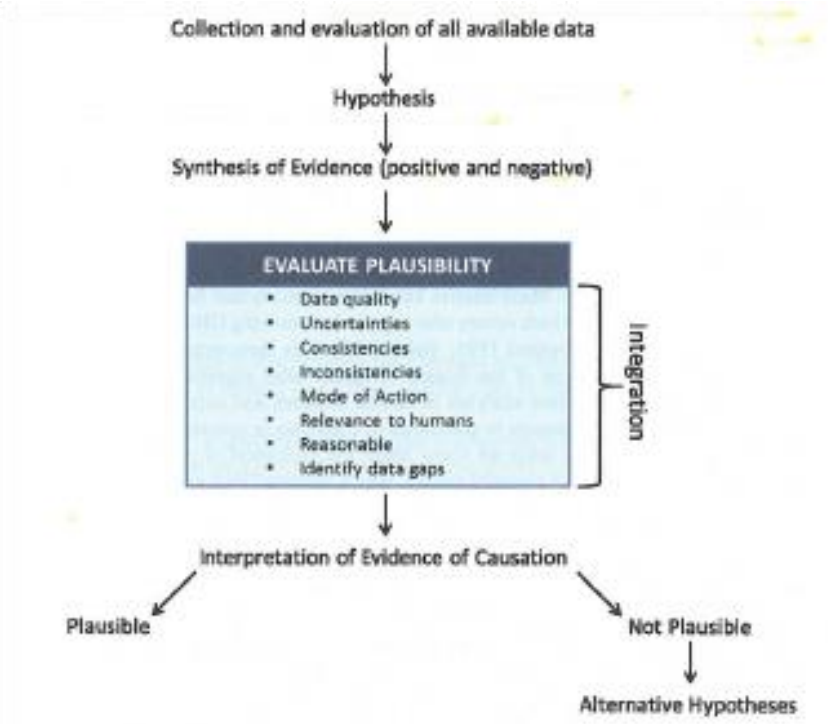


Fig. 2.3 Illustrates the process of assessing and integrating evidence during hazard identification. The integration of various lines of evidence is sometimes called a weight of evidence analysis wherein available data is evaluated to determine if exposure to a chemical of concern causes the observed adverse effect(s).

Reference: Bredfeldt and Arrieta, Hazard Identification in Toxicological Risk Assessment for Beginners; EditorsTorres and Bobst, Springer 2015, 19-41.

US FDA's regulatory utility of the IARC monographs could improve if the following points would be considered while updating the IARC preamble

1. Shorten the preamble

– concisely state the IARC monograph's scope and objectives being restricted to only Hazard identification within the Risk assessment process

a. Clearly define all assessment related terminology

b. Highlight what falls in the scope and objectives

c. Emphasize that IARC does not conduct the risk assessment itself

b. Eliminate all information in the preamble that contradicts point 1) c.

2. Reword the Monograph conclusion categories so that they cannot be confused with risk assessment terminology

a. Each category should include unequivocal terms that tie it specifically to Hazard identification (not risk assessment) and

b. speak specifically to data quality pointing to an overall weight of evidence of

– positive,

– equivocal or

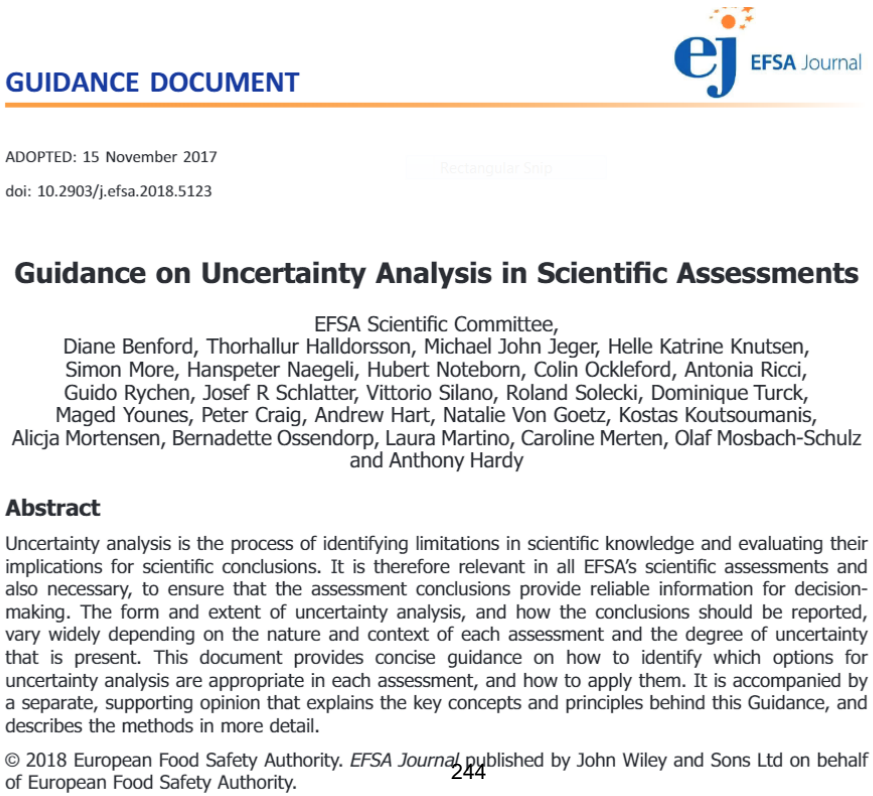
– negative carcinogenic test results.

2. cont. Reword the Monograph conclusion categories so that they cannot be confused with risk assessment terminology - Examples

- Quality and quantity (weight of evidence) of the materials evaluated point to overall positive test results pertaining to the carcinogenic potential of compound x
- Quality and quantity (weight of evidence) of the materials evaluated point to some positive test results and some negative test results pertaining to the carcinogenic potential of compound x – therefore, further studies are necessary and the compound will be re-evaluated in y amount of time
- Quality and quantity (weight of evidence) of the materials evaluated are overall inconclusive pertaining to the carcinogenic potential of compound x – therefore, an assessment cannot be made for the following reasons….
- Quality and quantity (weight of evidence) of the materials evaluated point to overall negative test results pertaining to the carcinogenic potential of compound x

3. Include statements addressing the Uncertainty in IARC's Hazard identification

(e.g. EFSA 2018 guidance)



GUIDANCE DOCUMENT

EFSA Journal

ADOPTED: 15 November 2017

doi: 10.2903/j.efsa.2018.5123

Guidance on Uncertainty Analysis in Scientific Assessments

EFSA Scientific Committee,
Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Maged Younes, Peter Craig, Andrew Hart, Natalie Von Goetz, Kostas Koutsoumanis, Alicja Mortensen, Bernadette Ossendorp, Laura Martino, Caroline Merten, Olaf Mosbach-Schulz and Anthony Hardy

Abstract

Uncertainty analysis is the process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions. It is therefore relevant in all EFSA's scientific assessments and also necessary, to ensure that the assessment conclusions provide reliable information for decision-making. The form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of each assessment and the degree of uncertainty that is present. This document provides concise guidance on how to identify which options for uncertainty analysis are appropriate in each assessment, and how to apply them. It is accompanied by a separate, supporting opinion that explains the key concepts and principles behind this Guidance, and describes the methods in more detail.

4. Update literature references

→ to current state of the science and professional best practices (consider Society of Toxicologic Pathology /European Society of Toxicologic Pathology best practice papers)

5. Mindfully nurture stakeholder confidence in the IARC assessment results

→ provide the greatest possible level of transparency during the monograph development by

→ publicly communicate changes to the monograph drafts and their scientific rationale, proactively as the changes occur.

- E.g. post session minutes that summarize the discussion points and committee agreements of each draft revision.[10]

Thank you for the opportunity to speak

and

for your consideration of these comments.

3 - David Christiani (see video)

4 - Bernard W. Stewart

The IARC *Monograph* Preamble
What's to be done in 2018?

Bernard W. Stewart

Faculty of Medicine, University of New South Wales

and

Cancer Control Program,

South Eastern Sydney Public Health Unit

Who's best informed?

Since 2006, at least 35 volumes of *Monographs* have been published

Some *Monograph* Programme staff members (including the Head) have probably participated in more that 30 meetings

By comparison, visiting scientists heavily engaged in the *Monographs* may have been involved in as many as six meetings.

IARC staff have greatest knowledge, but are limited in the extent of their participation.

The basis of previous updates

Typically, revisions of the Preamble have concerned changes necessary to incorporate new scientific insight or new procedures on the basis of

(1) IARC investigations achieved through Scientific Publications or Advisory Group meetings

Or

(2) Procedures seen to have been productive or necessary at one or more then-recent *Monograph* meetings

Recent IARC investigations

Recent *Monograph* Advisory Group meetings have concerned:

- Quantitative aspects of *Monograph* evaluations. Report addressed options but did not specify text changes to the Preamble.
- Concordance between tumour sites in humans and in animals following comparable carcinogen exposure: 'in press' as an IARC Scientific Publication
- Mechanisms of carcinogenesis: Peer review publication of the 'key characteristics'

Recent *Monograph* precedents

Recent *Monograph* Working Group meetings have resulted in decisions to:

- Accord greater confidence in cohort studies than in case-control studies for determining relevant associations
- Order 'key characteristic data' according to its relevant human cancer(s) rather than according to matters most studied.
- Determine matters to be subject to evaluation (apart from *Monograph* title), modify *Monograph* title and change the Volume title.

And what's new in 2018?

The *Monographs* are under attack.

Issues include (but are not limited to)

Reliance on 'experts who have a vested interest' (ie Working Group members are chosen specifically because of their contribution to the research being evaluated)

and

Reliance on peer-reviewed (journal) publications

Are any such matters to be affirmed or justified in the Preamble?

And what's new in 2018?

As originally envisaged both the Preamble and the *Monographs* themselves were 'scientist-to-scientist communications.

Not any more!!

***Monograph* evaluations are 'explained' by the media to the wider community.**

The headlines include

Red meat ‘probably’ causes bowel cancer

Bacon, Hot Dogs: carcinogens from the corner store

WHO lists processed meat with asbestos and tobacco smoke

These statements cannot be dismissed as lies;

These statements require explanation, but relevant explanations are not achieved by quoting the corresponding IARC evaluations.

5 - Julie E. Goodman

Improving the Monograph Preamble

Julie E. Goodman, Ph.D., DABT, FACE, ATS

Preparation of this presentation was funded by the American Chemistry Council.

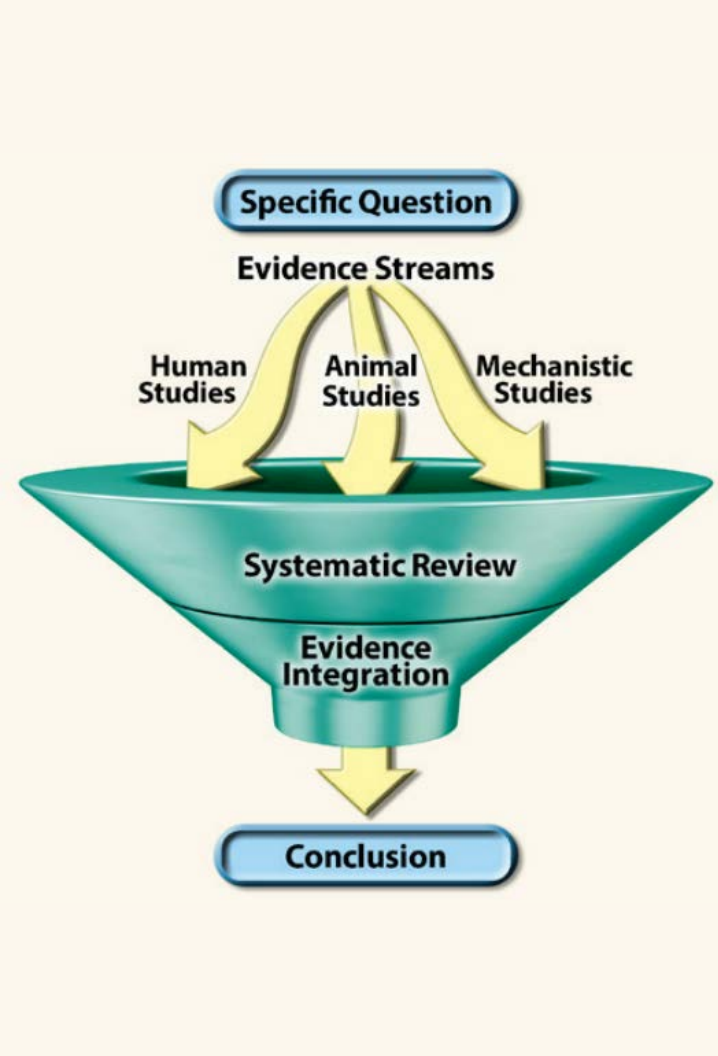
IARC Preamble Scientific Webinar
17 September 2018

Overview

- Current Preamble and Author Instructions, while providing useful information regarding general guidance, do not entirely conform to evidence-based systematic review methodology
- A thorough and comprehensive upgrade to the Monographs' guidance and procedures is needed to ensure they meet contemporary 21st century standards and best practices
- **Recommendations:** Include more specific guidance so all reviews are
    - Consistent
    - Systematic
    - Transparent
    - Comprehensive
    - Coherent

Systematic Review

- Detailed protocols for systematic review are needed
  - Could be in separate document and updated independently of the Preamble, as needed
  - Should be consistent across Monographs
  - Can be developed based on available methods

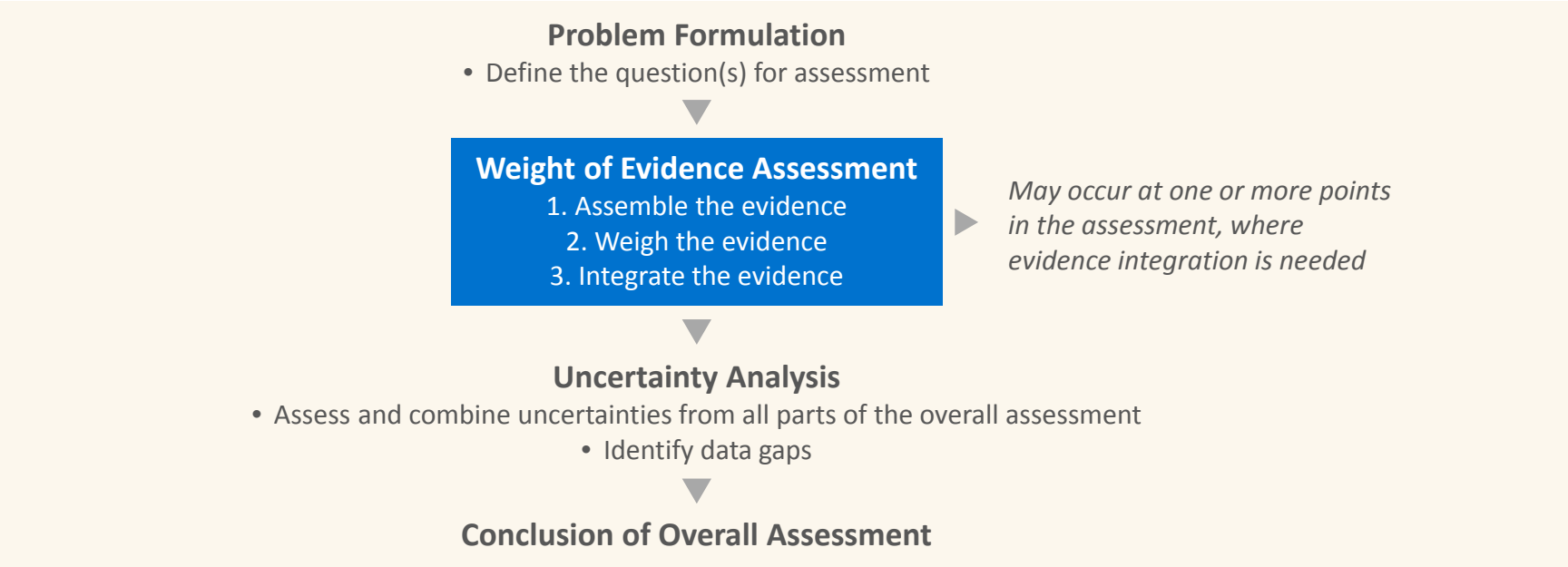


Study Quality

- Importance of study quality discussed in Preamble very broadly
- Should be expanded to include:
  - How factors that affect study quality impact the interpretation of study results
  - How results from low quality studies will be considered
  - How study quality information will be utilized when considering the body of literature as a whole.
- **Examples:** EFSA, US EPA, NTP, Texas Commission on Environmental Quality (TCEQ)

Evidence Integration

- Consider study quality
- Take into account null/negative associations
- Consider human relevance
- Adopt Mode of Action (MoA) as a central organizing principle



Mechanistic and Mode-of-Action Evidence

- Current key-characteristics-of-carcinogens approach for mechanistic data is scientifically flawed
- Evaluate the totality of evidence (including high-throughput assay data) on plausible MoAs
- Consider study quality
- Determine the relevance of observed MoAs to humans
- Integrate equally and concurrently with other lines of evidence

Goodman, J; Lynch, H. 2017. "Improving the International Agency for Research on Cancer's consideration of mechanistic evidence." *Toxicol. Appl. Pharmacol.* 319 :39-46. doi: 10.1016/j.taap.2017.01.020.

Other Recommendations

- Consider experts from all sectors (balance of perspectives)
- Formalize chemical selection process
- Have MoA guiding principle for problem formulation
- Develop clear methodology for study selection
- Consider exposure route and dose in hazard assessment
- Formalize process for resolving conflicting opinions
- Make the decision-making process transparent
- Consider assessments by other scientific and regulatory bodies
- Consider public comments and independent peer reviews
- Improve hazard (*vs*. risk) communication

Questions?

Julie E. Goodman, Ph.D., DABT, FACE, ATS

Principal

jgoodman@gradientcorp.com
(617) 395-5525

The full set of comments can be accessed at:
https://www.americanchemistry.com/ACC-ASARP-IARC-Preamble-Comments-28-Aug-2018.pdf

Preparation of written comments and this presentation were funded by the American Chemistry Council.

6 - Daniele Wikoff

ToxStrategies

Public Webinar Comments: Advisory Group to Recommend an Update to the Preamble

Dr. Daniele Wikoff

Health Sciences Practice Director, ToxStrategies

Vice-Chair, Evidence-Based Toxicology Collaboration Scientific Advisory Board

Associate Editor (Systematic Review), Toxicological Sciences

Supported by the American Beverage Association

Innovative Solutions
Sound Science

Written and oral comments

Submitted written comments for consideration

- Key comments summarized herein

Most comments reflect text that does not currently exist in the Preamble

- Difficult to use the template provided

Omit use of the term “risk” ☐ replace with “hazard”

The term “risk” should be replaced with the term “hazard” throughout the Preamble. It is important that authorities have clear definitions of what the output represents, such that they can appropriately use the Monographs in evaluations of risk. It is critical that the preamble reflect the underlying scientific process which is only of hazard identification (not risk).

- *Issues addressed:*
  - *Confusion regarding the use of the term “risk” continues to increase.*
  - *While the issue regarding the use of the term “risk” has been deliberated in the past, the IARC Monographs still retain the term “risk” in their title. The 2015 IARC Monographs Q&A points out their cancer classifications are hazards, not risks: “IARC classifies carcinogens in five categories ... The classification indicates the weight of the evidence as to whether an agent is capable of causing cancer (technically called ‘hazard’), but it does not measure the likelihood that cancer will occur (technically called ‘risk’) as a result of exposure to the agent.” The Preamble acknowledges, “The Monographs are used by national and international authorities to make risk assessments…” and, “these evaluations represent only one part of the body of information on which public health decisions may be based.”*

ToxStrategies

The directives and role of the exposure working group should be clarified

Exposure information (i.e., the range of potential exposures currently summarized in IARC monographs) is not used in developing hazard classifications. While exposure information is useful to prioritization, the appropriateness of the exposure working group's role in evaluating evidence and voting on hazard classifications based on epidemiological, animal, and mechanistic studies is unclear.

- Available exposure information should be used solely to better understand context around exposure to the agent (e.g., route of exposure), not as a surrogate for agent identification and presumed risk characterization. This information *could* be used to inform appraisal criteria (particularly for epidemiological studies, i.e., has exposure been confidently characterized).
- Further clarification of the scientific principles and procedures associated with the evidence reviewed by the exposure group is needed given that exposure information is not used in the assessment of carcinogenicity hazard.
  - *Exposure information is not part of the evaluation of the potential for hazard.*
  - *The exposure working group's role in developing and voting on overall classifications is unclear. Rationale should be provided regarding the appropriateness of having exposure working group members vote on overall hazard classifications based epidemiological, animal, and mechanistic studies.*

Preamble should address the principles, *as well as the procedures* for carrying out the principles

Currently:

- *Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous Monograph meetings but remain, predominantly, the prerogative of each individual Working Group*.

Without specific guidance on procedures, working groups cannot consistently or transparently carry out the principles

The Preamble should be updated to reflect both principles and procedures

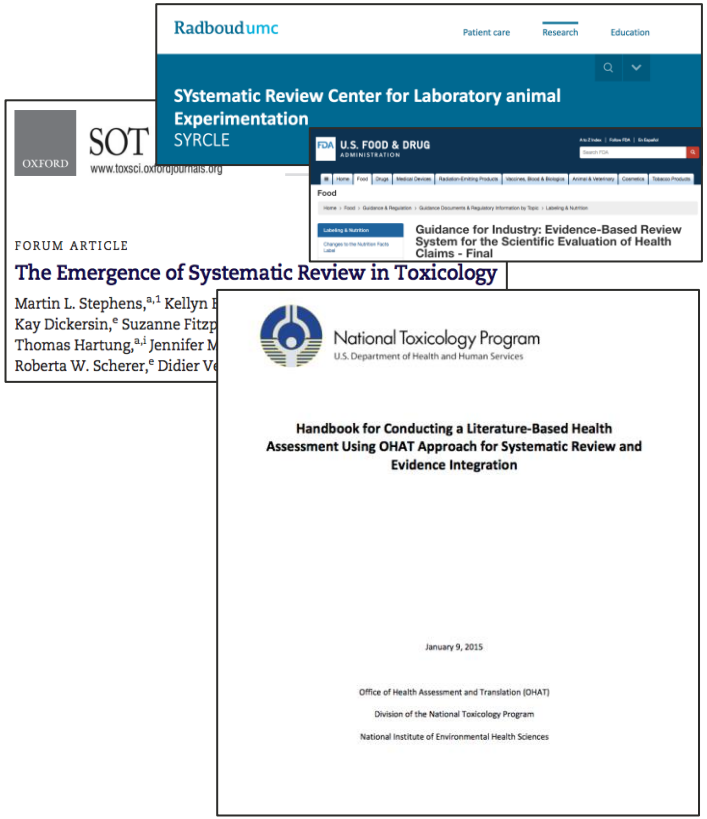
- Principles and procedures should integrate the practice of evidence-based reviews, allowing classifications and monographs to produced with increased rigor, transparency, and reproducibility

Use evidence-based methods: systematic review, meta-analysis to evaluate the totality of evidence

Systematic review: *"A scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies"* □ *IOM, 2011*

Suggest Preamble refinements that better reflect use of evidence-based systematic review methods:

- Emphasis on *a priori* identification of inclusion/ exclusion criteria for study selection, as well as determination of relevance and adequacy
- Incorporate formal study quality evaluation (i.e., critical appraisal of internal validity) by study type
- Implement *a priori* determination of topic-specific refinements for study quality and decision criteria (e.g., criteria specific to confounding and route of exposure for the agent under consideration) as part of considering the totality of evidence



ToxStrategies

Refine Preamble to better describe principles and procedures of the *entire process*

- Problem Formulation
- Protocol Development
- Identify Evidence Base
- Individual Study Assessment
- Body of Evidence Assessment
- Reporting

Structured guidance and formal criteria are needed: clarify process and procedures for what data are evaluated (i.e., relevant and adequate) and how *(= more detail than currently provided in Preamble)*

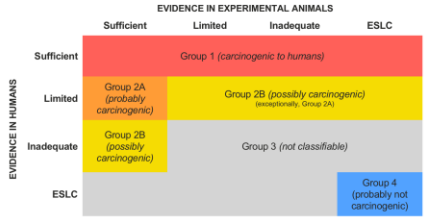
Study appraisal criteria need to be tailored to the agent *a priori (e.g., identification of specific confounding biases)*– including how such criteria will be considered in decision making

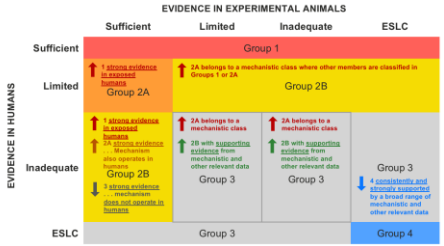
????

Approach must consider the totality of evidence (from all streams)

Refinements will aid in transparency, objectivity, and reproducibility

273

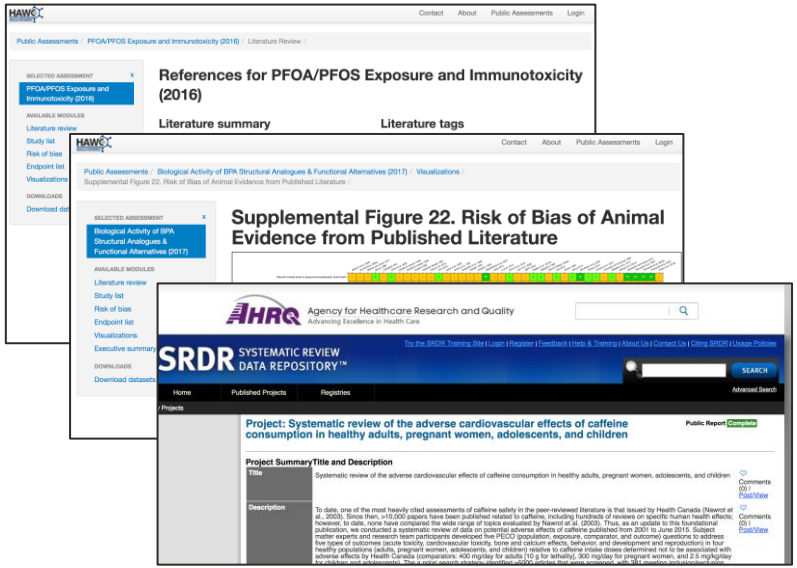


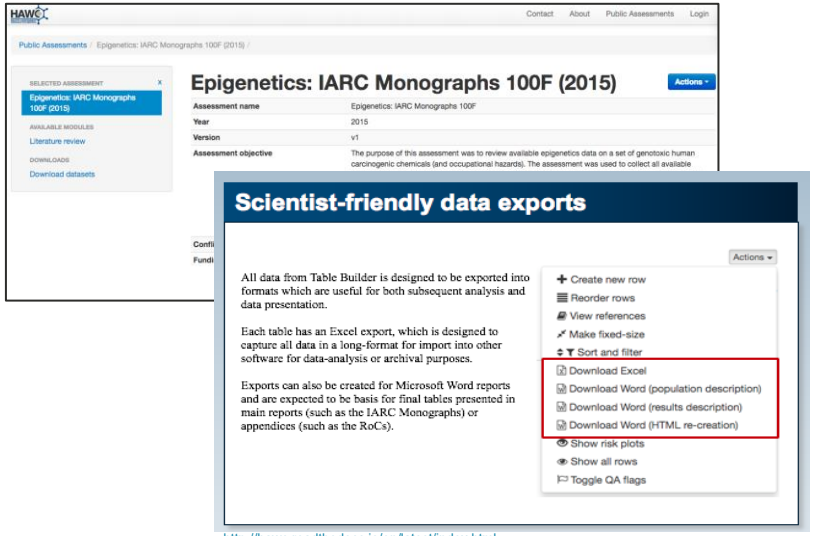


Increase transparency in the conduct and reporting of monograph reviews:

Government agencies, academic institutions, journals, and private entities using a variety of tools to transparently document assessments

IARC is *already using* some of these tools (HAWC, TableBuilder) → additional transparency in conduct and reporting could be implemented easily





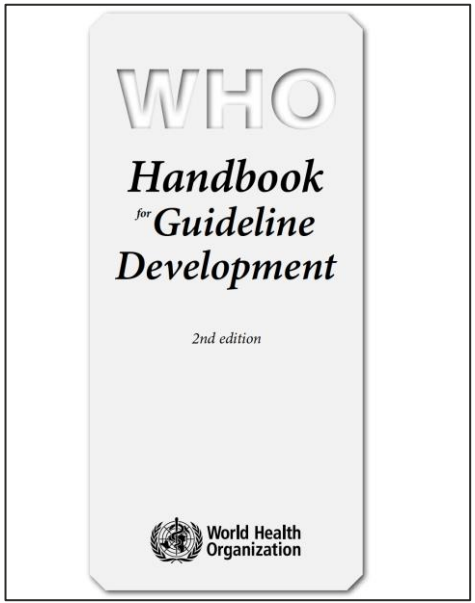
http://hawc.readthedocs.io/en/latest/index.html

Shapiro A, Lunn R, Jahnke G, Schwing P, Guyton K, Loomis D, Guha N. 2017 TableBuilder: A content management system for carcinogenicity health assessments for the IARC Monographs and the NTP Report on Carcinogens. Presented at: 4th International Symposium on Systematic Review and Meta-Analysis of Laboratory Animal Studies.

274

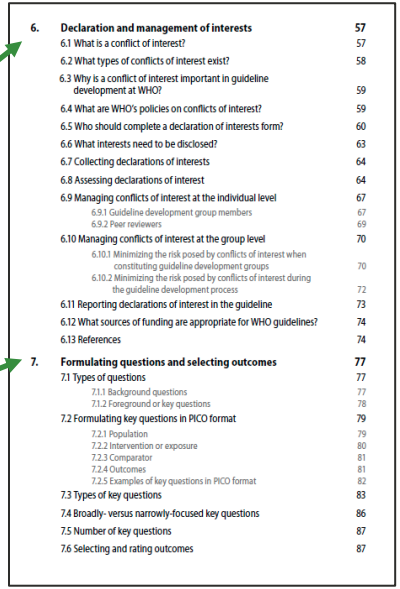
ToxStrategies

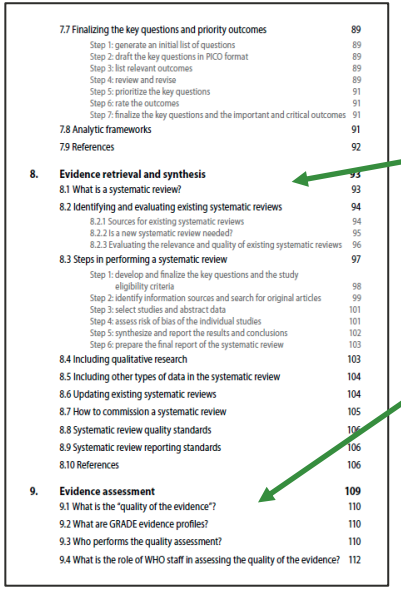
Consider the 2014 WHO Handbook when updating the Preamble



Declaration and management of interests

Formulating the review (including exposure)





Systematic review

Quality assessment

275

ToxStrategies

Consider (and actively manage) both financial and non-financial interests of working-group members

Conflict of Interest: "*circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest*" □ WHO 2014, IOM 2011, IOM 2009

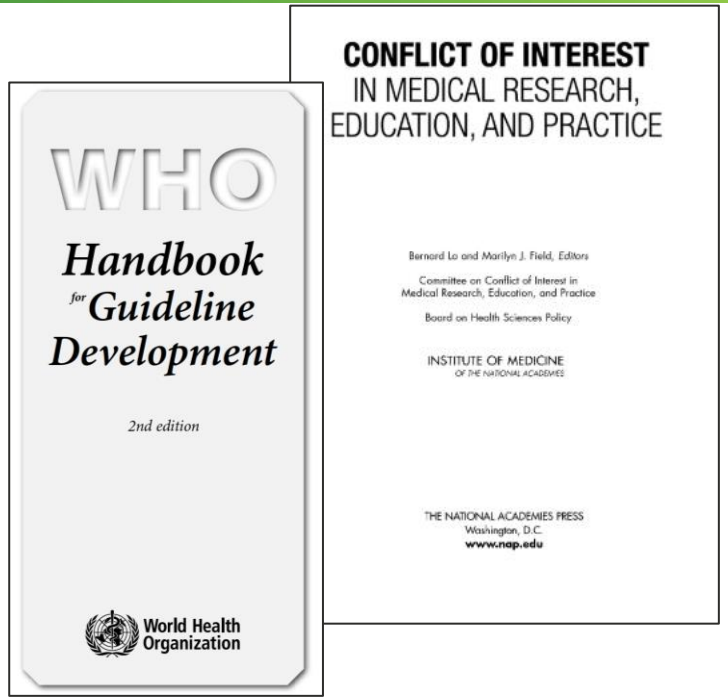
- Secondary interests include not only financial interests but also other interests, such as the pursuit of professional advancement.

Example from WHO *Handbook for Guideline Development* (2014):

> *"…[C]ertain individuals should not participate at all in the development of a guideline… those who have intellectual conflicts of interest that are severe and/or cannot be adequately managed at the group level … (such as) an author or co-author of one or more key studies within the body of evidence underpinning a recommendation, particularly if the body of evidence is limited… (see Section 6.10) (p.68)".*

Current Preamble does not provide guidance as to how disclosures are to be evaluated and managed

- **It is well-recognized that <u>both financial and non-financial interests</u> need to be declared and appropriately managed**
- **IARC is strongly encouraged to follow the 2014 WHO *Handbook on Guideline Development,*** broadly speaking and as it pertains to disclosure and management of both financial and non-financial conflicts of interest, when refining the Preamble



276

ToxStrategies

Summary Themes of Comments

- Omit use of the term “hazard” and replace with “risk”
- Clarify principles and procedures related to exposure (e.g., priority setting primarily, as evaluations are hazard-based)
- Refine preamble to address the principles, as well as the procedures for carrying out the principles
- Use evidence-based methods (i.e., systematic review, meta-analysis)
  - Emphasis on *a priori* identification of inclusion/exclusion criteria for study selection, as well as determination of relevance and adequacy
  - Integrate formal study quality evaluation (i.e., critical appraisal of internal validity) by study type and structured decision criteria
- Increase transparency in the conduct and reporting of monograph reviews
  - Encourage use of tools already in practice to do so
  - Consider more public participation, including opportunities to comment (early and frequently) throughout monograph process
- Consider (and actively manage) both financial and non-financial interests of working-group members

Thank you for the opportunity to submit written comments and share verbal comments via webinar.

Remaining slides not presented during webinar; provided as support for key comments presented (additional details can also be found in the written submission).

Principles should be updated to be consistent with the WHO 2014 *Handbook for Guideline Development*

The Preamble should specifically identify multiple points in the update process when public and stakeholder comments will be collected, how they will be collected, and subsequently how they will be disseminated, evaluated, and integrated into the process. During this process, *all* comments should be considered.

- *Issues addressed: The current IARC preamble does not specifically address how and when public or stakeholder comments will be collected, considered, and reflected on in the monograph development process. Available materials suggest that only "pertinent" comments will be provided to the Advisory Group*.

The Preamble should include a mechanism that parallels *WHO's Handbook for Guideline Development,* by which both financial and non-financial conflicts of interest (COIs) for prospective IARC working-group experts can be evaluated and managed in a systematic manner. IARC is strongly encouraged to align its COI process relative to how COI will be evaluated and managed for full transparency in selection of working-group members, especially as it relates to invited experts, to the *2014 WHO Handbook for Guideline Development.*

- *Issues addressed:*
  - *The current Preamble briefly addresses disclosure of only financial conflicts (non-financial conflicts are not addressed). It provides no guidance as to how disclosures are to be evaluated and managed.*
  - *Criticism has been raised that some Working Groups are unbalanced and possibly prone to bias. It is well-recognized that both financial and non-financial bias need to be declared and appropriately managed. Criticisms received regarding unbalanced working groups could be addressed by revising the principles related to selection of working groups, including a more formalized plan for disclosure and management of financial and non-financial COI, consistent with globally accepted standard practice (NAS, 2013; WHO, 2014).*

279

ToxStrategies

Evidence-based principles *and procedures* should be implemented

In an effort to provide transparent, comprehensive, and consistent evaluations of potential human carcinogenicity, the Preamble should be updated to reflect the scientific principles, as well as the systematic procedures and decision criteria that are implemented to achieve the principles. Updates should reflect a more transparent and comprehensive statement of principles, decision criteria, and operating procedures.

- *Issues addressed: The current Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous Monograph meetings but remain, predominantly, the perogative of each individual Working Group.*

The IARC Preamble scientific principles and procedures should be updated to integrate the practice of evidence-based reviews conducted systematically to provide evidence-based monographs produced with rigor, transparency, and reproducibility in the monograph process. Evidence-based practice involves systematic reviews and meta-analyses, as well as other "state-of-the-science" techniques, which utilize a predefined, multi-step process to identify, select, critically assess, analyze, and synthesize evidence from the totality of scientific studies to reach a conclusion.

- *Issues addressed:*
  - *The current Preamble does not fully employ evidence-based methods. Lack of such methods is associated with inconsistent evaluations, lack of transparency and reproducibility, and uncertainty in the underlying rigor.*
  - *The current Preamble indicates that only studies considered to be relevant are included. No principles or procedures are provided as to how such selections are made, suggesting that the evidence is not reviewed in totality.*

280

Emphasis should be placed on the need for *a priori* identification of criteria to select literature and determine relevance and adequacy

- **All data should be identified using a systematic approach that involves development and implementation of agent-specific protocols, in addition to refinement of principles and procedures in the Preamble. Pertinent epidemiological studies, cancer bioassays in experimental animals, other relevant data (including mechanistic data), and exposure studies, should be determined via implementation of processes developed *a priori* and documented in a protocol for each agent. As part of the protocol, a detailed search strategy will be developed, validated, and documented *a priori* by an Information Specialist. The search strategy should include syntax specific to each database (e.g., MeSH in PubMed), a list of databases (including grey literature sources if included), and dates of searching. The strategy should detail the process for screening titles and abstracts, as well as full text against inclusion/exclusion criteria. Such criteria should be developed to specifically characterize populations, exposures, comparators, and outcomes for inclusion/exclusion. These criteria should be developed *a priori* by the IARC Secretariat and reviewed and approved by working-group members prior to implementation.**
  - *Issue addressed: The Preamble is void of transparency principles and procedures related to systematic and objective identification of key studies.*
- **All available data that are identified during the literature search (which, by default, should capture data relevant to the evaluation if using an agent-specific protocol and search strategy) must be considered by the working group. That is, data sets should not be "cherry-picked." All data should be subjected to critical appraisal; criteria for critical appraisal (quality, adequacy) should be included in the Preamble and refined as warranted for each Agent.**
  - *Issues addressed:*
    - *The Preamble is currently void of scientific principles related to what is "relevant" or "adequate."*
    - *The Preamble does not address methods for identifying, selecting, evaluating, and integrating other relevant data, including for key characteristics of carcinogenesis*
    - *Each working group selects what they find to be relevant (which is not consistent with a systematic or evidence-based approach); clear and consistent criteria or descriptions are needed to inform working-group determinations of what constitutes exclusion based on inadequacy and/or irrelevance.*
    - *While the Preamble directs the Working Group to provide reasons for not giving consideration to a study in the "square brackets"; in practice, the monographs often do not provide clear or concise information as to the reason.*

Principles should include specific criteria for evaluation of study quality (adequacy) and procedures for evaluating and integrating considerations of quality as part of assessing the totality of evidence

The Preamble should be revised to include structured and defined criteria for evaluation of internal and external validity of study quality. An entire new section (is needed to describe these criteria. In addition to the definitions, the scientific principles for applying and integrating such data quality criteria should also be included. An entire section (not drafted as part of these comments) is needed to describe how to apply the data quality criteria.

- *Issues addressed:*
  - *While the Preamble alludes to evaluation of study quality, it does not provide clear criteria or principles to do so.*
  - *Because each set of evaluations is done by a different working group, and different staff within the IARC Secretariat, the preamble, having clear criteria for evaluation and integration of external validity as part of inclusion/exclusion, as well as the weight of the totality of the evidence, would improve the quality and consistency of the IARC monographs.*

The scientific principles for how bias domains (e.g., confounding, exposure, outcome, selection) are to be critically appraised <u>for every study</u> - as part of an evaluation of potential systematic error and, consequently, potential impact on direction, magnitude, consistency, and strength of results - need to be included, along with how study quality will be integrated into the weight-of-evidence assessment <u>when all data</u> are considered in totality.

- *Issues addressed:*
  - *The Preamble is void of principles and regarding how domains such as bias and chance should be assessed and subsequently weighted in evaluating the totality of the evidence.*
  - *The Preamble is a void of principles that clearly identify which bias domains should be evaluated for each study type, including, for example, agent-specific identification and evaluation of exposure and confounding biases in epidemiological studies as part of assessing the totality of the evidence.*
  - *The IARC Preamble indicates that evaluations consider studies that support a finding of cancer hazard, as well as studies that do not; however, there is no description of the scientific principles that describe how this is defined or implemented in practice.*

Clarification is needed for methods of identifying, selecting, evaluating, and integrating other relevant data, including information on key characteristics of carcinogenesis

The Preamble should be updated to reflect both the principles and the procedures related to the use of the "key characteristics of carcinogenesis" (KCC) approach for identifying and evaluating mechanistic data, as well as consideration of other possibly relevant data that are not considered KCC. Include descriptions of the principles and procedures as to what and how data organized by KCC (and "other" possibly appropriate characteristics) should be evaluated relative to up- and down-grading classifications in context of adverse outcome pathways *that are pertinent to the specific cancer type under evaluation.* It is also important that the Preamble consider "other" possibly appropriate characteristics that are not yet identified as KCC (i.e., characteristics of carcinogens that are not yet known).

- *Issues addressed:*
  - *The Preamble is void of reference to the KCC approach, despite numerous publications by IARC scientists and references to those in the Instructions to Authors*
  - *It is unclear how mechanistic data are identified, selected, evaluated, and integrated into IARC assessments, particularly KCC data*
  - *The preamble is currently void of discussion related to use of high-throughput screening (HTS) data as a source of information to be considered*

Paramount to the inclusion of KCC (and other relevant data), the Preamble must address how the collective mechanistic evidence (which is likely to include data demonstrating both activity and lack of activity) will be evaluated in the context of (a) adverse outcome pathways pertinent to specific cancer type(s) under evaluation, **and** (b) evidence from other streams (human, animal, exposure). The principles and procedures for considering study quality and relevance should be included in this update.

283

7 - Tracey Woodruff

Comments on update to IARC Preamble

Tracey J. Woodruff, PhD, MPH
Professor and Director
UCSF Program on Reproductive Health and the Environment

Program on Reproductive Health and the Environment

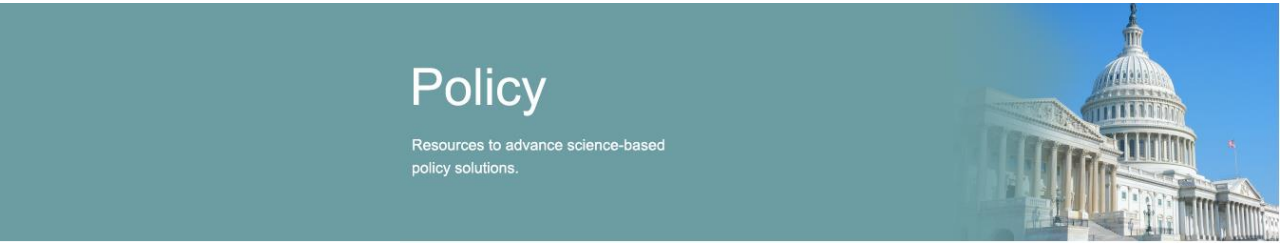
UCSF University of California San Francisco

Program on Reproductive Health and the Environment (PRHE)

Mission: To create a healthier environment for human reproduction and development

by advancing scientific inquiry, clinical care, and health policies

that prevent exposures to harmful chemicals in our environment



UCSF
University of California San Francisco

Outline

- Introduction of systematic reviews in environmental health
  - Development by universities (Navigation Guide) and government agencies (NTP/Office of Health Assessment and Translation (OHAT))
  - Reviews/recommendations by NAS
- Recommend using and applying new tools and methods to increase transparency and constancy
- Continue to support conflict of interest policies

THE COCHRANE COLLABORATION®

GRADE

Navigation Guide – 2009

BRIDGING CLINICAL & ENVIRONMENTAL HEALTH

By Tracey J. Woodruff, Patrice Sutton, and The Navigation Guide Work Group

An Evidence-Based Medicine Methodology To Bridge The Gap Between Clinical And Environmental Health Sciences

ABSTRACT Physicians and other clinicians could help educate patients about hazardous environmental exposures, especially to substances that could affect their reproductive health. But the relevant scientific evidence is voluminous, of variable quality, and largely unfamiliar to health professionals caring for people of childbearing age. To bridge this gap between clinical and environmental health, we created a methodology to

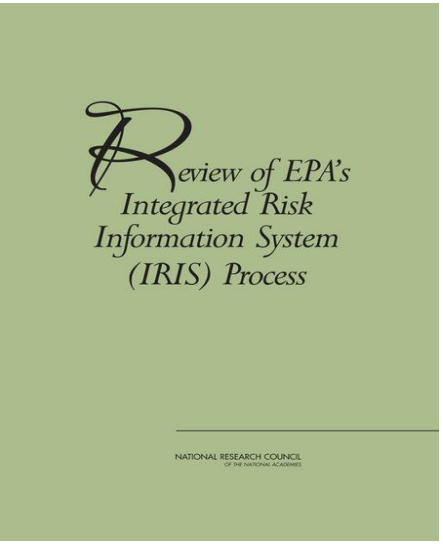
National Toxicology Program
U.S. Department of Health and Human Services

Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

January 9, 2015

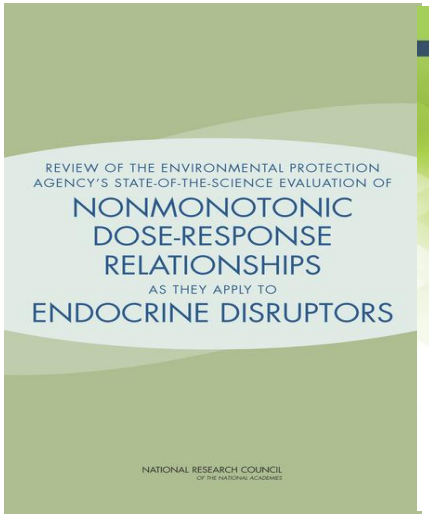
NATIONAL ACADEMY OF SCIENCES

2014



…**systematic-review standards** provide an approach that would substantially strengthen the IRIS process…"

2014



"EPA should consistently use a more **systematic approach** to evaluating the literature ……." NAS 2014

2017

Systematic review process framework valuable for identifying, selecting, and evaluating evidence in a consistent and explicit manner

World Health Organization

International Labour Organization

2018

Using the Navigation Guide systematic review method for estimating the burden of work-related disease and injury

Systematic Review approach

A pre-specified analytic plan (protocol) is developed and applied consistently to the evidence.

Human Data

Non Human Data

- Systematic, transparent, consistent, and reproducible
- Does not eliminate need for expert judgment, but outlines judgments made along the way

Recommendations

- Protocol
- Search
  - Work with a expert on search
  - Make transparent the search strategy and results of study inclusion/exclusion
- Continue to adopt the different steps of systematic reviews
- Recommend using and applying available tools and methods to increase transparency and constancy
  - Health Assessment Workspace Collaborative (HAWC)
- Continue to support conflict of interest policies
  - Evaluate financial conflicts as part of risk of bias

Support Infrastructure Development

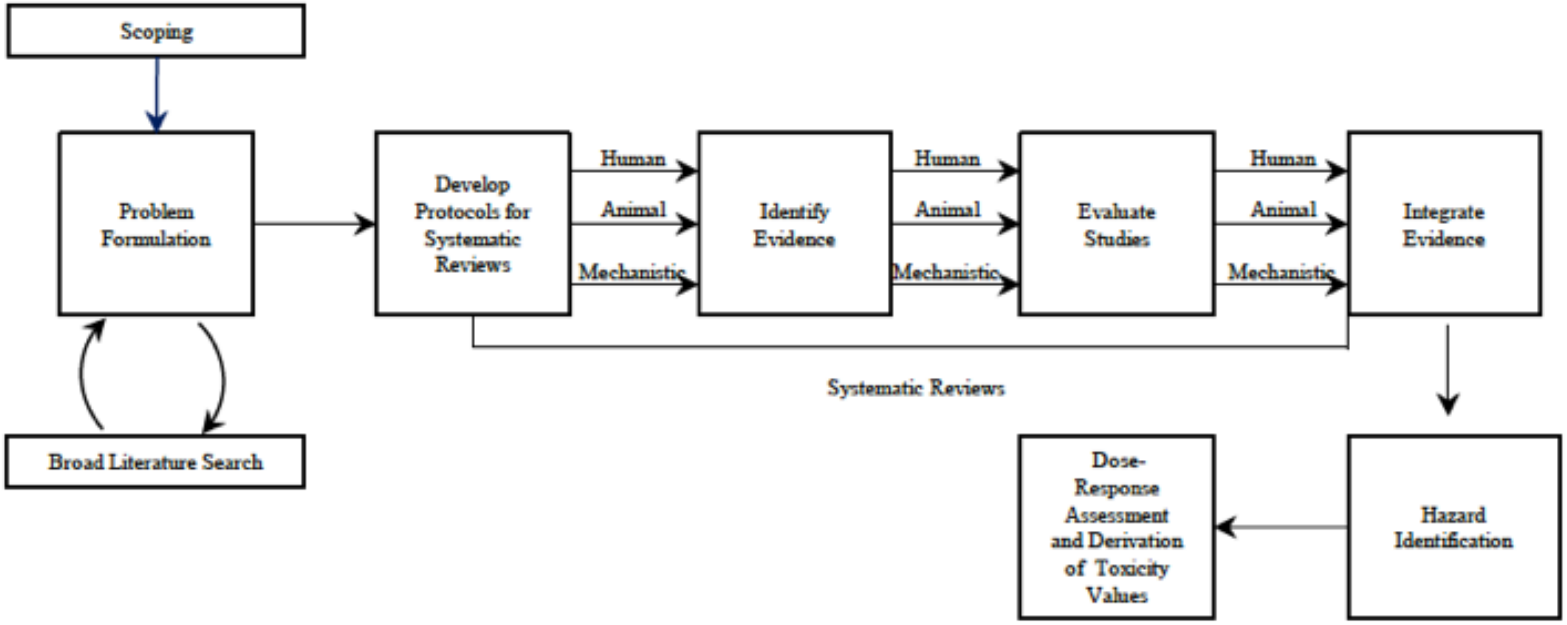


Thank you!

University of California
San Francisco

Program on Reproductive
Health and the Environment

Evaluate each evidence stream separately using systematic and transparent approaches



8 - Martyn Smith

The key characteristics approach to evaluating mechanistic data in carcinogen hazard identification

Martyn Smith

School of Public Health,

University of California, Berkeley CA, USA

UC BERKELEY SUPERFUND RESEARCH PROGRAM SCIENCE FOR A SAFER WORLD

martynts@berkeley.edu

http://superfund.berkeley.edu

How Mechanistic Evidence is Currently Evaluated?

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data

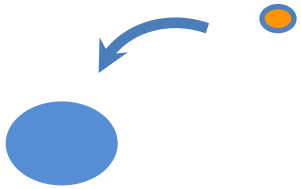
—Part B, Section 6(c)

• Are the mechanistic data "weak," "moderate," or "strong"?	Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent? Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?
• Is the mechanism likely to be operative in humans?	Are there data from exposed humans or human systems? Consider alternative explanations before concluding that tumours in experimental animals are not relevant to humans

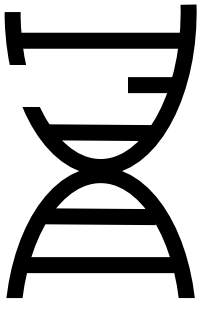
297

The Key Characteristics of Human Carcinogens

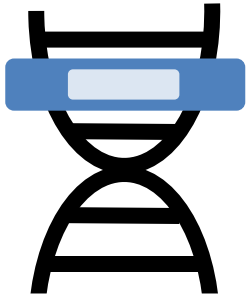
Electrophilic



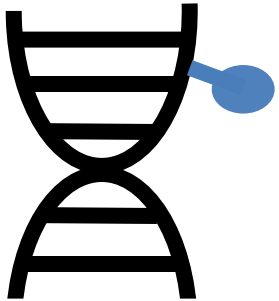
Genotoxic



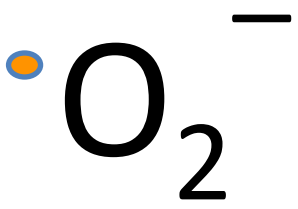
⬇ DNA repair



➡ Epigenetic alteration



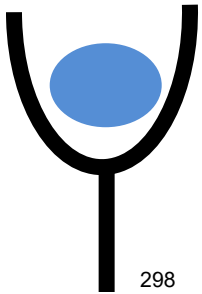
⬆ Oxidative stress



➡ Chronic inflammation

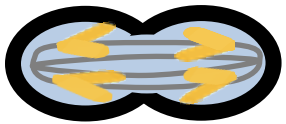
⬆⬇ Immune response

➡ Receptor-mediated effects

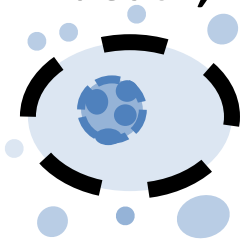


➡ Cell immortalization

⬆ Cell proliferation,



⬇ cell death,



or alter nutrient supply

Courtesy of Amy Wang, NTP

Characteristic	Examples 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 cross-links, 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)

Characteristic	Examples of relevant evidence
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, altered telomeres
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

A Hallmark *versus* a Key Characteristic

- A Hallmark describes what *IS*

- A Key Characteristic (KC) describes Something that makes “what is” happen

INTEGRATION OF THE KCs WITH HALLMARKS
Characteristics 1,2,4 and 8 can influence all Hallmarks

Key Characteristics

1. Is electrophilic or can be metabolically activated

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

Hallmarks

1. Genetic Instability

2. Sustained Proliferative Signalling

3. Evasion of Anti-growth Signalling

4. Resistance to Cell Death

5. Replicative Immortality

6. Dysregulated Metabolism

7. Immune System Evasion

8. Angiogenesis

9. Inflammation

10. Tissue Invasion and Metastasis

PLUS - Tumor Microenvironment

MT Smith, UCB Sept 2018

KCs act by disrupting Hallmark processes – Conclusion of Working Group convened in Berkeley, August 21-22, 2018

INTEGRATION OF THE KCs WITH HALLMARKS
Characteristics 3,5,6,7,9,10 influence specific Hallmarks

KC3: Alters DNA Repair or Causes Genomic Instability	(Hallmark) Genetic Instability
KC5: Induces Oxidative Stress	(Hallmark) Dysregulated Metabolism
KC6: Induces Chronic Inflammation	(Hallmark) Inflammation
KC7: Is Immunosuppressive	(Hallmark) Immune System Evasion
KC9: Causes Immortalization	(Hallmark) Replicative Immortality
KC10: Alters Cell Proliferation, Cell Death, or Nutrient Supply	(Hallmark) Sustained Proliferative Signalling (Hallmark) Evasion of Anti-growth Signalling (Hallmark) Resistance to Cell Death (Hallmark) Angiogenesis
NO KCs	(Hallmark) Tissue Invasion and Metastasis (Hallmark) Tumor Microenvironment

Several KCs act by disrupting specific Hallmark processes – From Leroy Lowe's presentation to Working Group convened in Berkeley, August 21-22, 2018

303

Application of the KCs at IARC

Use the KCs to:

- Identify the relevant mechanistic information
- Screen and organize the search results
- Evaluate quality of the identified studies
- Summarize the evidence for each KC as strong, moderate or weak and determine if it operates in humans or human in vitro systems

Systematic Approach
Using Key Characteristics of Carcinogens

Targeted searches for each key characteristic

Is Genotoxic (#2) — Actions

Description	First three characteristics
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Genetic Processes"[Mesh] OR "genomic instability"[MeSH] OR chromosom* OR clastogen* OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "DNA damage" OR "DNA adducts" OR "SCE" OR "chromatid" OR micronuclei* OR mutagen* OR "DNA repair" OR "UDS" OR "DNA fragmentation" OR "DNA cleavage")

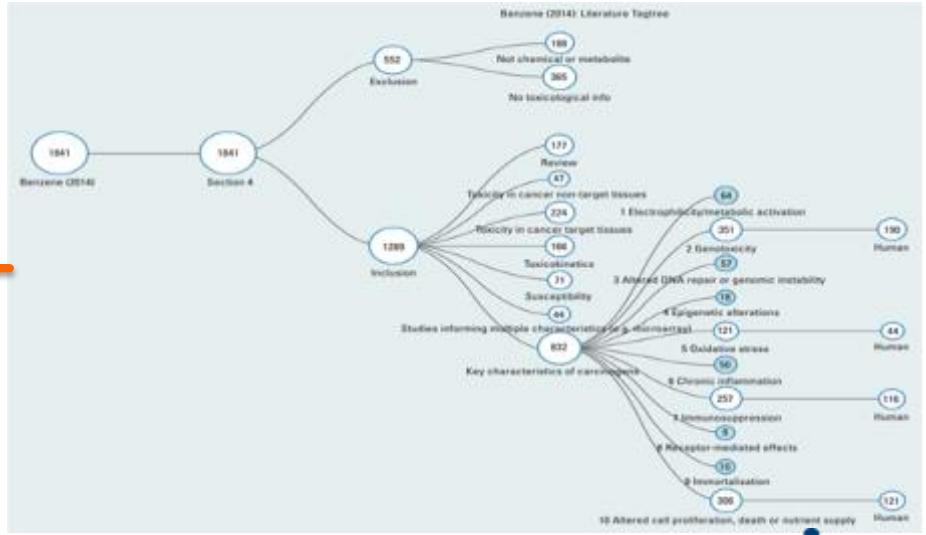
Induces Epigenetic Alterations (#4) — Actions

Description	Epigenetics
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("rna"[MeSH] OR "epigenesis, genetic"[MeSH] OR rna OR "rna, messenger"[MeSH] OR "rna" OR "messenger rna" OR mrna OR "histones"[MeSH] OR histones OR epigenetic OR miRNA OR methylation)

Induces oxidative stress (#5) — Actions

Description	Oxidative stress
Search type	Search
Search database	PubMed
Search text	Benzene[Mesh] AND ("reactive oxygen species"[MeSH] OR "reactive nitrogen species"[MeSH] OR "reactive oxygen species" OR "oxygen radicals" OR "oxidative stress"[MeSH] OR oxidative OR "oxidative stress" OR "free radicals")

Organize results by key characteristics, species, etc



HAWC HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

305

Smith MT, Guyton KZ, Gibbons CF, Fritz JM et al.. *Env Health Persp.*, *124(6):713-21*

Use of KCs in Recent IARC Monographs Evaluations

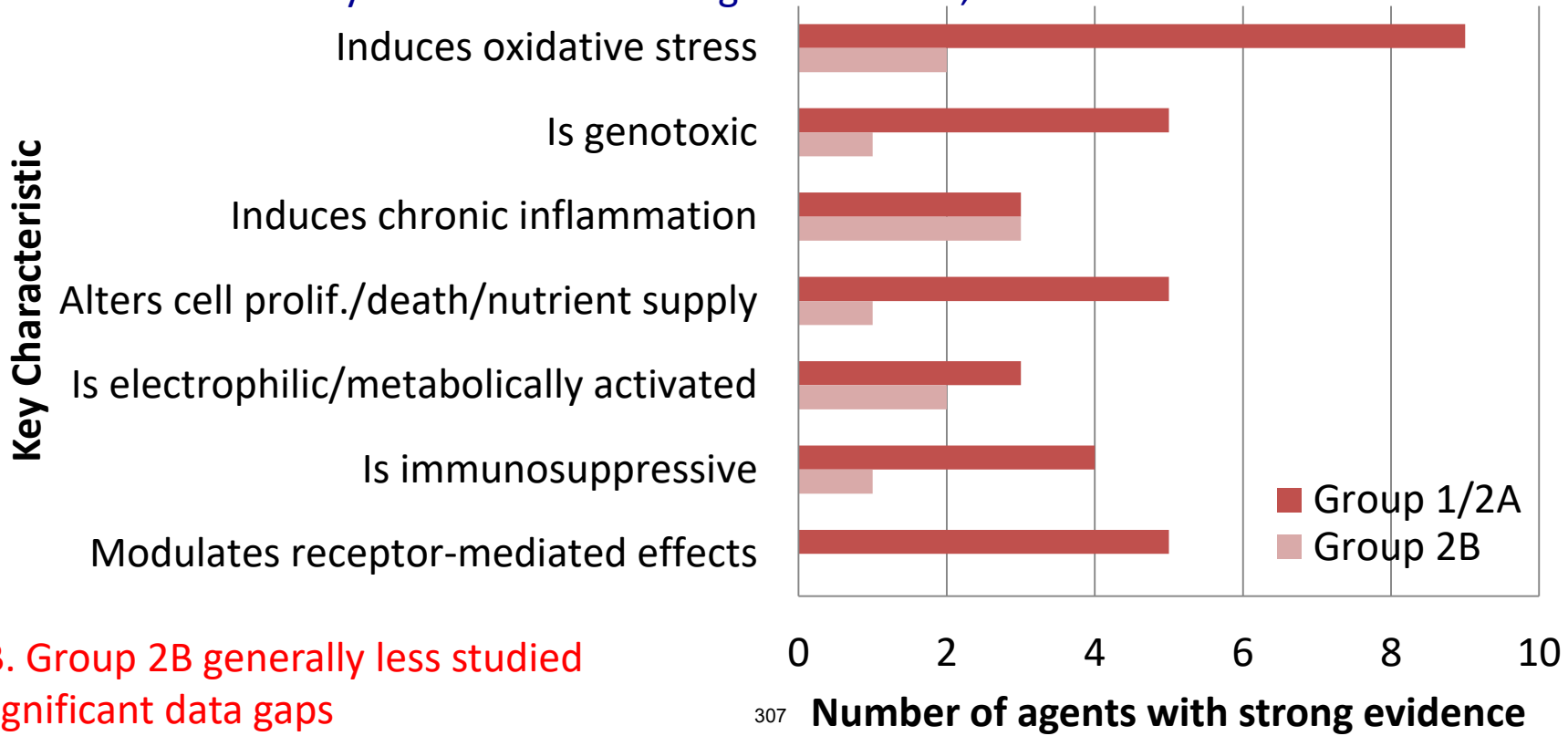
Agent	Group	Cancer in humans	Cancer in animals	Strong mechanistic evidence (key characteristic)
Penta-chlorophenol	1	**Sufficient**	Sufficient	Is metabolically activated, is genotoxic, induces oxidative stress, modulates receptor-mediate effects, alters cell proliferation or death (1, 2, 5, 6, 8, 10)
Welding fumes	1	**Sufficient**	Sufficient	Are immunosuppressive, induce chronic inflammation (6, 7)
DDT	2A	**Limited**	**Sufficient**	Modulates receptor-mediated effects, is immunosuppressive, induces oxidative stress (5,7,8)
Dimethyl-formamide	2A	**Limited**	**Sufficient**	Is metabolically activated, induces oxidative stress, alters cell proliferation (1, 5, 10)
Tetrabromo-bisphenol A	**2A***	Inadequate	**Sufficient**	**Modulates receptor-mediated effects, is immunosuppressive, induces oxidative stress (5, 7, 8)**
Tetrachloro-azobenzene	**2A***	Inadequate	**Sufficient**	**Induces oxidative stress, is immunosuppressive, modulates receptor-mediated effects (6, 8, 10)**
ITO, melamine	2B	Inadequate	**Sufficient**	Induces chronic inflammation (8)
Parathion, TCP	2B	Inadequate	**Sufficient**	

*Overall evaluation upgraded to Group 2A with supporting evidence from other relevant data

Guyton KZ et al. Carcinogenesis. 2018;39:614-622.

Key Characteristics with Strong Evidence across Multiple Evaluations (IARC Monographs Vol. 112-119)

Guyton KZ et al. Carcinogenesis. 2018;39:614-622.



N.B. Group 2B generally less studied – significant data gaps

Key characteristics don't require risk assessor to guess the mechanism

- Mechanistic hypotheses in science are beneficial because if you test it and are wrong then you modify the hypothesis and get closer to the truth

- Mechanistic hypotheses in risk assessment are problematic because if you are wrong you may have made a bad risk decision that cannot easily be changed and may have caused medical or economic harm

National Academy of Sciences report released January 5, 2017

https://www.nap.edu/download/24635

Using 21st Century Science to Improve Risk-Related Evaluations

The KC "approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence." (P.144)

AUTHORS

Committee on Incorporating 21st Century Science into Risk-Based Evaluations; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine

309

Questions

- Does only ‘Strong’ evidence matter?
- How do we make ‘Strong’ consistent?
- How many strong KCs are needed?
- If a chemical possesses multiple KCs can we classify it as a possible/probable human carcinogen without any animal bioassay or epidemiological data?

9 - Elaine Faustman

Elaine M. Faustman, Ph.D. DABT

Professor and Director

Institute for Risk Analysis and Risk Communication

Department of Environmental and Occupational Health Sciences

SCHOOL OF PUBLIC HEALTH

UNIVERSITY of WASHINGTON

- My comments are directed to:
- Maximizing this opportunity to update the Preamble and to
- Optimizing the use of new mechanistic and “other”
- types of “alternative” data to improve our assessments

- How have I interacted the IRAC monographs:
- I have been a consumer
- For risk assessments and evaluations on chemicals
- For exposure assessments
- For teaching
- I have been a participant
- I have been a working group member

Preamble:

The Preamble to the IARC Monographs describes the:

1) objectives and scope of the programme,

2) scientific principles and procedures used in developing a Monograph,

3) types of evidence considered and

4) scientific criteria that guide the evaluations.

From IARC preamble, 2006

- Of the four components of the Preamble I will focus on:
-
- Component 3: Increasing the types of information considered
-
- As a toxicologist and bench scientist as well as risk assessor I would

- Encourage IARC to look methodically at the types of new and
- alternative evidence that is rapidly becoming one of the largest
- categories of health and toxicology literature

- Build upon the white papers produced as products from a IARC
- Workshop held in Lyon to examine carcinogen mechanisms

- Example papers from these workshops built upon the Hallmarks of
- Cancer manuscripts and illustrated how a systematic method for
- identifying, organizing and summarizing mechanistic data could
- be developed. (For example Smith, et al 2016)
-
- This approach was applied to case studies, it addressed how biomarkers
- can inform our evaluations and also how time and how the various order
- of mechanistic signals may be working towards a common endpoint of
- cancer.
- Additional actions are needed to apply this more widely, add to the Preamble
- and ensure that it becomes standard practice.
-

- Why IARC?
- IARC is an internationally recognized and scientifically based agency that
- has over 40 years of successfully evaluated carcinogenic hazards for humans
- This has been done using a transparent and well-defined set of criteria for assessments as well as for defining participants and their roles in the workshop and monograph reports.

- Although many nations have capabilities to prepare assessments, IARC has this long history, successful partnerships and a context that has allowed for extra workshops that have facilitated new developments and set the standards within the discipline for assessment methods (for example applications of evidence for causality, quantitative dose-response evaluations, and epidemiology modeling to name a few in addition to the mechanistic workshops mentioned above).

- Additional research and systematic procedures are needed in considering the various types of alternative approaches such as in vitro, microfluidic platforms and also computational assessment. Just like the recent advances for assessing mechanistic data, IARC could help move forward systematic assessment of these methods for cancer hazard assessment.

- Exposure assessments have also been a key strength of IARC and the use of personal sensors linked with biomarkers of exposure could advance how such multiple pathway assessments are used especially for epidemiology studies but also in communicating potential for exposure.
- Keep the key strengths at IARC that have provided flexibility in looking at classes of chemicals by type and process and use. IARC is a “go to” source for this information.

- Kudos to IARC for over 40 years of carcinogen assessment. I look forward to the next decades and the innovations that IARC will make in integration of exposure and response for public and worker health.

10 - Nathaniel Rothman

National Cancer Institute

Study design issues in evaluating human biomarker studies of suspected carcinogenic agents

Nathaniel Rothman, MD, MPH, MHS

Senior Investigator & Head, Molecular Epidemiology Studies

Occupational and Environmental Epidemiology Branch
Division of Cancer Epidemiology and Genetics
NCI, NIH DHHS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Cross-sectional molecular epidemiology studies of humans exposed to suspect carcinogenic agents

- Cross-sectional (*in vivo*) biomarker studies of humans exposed to potential carcinogenic agents will continue to play an important role in evaluating mechanistic data (Smith et al. 2016 EHP; Guyton et al. 2018 Carcinogenesis)

- In addition to standard epidemiological QC criteria, there are additional characteristics that need to be evaluated in these studies and should be addressed in revised sections B.2.a, B.2.e and B.4.

Selected study design issues

- Characterization of "exposed population"
  - Very recent as well as past quantitative exposure assessment
  - Range and relevance of exposure level
  - Current and past co-exposure characterization
  - Assessment of all important sources of exposure

Selected study design issues

- **Characterization of control "unexposed" population**
  - **Comparability to exposed population by standard demographic characteristics**
  - **Comparability by SES, physical activity, work patterns, diet, other factors that could influence biomarker endpoints and may not be easily amenable to statistical adjustment**

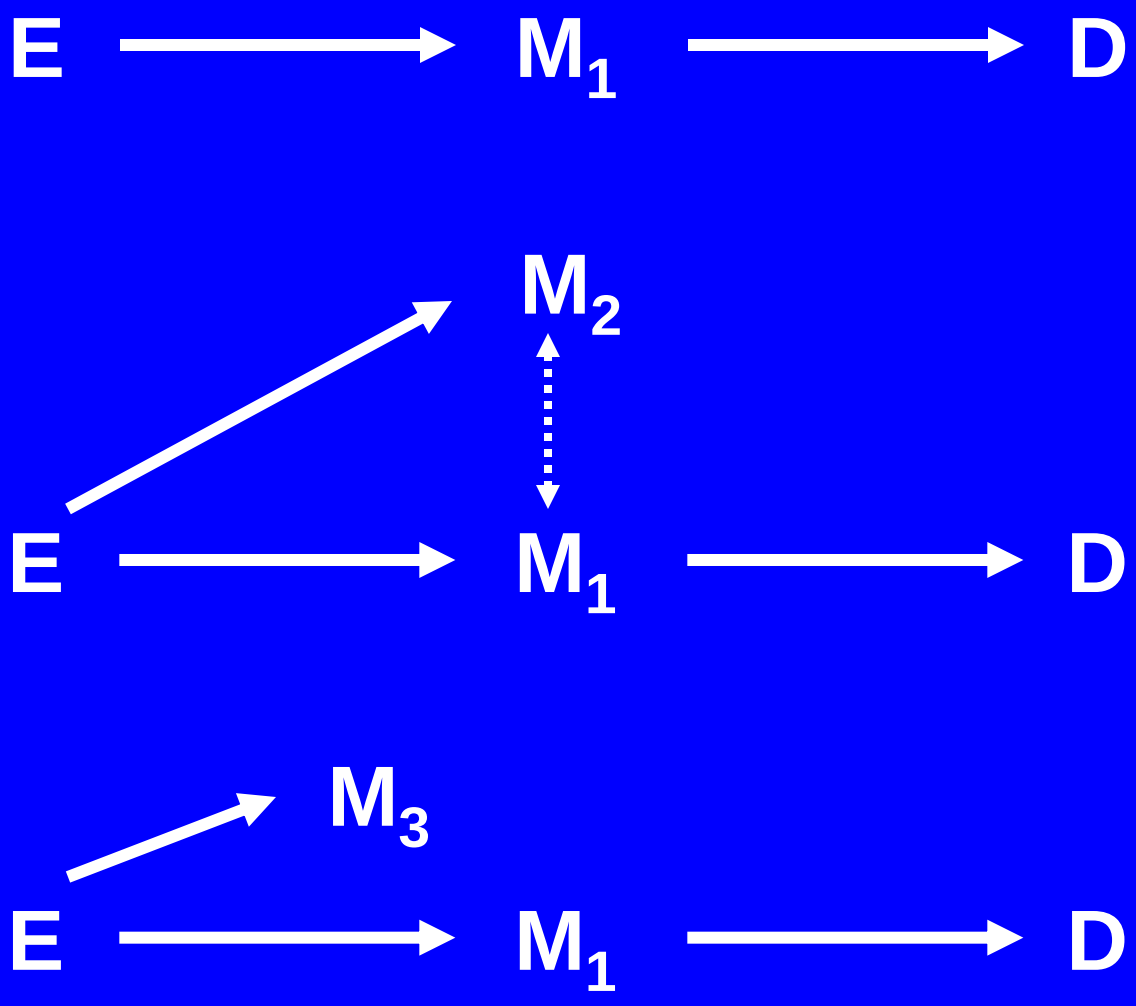
Selected study design issues

- **Quality of biomarker data and analysis**
  - **Assay accuracy**
  - **Assay precision - CVs and especially ICCs critical**
  - **Important to incorporate assay precision into interpretation of results**

Evaluating relevance of exposure-biomarker association for a specific type of cancer

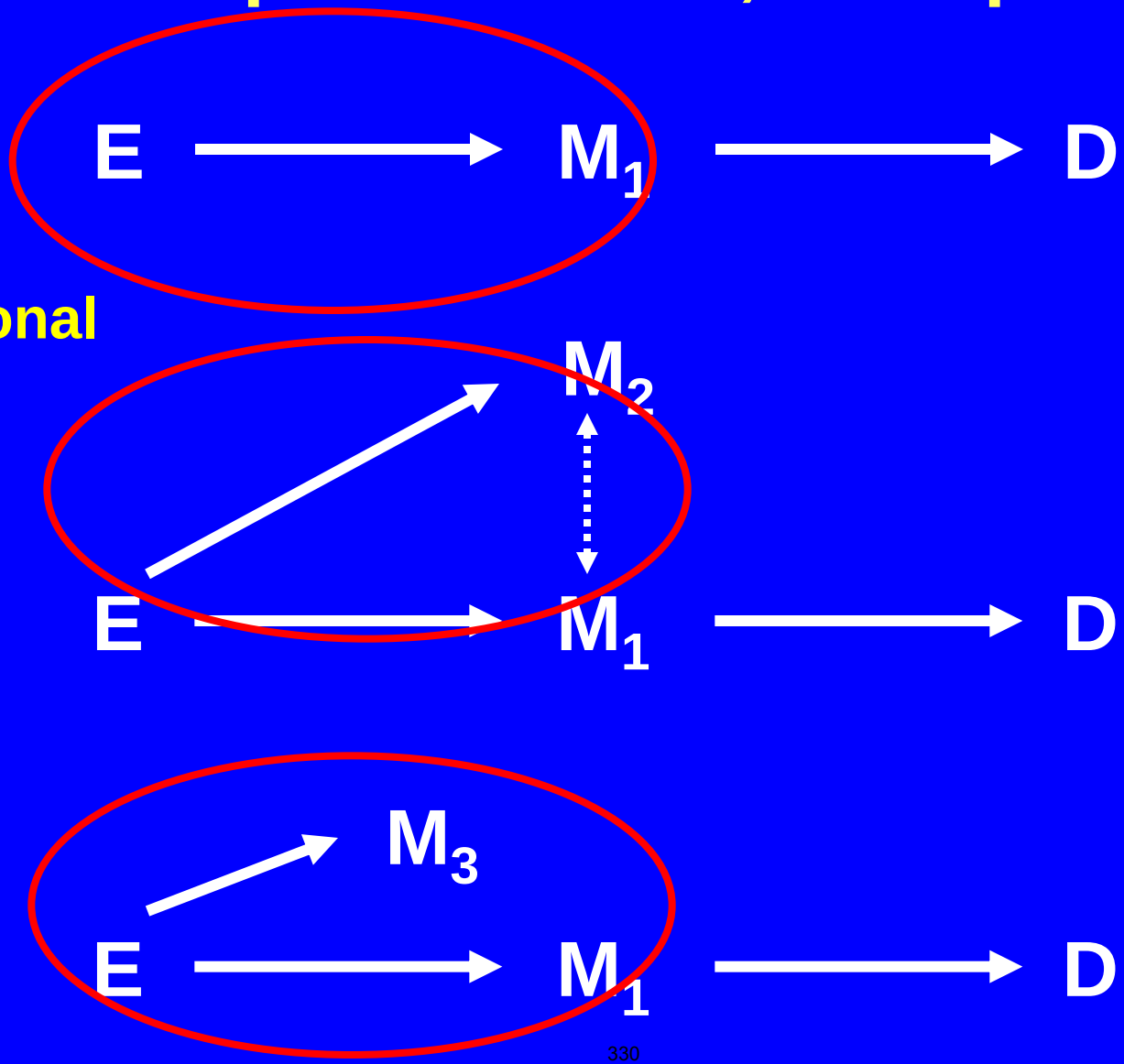
- Several million people enrolled into prospective cohorts/biobanks
- About to generate massive amount of omic data measured primarily in blood linked to future risk of developing specific cancers
- Can incorporate knowledge of this ongoing biomarker "validation" process in interpreting cross-sectional biomarker studies, which can provide biological plausibility to epidemiological observations made between an exposure and a specific cancer

Potential relationships between exposure, biomarker in specific tissue, and specific disease

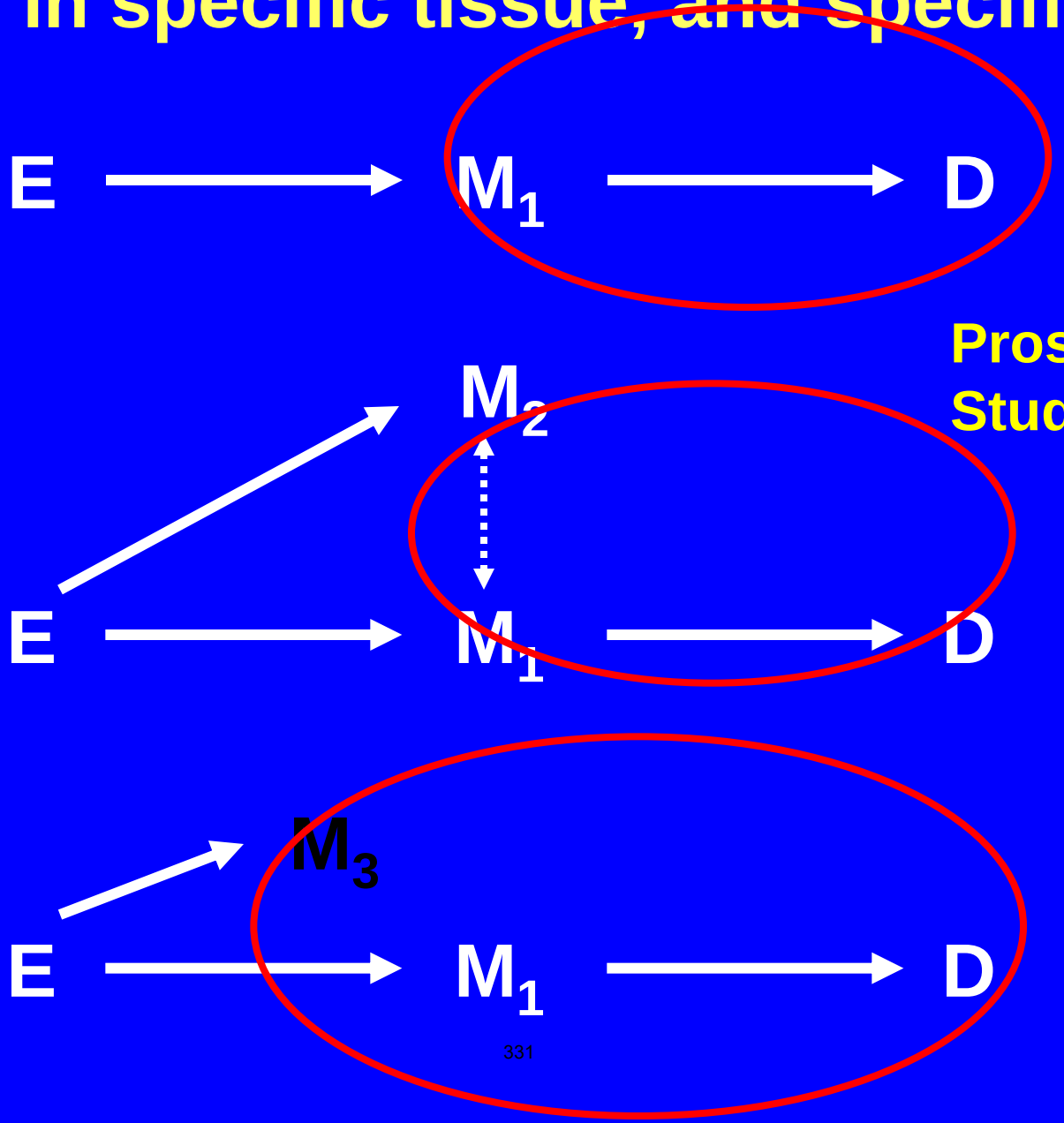


Potential relationships between exposure, biomarker in specific tissue, and specific disease

Cross-Sectional Studies



Potential relationships between exposure, biomarker in specific tissue, and specific disease



Prospective Cohort Studies

Summary

IARC review of cross-sectional biomarker studies of humans exposed to suspect carcinogenic agents can be improved by:

1) Formal definition of criteria for assessing molecular epidemiology cross-sectional study design quality and interpretation

2) Formal consideration of relevance of biomarker measured in a specific tissue for risk of specific types of cancer, informed by latest empirical results from prospective cohorts

11 - Ron Melnick

Comments on IARC Monographs Preamble

Ronald L. Melnick
Retired Toxicologist - NTP, NIEHS
Ron Melnick Consulting, LLC

IARC Public Webinar
17 September 2018

1. Cancer in Experimental Animals

Preamble needs to provide additional guidance on how working groups should judge adequacy and validity of experimental studies

1a. Aspects of Study Design

- Basis for dose selection
  - Adequately challenging to ID a cancer hazard
  - Characterize dose-response relationship
- Study duration
  - Sufficient to detect late developing tumors
- Animal group size
  - Large enough to detect rare or uncommon tumors

1b. Conduct of Studies

- Agent
  - Purity
  - Stability in storage and in exposure medium
  - Exposure uniformity
- Compliance with GLP requirements
  - Non GLP studies should not be ignored if information is adequate to evaluate potential carcinogenicity
- Identification of lesions
  - Complete necropsy and histopathology
  - Extent of pathology review

1c. Evaluation of Experimental Data

- **Reporting lesions**
  - Malignant and non-malignant lesions reported separately and combined
  - Incidence of preneoplastic lesions
- **Statistical analyses**
  - Trend and pairwise comparisons
  - Survival adjustment if differences in survival between controls and treatment groups
- **Use of historical control rates**
  - Most useful for rare or uncommon tumors
  - Most appropriate comparison is to the concurrent control group
  - For tumors with highly variable rates, account for variability in comparison to historical control rates

2. Overall Evaluation of Carcinogenicity

- **Application of mechanistic data, when less than sufficient evidence in humans:**
  - **Current: upgrade to carcinogenic to humans if strong evidence in exposed humans**
  - **Suggested change: upgrade to carcinogenic to humans if strong evidence in exposed human cells or tissues**

- **Downgrades to not classifiable (group 3)**
  - **Current: strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans – Needs clarification**
  - **Cannot rely on inadequately tested mechanistic hypotheses**

3. Confounding, Bias, and Follow-up

- **Chance, bias and confounding must be ruled out with reasonable confidence for sufficient evidence of carcinogenicity**
- **These criteria plus adequate follow-up need full written analyses before concluding there is *evidence suggesting lack of carcinogenicity***

12 - John E. French

Carcinogenic Hazard Identification using GEMM

John Edgar French, Ph.D.

UNC NRI & Gilling's School of Global Public Health – Chapel Hill, North Carolina USA

Formerly NIEHS, NTP

Research Triangle Park, North Carolina USA

Hypothesis

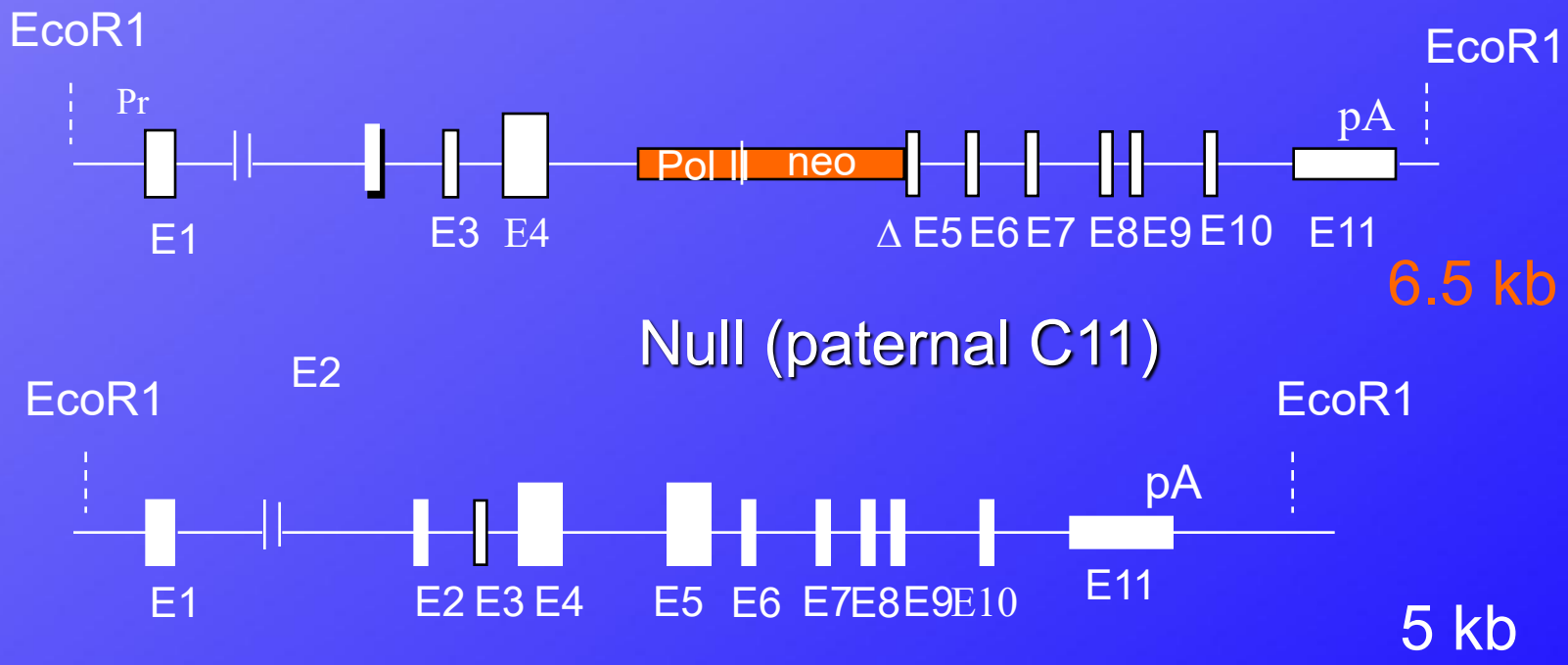
- An inducible proto-oncogene or inactivated tumor suppressor gene by itself increases susceptibility but does not cause cancer without activation or loss
- Exposure to a carcinogen will induce cancer with reduced latency due to additional genetic or epigenetic modifications

Criteria

- Broad range of susceptible tissues (**genetic background** dependent)
- Zero to low incidence of sporadic tumor incidence due to shortened latency
- Zero to low frequency of false negatives and false positives
- Mode or mechanism consistent with development of human cancers

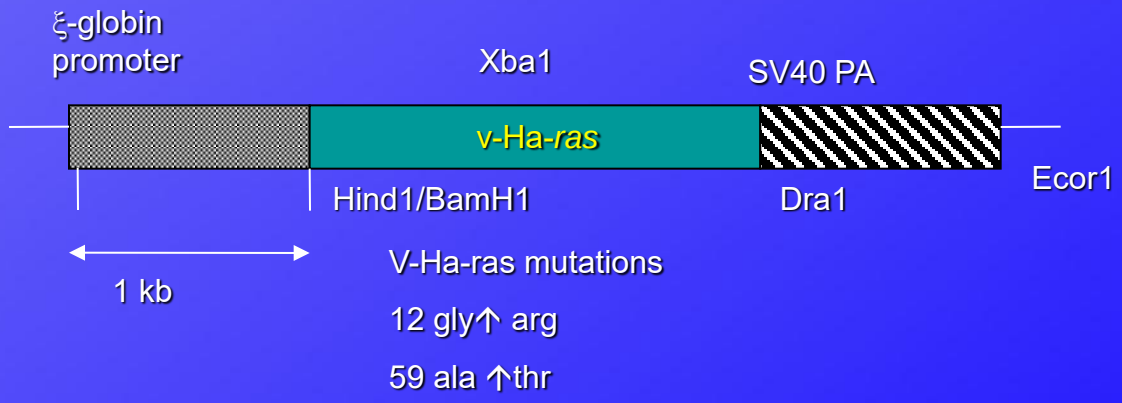
Heterozygous *Trp53* deficient Mice

(Donehower et al., *Nature* 356:212, 1992)

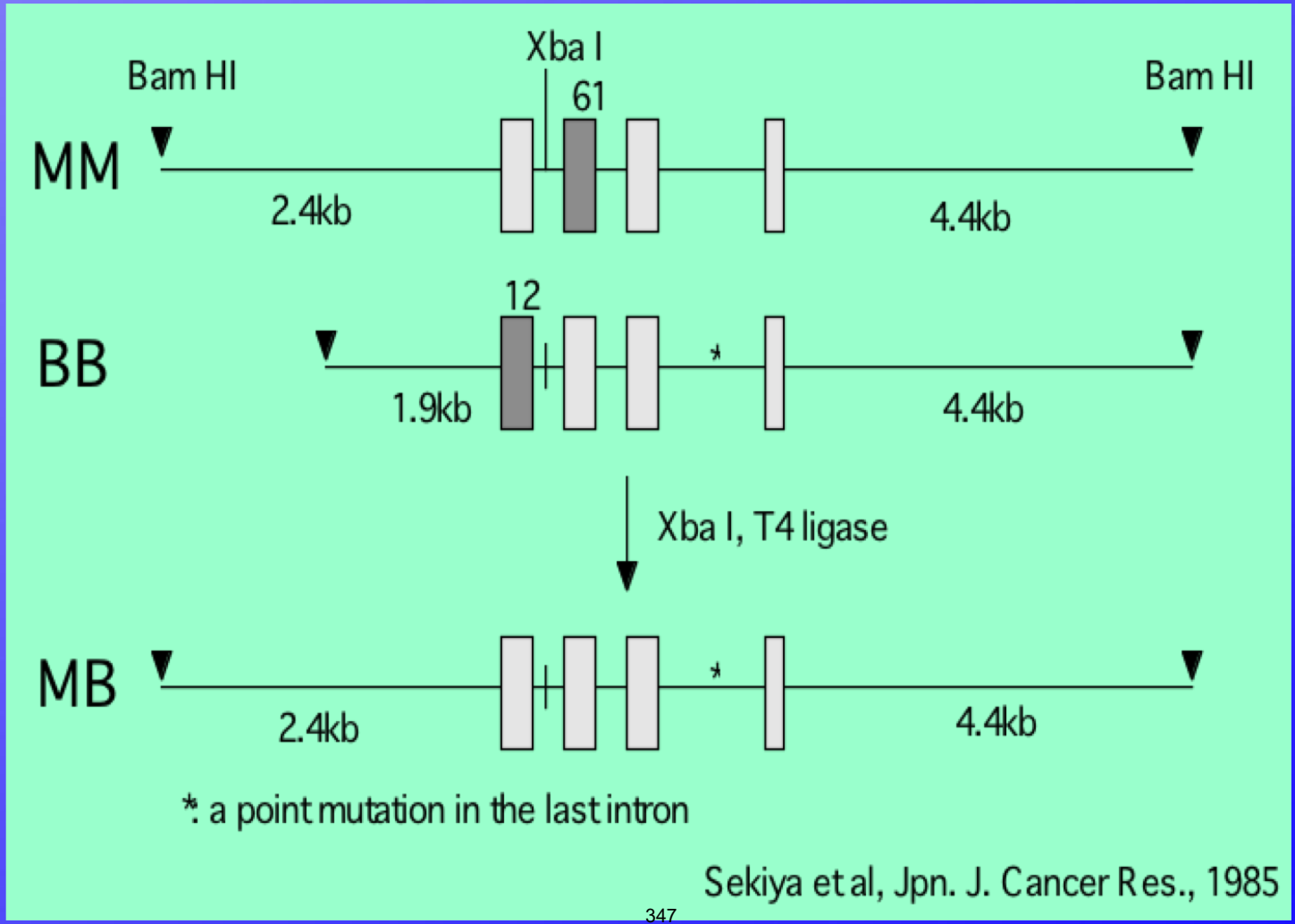


FVB/N-TgN(*v-Ha-ras*)^{Lep}(*Hras*)

- Tripartite construction
- Ectopic (integration site) expression
- Induced and/or clonally expanded
- Reporter phenotype



CB6F1-TgN(*RasH2*)^{Sel}



GEMM Predictability

Data set for prediction (99 test chemicals)

B6.129-Trp53^{tm1Brd}	FVB/N-TgN(v-ras)^{Lep}	CB6F1-TgN(rasH2)^{Sel}

[+]
- 47 IARC Group1/2 NTP ROC - Known/Probable Human Carcinogens

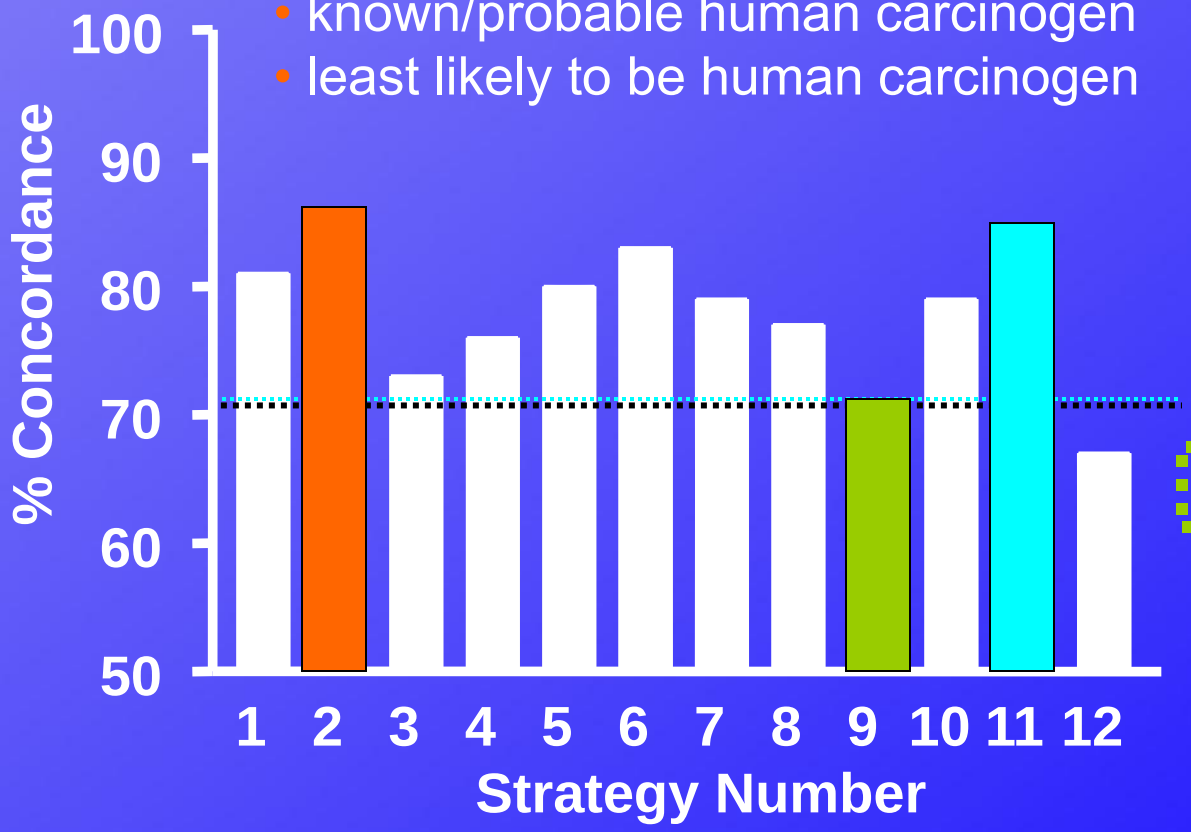
[-]
- 52 IARC Group 3/NTP ROC Least likely to be a human carcinogen

Pritchard et al. Environ Health Perspectives 111:444-54, 2003

Toxicologic Pathology 29 Issue 1_Suppl, 2001

GEMMs Predictability

Discrimination between
- known/probable human carcinogen
- least likely to be human carcinogen



1 = Trp53+/-

2 = Trp53-G

3 = Tg.AC

4 = RasH2

5 = p53-G/Ras-N

6 = p53-G/Ras-All

7 = p53-G/Tg.CA-N

8 = p53-G/Tg.AC-All

9 = NTP Rodent Bioassay

10 = Rat Bioassay Plus Tg.AC-N or Trp53-G

11 = Rat Bioassay Plus RasH2-N or Trp53-G

12 = Rat Bioassay Plus Genotoxicity

Pritchard et al. Environ Health Perspectives 111:444-54 (2003)

Conclusions

- Overall, GEMM performed well; issues of validation and standardization of protocols remain
- Combination of GEMM plus Rat (2-yr) bioassay missed no IARC Group 1/2 carcinogens and reduced the number of potential false positives for the expected human non-carcinogens (IARC Group 3)
- **Inclusion and elaboration in IARC Preamble warranted**

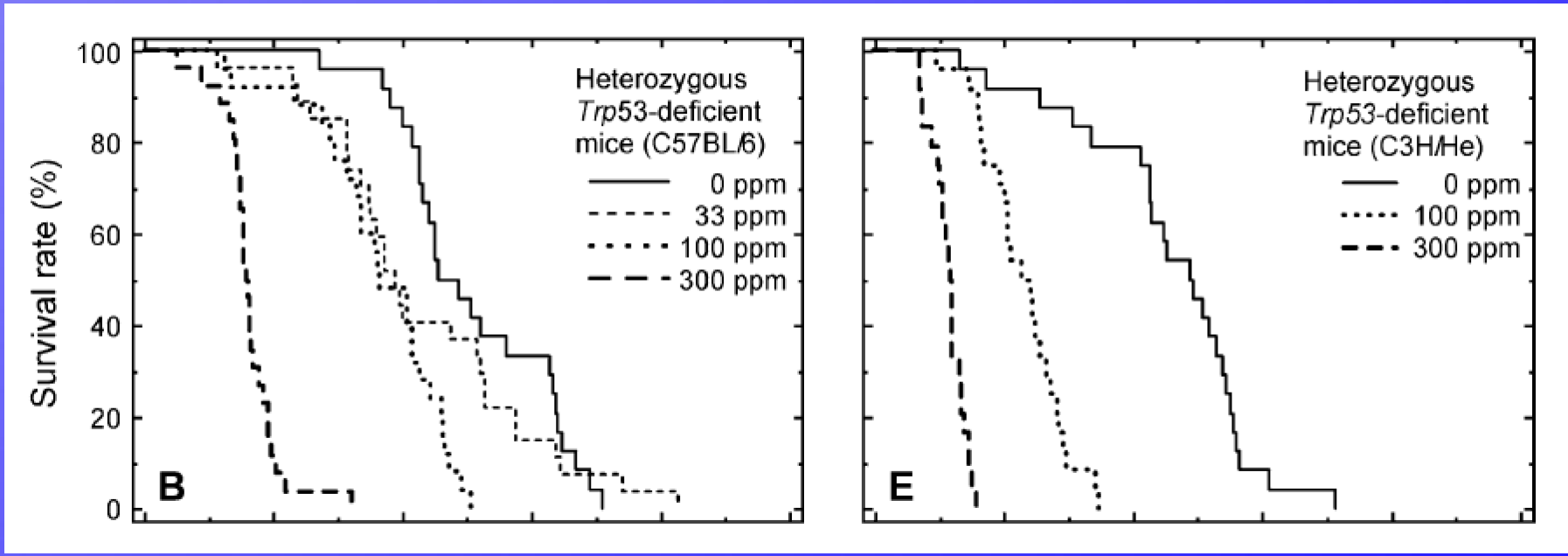
Population-based Mouse Models

GEMMs outcross to:

- homozygous inbred strains to create relevant population based models
- Collaborative-Cross Recombinant Inbred lines
- Diversity Outbred mice

for genome-wide analysis and mechanistic studies

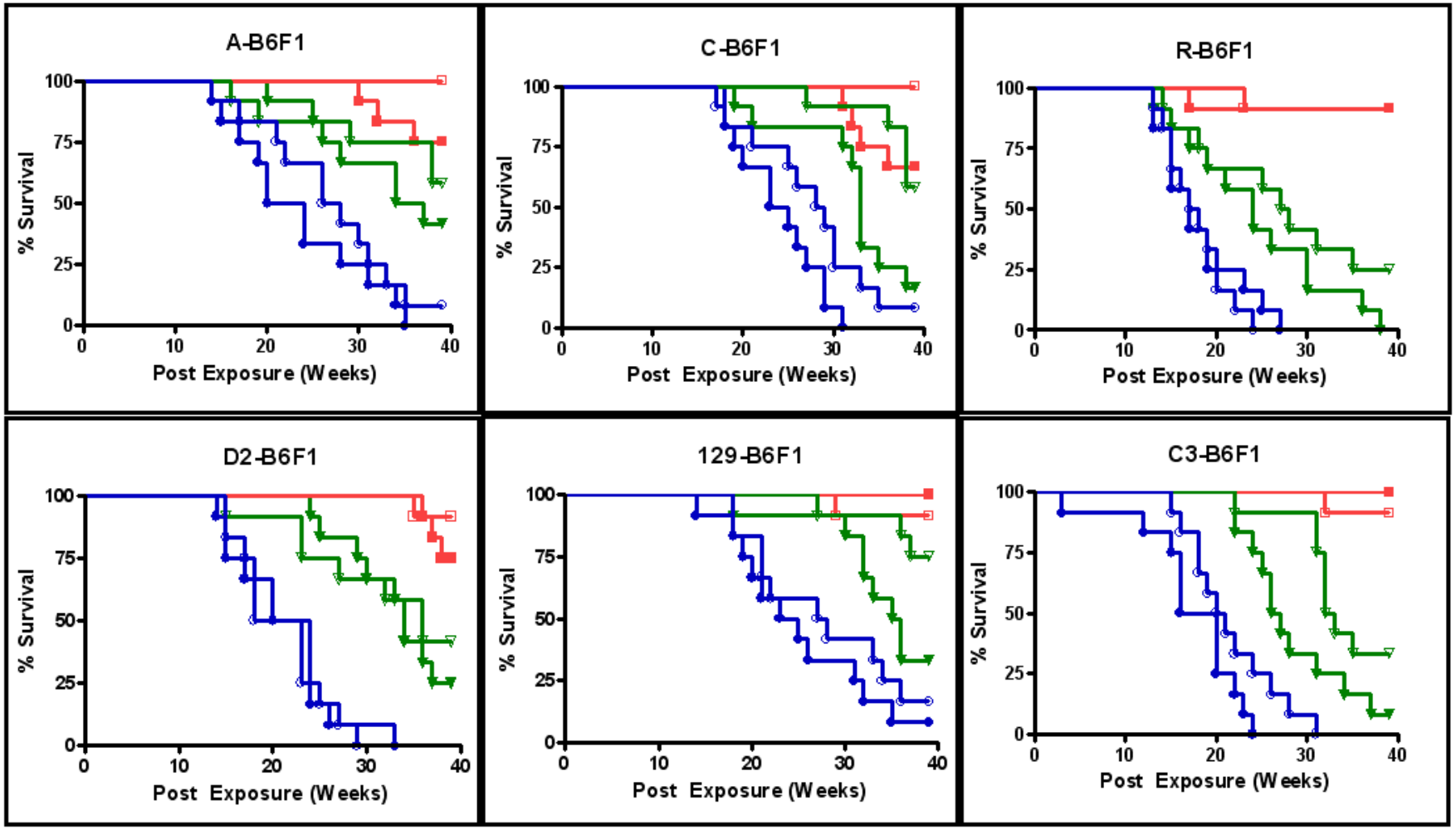
Benzene induced myeloid leukemia in B6- & C3-*Trp53* heterozygous mice

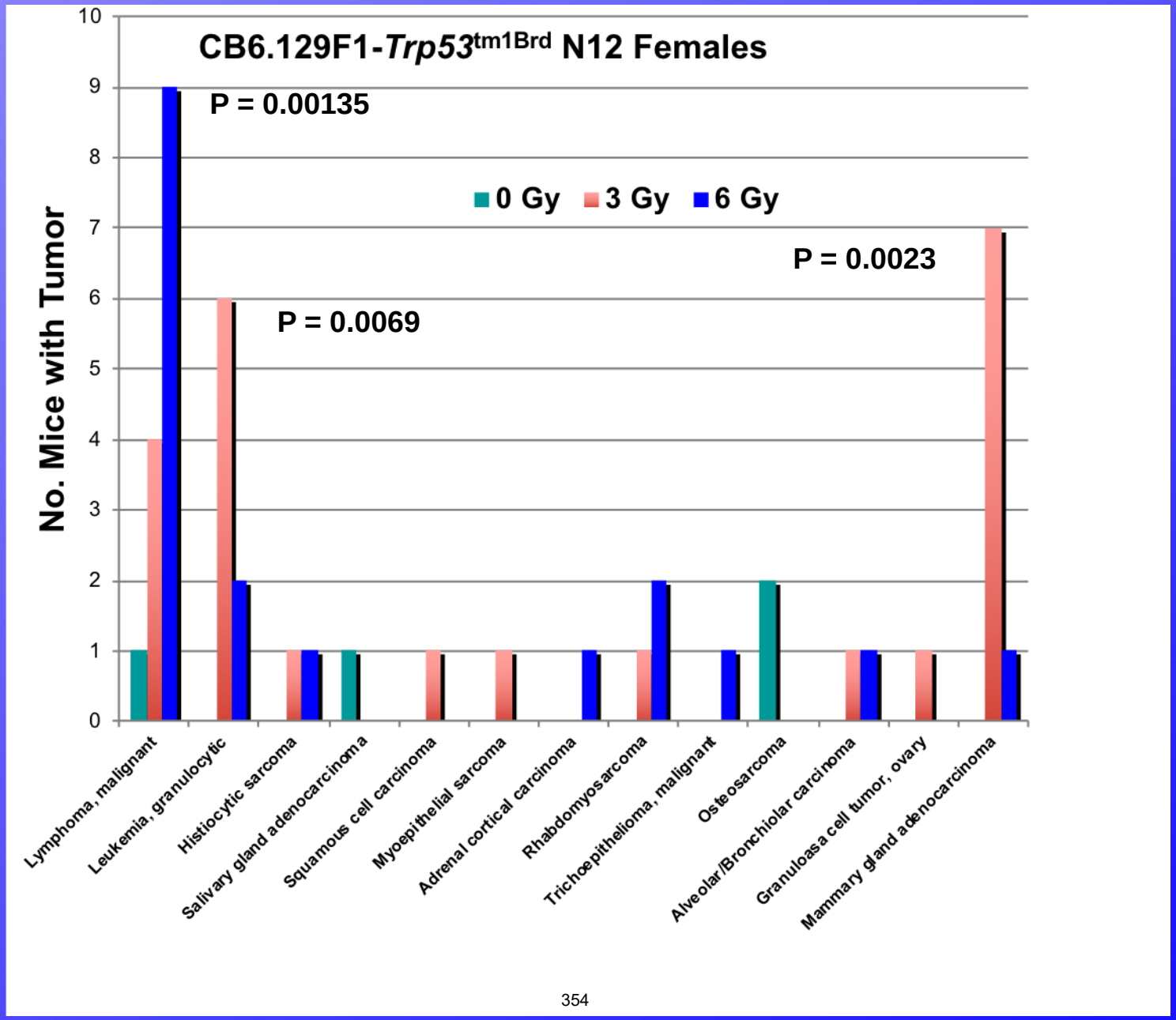


Myeloid leukemia: B6 (0, 0, 0, 2); C3 (2, 2, 9)

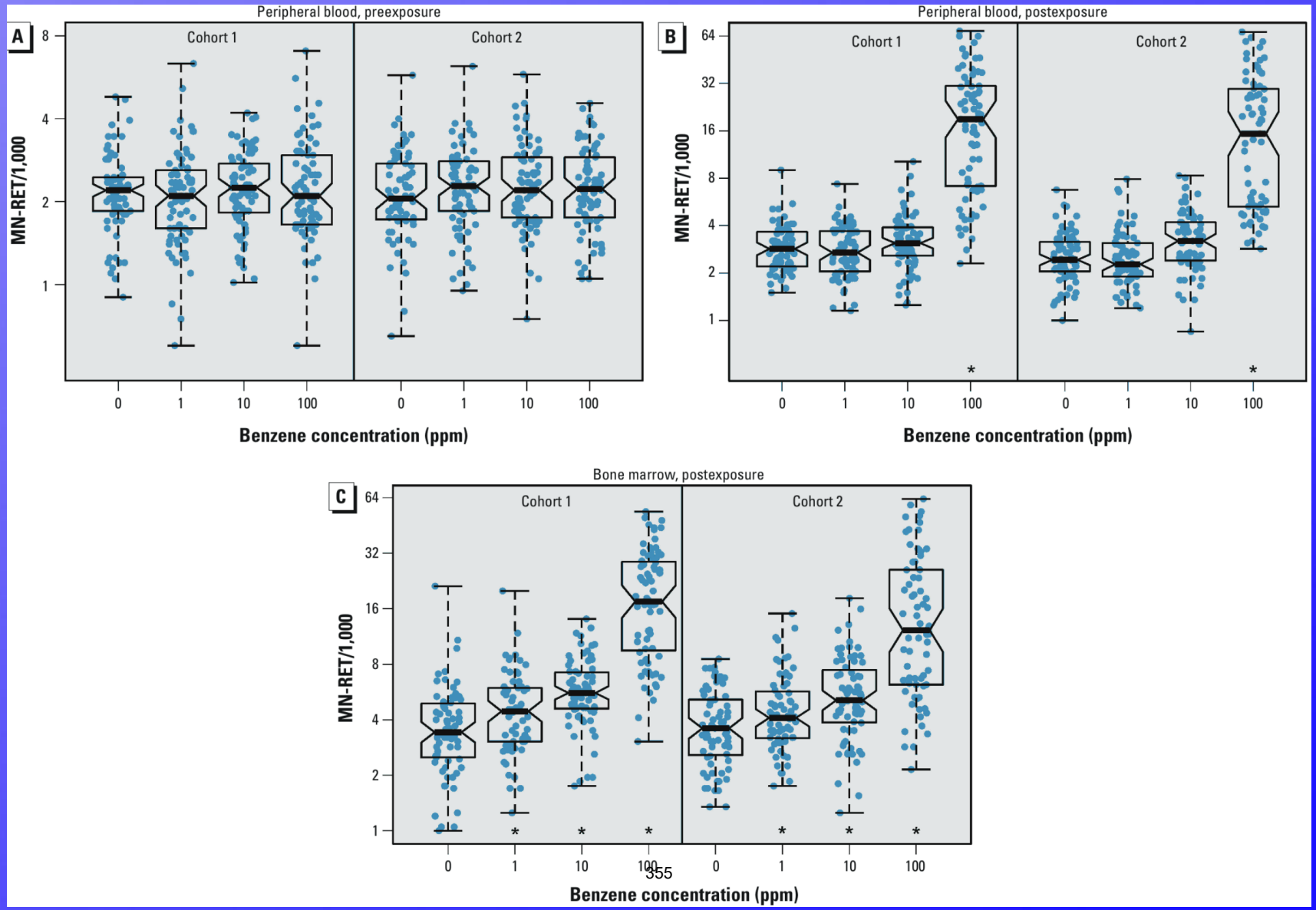
Kawasaki et al. TOXICOLOGICAL SCIENCES 110(2), 293–306 (2009)

Survival (0, 3, or 6 Gy) *Trp53* def F1 Hybrids

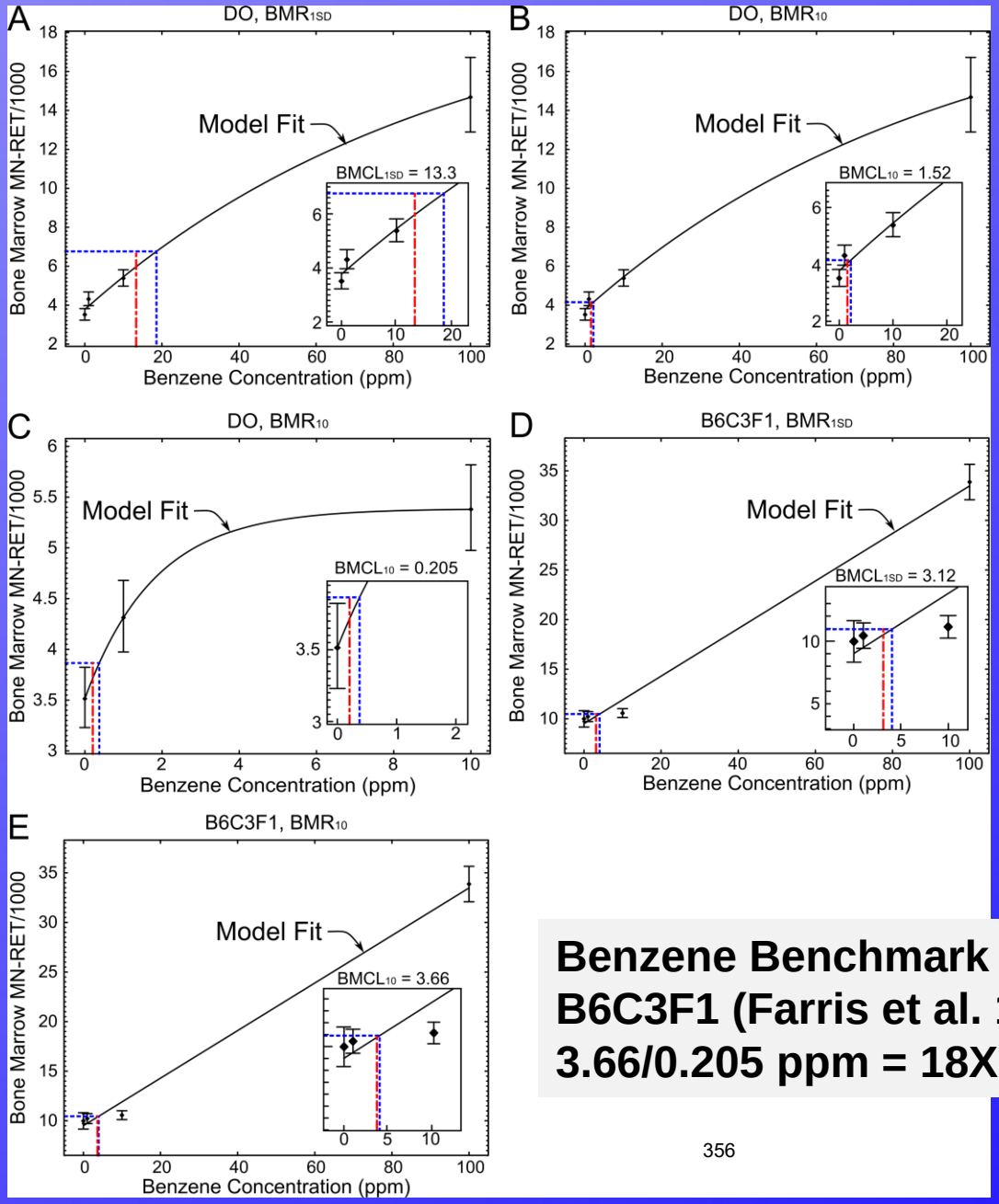



CB6.129F1-Trp53tm1Brd N12 Females
P = 0.00135
P = 0.0069
P = 0.0023
0 Gy
3 Gy
6 Gy
No. Mice with Tumor
0
1
2
3
4
5
6
7
8
9
10
Lymphoma, malignant
Leukemia, granulocytic
Histiocytic sarcoma
Salivary gland adenocarcinoma
Squamous cell carcinoma
Myoepithelial sarcoma
Adrenal cortical carcinoma
Rhabdomyosarcoma
Trichoepithelioma, malignant
Osteosarcoma
Alveolar/Bronchiolar carcinoma
Granuloasa cell tumor, ovary
Mammary gland adenocarcinoma

French et al. EHP 2015 Benzene induced micronuclei in Diversity Outbred Mice



French et al. EHP 123, 237, 2015



Benzene Benchmark Concentration Models B6C3F1 (Farris et al. 1996) and DO mice: 3.66/0.205 ppm = 18X difference


LOONEY TUNES
That's all Folks.

13 - Paul Lambert

Section 3: Animals testing of human viruses suspected of causing cancer

Cannot directly test human viruses in animals because they are species specific (i.e. they do not infect mice or other experimental animals).

Alternatives uses of animals for assessing the carcinogenicity of human viruses

1)Transgenic mice

2) Humanized mice

The absence of a Section 3 "Cancer in Experimental Animals" in the Monographs on viruses

The Working Group decided not to include in this Volume a separate section on "Cancer in experimental animals" in the *Monographs* on viruses, but rather to include description of such studies under Section 4 "Other Relevant Data" for the following reasons:

• The use of animals as surrogate hosts for the study of a human tumour virus is often problematic since species-specicity limits the feasibility of this approach for most of these viruses. HTLV-1 is one exception: this virus can infect several di erent animal species (rabbits, rats and monkeys) but does induce adult T-cell leukaemia/lymphoma in monkeys only. For some human tumour viruses (e.g. KSHV), the use of humanized SCID mice, in which the human target cell for the virus is placed into a mouse host context, can provide a platform for in- vivo infection. However, apart from EBV, which causes lymphoproliferative diseases in New World monkeys and humanized SCID mice, the use of surrogate hosts has not proven very useful for assessing the carcinogenicity of human viruses in humans.

• Cancer models for human tumour viruses that make use of animal viruses are very scarce. In fact, although many viruses that infect non-human primate species are related to the human tumour viruses, the incidence of cancer is low in these species – as it is in humans – which makes cancer studies costly and di cult. Moreover, animal tumour virus models in non-primate species often do not accurately reflect the mechanism of the disease caused by the cognate human tumour virus. For instance, woodchuck hepatitis virus induces HCC that is histopathologically very similar to that caused by HBV in humans, but it does so through a different mechanism.

• Transgenic mouse models provide powerful means for performing mechanistic studies to investigate the role of individual viral genes in cancer. Indeed, for many of the human tumour viruses described in this volume, transgenic mouse studies provide critical mechanistic evidence. However, such transgenic mouse models do not represent models for understanding the cancer etiology in the context of natural viral infections, and are therefore more appropriately discussed in Section 4.

HPV16 Transgenic Mice: Cervical Cancer

Chronic estrogen-induced cervical and vaginal squamous carcinogenesis in human papillomavirus type 16 transgenic mice.
Proc Natl Acad Sci U S A. 1996 93(7):2930-5. PMID: 8610145

Critical roles for non-pRb targets of human papillomavirus type 16 E7 in cervical carcinogenesis.
Cancer Res. 2006 66(19):9393-400. PMID: 17018593

The human papillomavirus E6 oncogene dysregulates the cell cycle and contributes to cervical carcinogenesis through two independent activities.
Cancer Res. 2007 67(4):1626-35. PMID: 17308103

A role for HPV16 E5 in cervical carcinogenesis.
Cancer Res. 2010 70(7):2924-31. PMID: 20332225

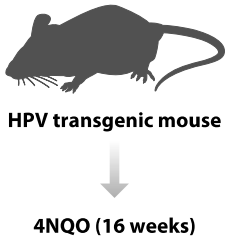
Human papillomavirus oncogenes reprogram the cervical cancer microenvironment independently of and synergistically with estrogen.
Proc Natl Acad Sci U S A. 2017 114(43):E9076-E9085. PMID: 29073104

HPV16 Transgenic Mice: Head and Neck Cancer

Identification of biomarkers that distinguish human papillomavirus (HPV)-positive versus HPV-negative head and neck cancers in a mouse model.
Proc Natl Acad Sci U S A. 2006 103(38):14152-7. PMID: 16959885

Role of Rb-dependent and Rb-independent functions of papillomavirus E7 oncogene in head and neck cancer.
Cancer Res. 2007 67(24):11585-93. PMID: 18089787

Human papillomavirus type 16 E6 and E7 oncoproteins act synergistically to cause head and neck cancer in mice.
Virology. 2010 407(1):60-7. PMID: 20797753



Annu Rev Virol. 2016 Sep 29;3(1):473-489. PMID: 27741405

Cutaneous High Risk HPVs: Skin Cancer

Skin hyperproliferation and susceptibility to chemical carcinogenesis in **transgenic** mice expressing E6 and E7 of human papillomavirus type 38.
J Virol. 2005 79(23):14899-908. PMID: 16282489

Development of skin tumors in mice **transgenic** for early genes of human papillomavirus type 8.
Cancer Res. 2005 65(4):1394-400. PMID: 15735026

Spontaneous tumour development in human papillomavirus type 8 E6 **transgenic** mice and rapid induction by UV-light exposure and wounding.
J Gen Virol. 2009 90(Pt 12):2855-64. PMID: 19692543

Beta HPV38 oncoproteins act with a hit-and-run mechanism in ultraviolet radiation-induced skin carcinogenesis in mice.
PLoS Pathog. 2018 14(1):e1006783. PMID: 29324843

MCPyV: Merkel Cell Carcinoma

Merkel Cell Polyomavirus Small T Antigen Induces Cancer and Embryonic **Merkel Cell** Proliferation in a **Transgenic** Mouse Model.
PLoS One. 2015 Nov 6;10(11):e0142329. PMID: 26544690

Tumorigenic activity of merkel cell polyomavirus T antigens expressed in the stratified epithelium of mice.
Cancer Res. 2015 Mar 15;75(6):1068-79. PMID: 25596282

Merkel Cell Polyomavirus Small T Antigen Initiates **Merkel Cell** Carcinoma-like Tumor Development in Mice.
Cancer Res. 2017 ;77(12):3151-3157. PMID: 28512245

EBV and KSHV: Humanized mice

Epstein-Barr virus type-2 infects T-cells and induces B-cell lymphomagenesis in **humanized mice**.
J Virol. 2018 Aug 8. pii: JVI.00813-18. PMID: 30089703

An EBNA3C-deleted Epstein-Barr virus (**EBV**) mutant causes B-cell lymphomas with delayed onset in a cord blood-**humanized** mouse model.
PLoS Pathog. 2018 Aug 20;14(8):e1007221. PMID: 30125329

Persistent KSHV Infection Increases **EBV**-Associated Tumor Formation In Vivo via Enhanced **EBV** Lytic Gene Expression.
Cell Host Microbe. 2017 Jul 12;22(1):61-73.e7. PMID: 28704654

Latent Membrane Protein 1 (LMP1) and LMP2A Collaborate To Promote Epstein-Barr Virus-Induced B Cell Lymphomas in a Cord Blood-**Humanized** Mouse Model but Are Not Essential.
J Virol. 2017 Mar 13;91(7). pii: e01928-16. PMID: 28077657

Knockout of Epstein-Barr virus BPLF1 retards B-cell transformation and lymphoma formation in **humanized mice**.
MBio. 2015 Oct 20;6(5):e01574-15. PMID: 26489865

An Epstein-Barr Virus (**EBV**) mutant with enhanced BZLF1 expression causes lymphomas with abortive lytic **EBV** infection in a **humanized** mouse model.
J Virol. 2012 Aug;86(15):7976-87. PMID: 22623780

Suggested addition to section 3

In the case of human viruses, assessment of their carcinogenic properties cannot be carried out directly in animals because most of the relevant viruses only infect humans. Alternative uses of animals to assess the carcinogenicity of human viruses are therefore appropriate. These include the use of genetically engineered mice in which viral genes are targeted in their expression to the tissues that are normally infected by the virus in humans and from which cancers are known to arise, or use of humanized mice in which the human cells normally infected by the human virus are implanted into mice.

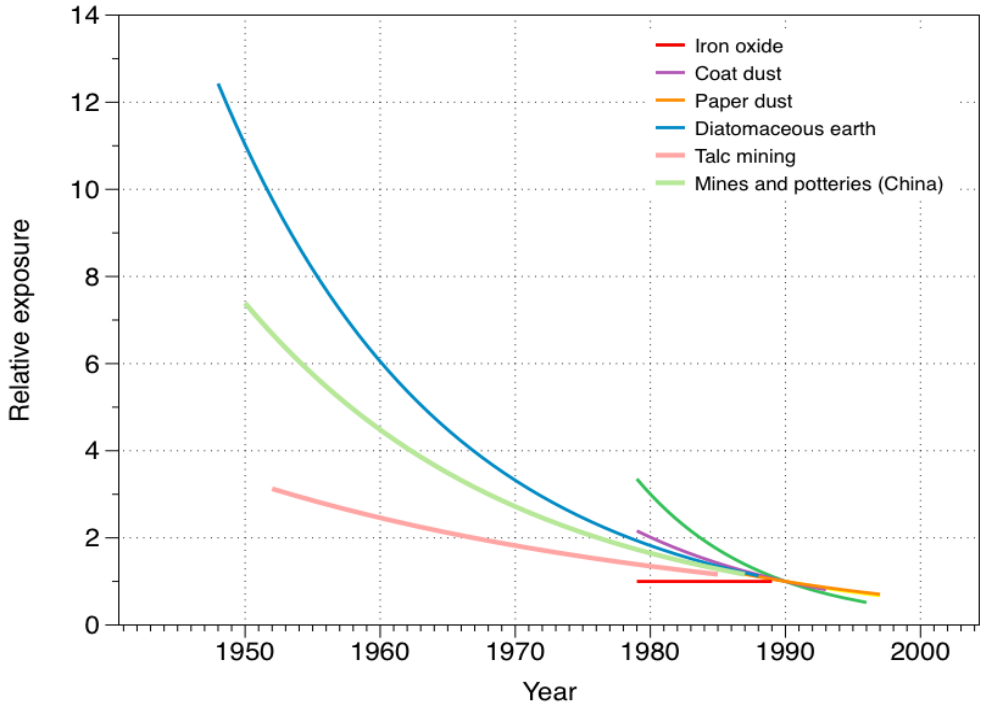
14 - John Cherrie

Exposure data…

- General information on the agent
- Production and use
- Methods of analysis and detection
- Occurrence, and sources
- Routes of human occupational and environmental exposures
- Regulations and guidelines

Availability of exposure data…

- Problems getting data from outside USA and Northern Europe
- Mostly fairly recent with little contextual data
- Exposure levels (and prevalence) higher in the past



Creely KS *et al.* (2007) Trends in inhalation exposure--a review of the data in the published scientific literature. Ann Occup Hyg., 51(8): 665-678.

Availability of exposure data…

- Co-exposures often not clearly described
- Today, for workplace exposure, commercial companies hold the majority of data
- Perhaps use exposure modelling to estimate exposures

Data on exposed population…

- Information on occurrence / production and use are insightful
  - However, data are often unavailable
  - Access to national/international databases, e.g. ECHA?
- Details of number of people exposed is mostly very limited
- Mostly little details of work or other activities where people may be exposed

Measurement methods…

- Descriptive: no critical evaluation or recommendation of any method is meant or implied
- It's unclear what purpose this serves!
- Perhaps important to highlight the reliability of methods to assess exposure and how different approaches relate to each other, e.g. air sampling and biological monitoring

Regulations and guidance…

- Workers, consumers and the environment
- Regulations are complex and vary between jurisdictions
- Impossible to give true international coverage
- Regulations and limit values frequently change
- Perhaps needs to highlight specific interventions, e.g. is the agent banned or is use restricted in specific countries

HERIOT WATT UNIVERSITY

Critical review of the epidemiological literature…

- Review exposure assessment methods of specific epidemiological studies identified collaboratively with the epidemiology group
- Past levels of exposure, reliability of assessments, inter-relationship of different measures
- Should highlight possible co-exposure to other risk factors
- Include in preamble

15 - Paul Demers

Comments on the IARC Monographs Preamble

Paul A. Demers, Ph.D.
Director, Occupational Cancer Research Centre
Cancer Care Ontario, Toronto Canada
Professor, Dalla Lana School of Public Health,
University of Toronto

17 September, 2018

Areas I will comment on

- A general need for clarity/transparency
- Selection of the Working Group members
- Studies of Cancer in Humans
  - Selection of Studies
  - Quality of Studies considered
  - Criteria for Causality
- Evaluation

More Clarity Needed

"The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous Monograph meetings but remain, predominantly, the prerogative of each individual Working Group."

Preamble Page 1: 41 to 2:2.

More Clarity Needed

- Although I understand that there may be some variability, working procedures should be presented in greater detail for transparency.
- In addition, despite a section entitled “Working procedures,” procedures are scattered throughout, even when related to the same topic
- For example, how are working group members (WG) chosen?
  - “participants are selected by IARC in consultation with other experts” (page 5: 30-31). Better detail on WG characteristics sought are provided on Page 4: 26-31.

Studies Considered by WG

- More clarity is needed in describing the selection of studies to be considered
  - IARC does an initial search using pubmed with other sources to supplement (page 5: 32-33)
  - After agents are assigned to WG, their responsibility to critically review and decide if any thing was missed and select the relevant data (4, 20-22)
- The basic criteria need to remain:
  - Published or accepted in the openly available literature and government reports
- IARC must consider all potentially relevant studies, even if some are given more weight in the evaluation

Quality of Studies Considered

- The quality issues currently described in the preamble are simple, but appropriate, although misclassification of exposure deserves more discussion.
- Various tools used for conducting systematic reviews and applying some type of quality screen would be inappropriate.
- Almost all studies considered by most WGs are observational in nature and must continue to examine the weight of the full body of epidemiologic evidence.

Criteria for Causality

- Under both Criteria for Causality (page 11) and Evaluation (page 16), the reader is reminded of the importance of chance, bias and confounding.
- Almost all observational studies have limitations which can result in bias.
- What is important is to consider is the direction and potential magnitude of those biases, which can help explain heterogeneity in study findings.

Procedures for Evaluation

- The reader gets very little sense of the formality of the WG plenary sessions or the rigour of the evaluation.
- The role of the epidemiology and animal studies sub-groups in proposing initial evaluations for their areas of responsibility does not seem to be mentioned.
- That their revised drafts are made available to the full WG prior to discussions in plenary should also be mentioned.

Preliminary Default Evaluation

Cancer in Humans	Cancer in Experimental Animals: *Sufficient*	*Limited*	*Inadequate*
Sufficient	*Group* **1**	*Group* **1**	*Group* **1**
Limited	*Group* **2A**	*Group* **2B** **Exceptionally: Group 2A**	*Group* **2B** **Exceptionally: Group 2A**
Inadequate	*Group* **2B**	*Group* **3**	*Group* **3**

Strong mechanistic evidence can move an evaluation up or down a category

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*

General Comments

- The working procedures need more clarity
  - For example, all WG meetings that I remember begin with a plenary session where the working procedures and the evaluation process are explained and issues such as conflict of interest are discussed
- Although nicely written prose, the Preamble is not the clearest document to find and locate information
- Better organization and a greater use of flow charts and other figures could help.

16 - Dana Loomis

Evaluating Epidemiologic Studies for the IARC Monographs

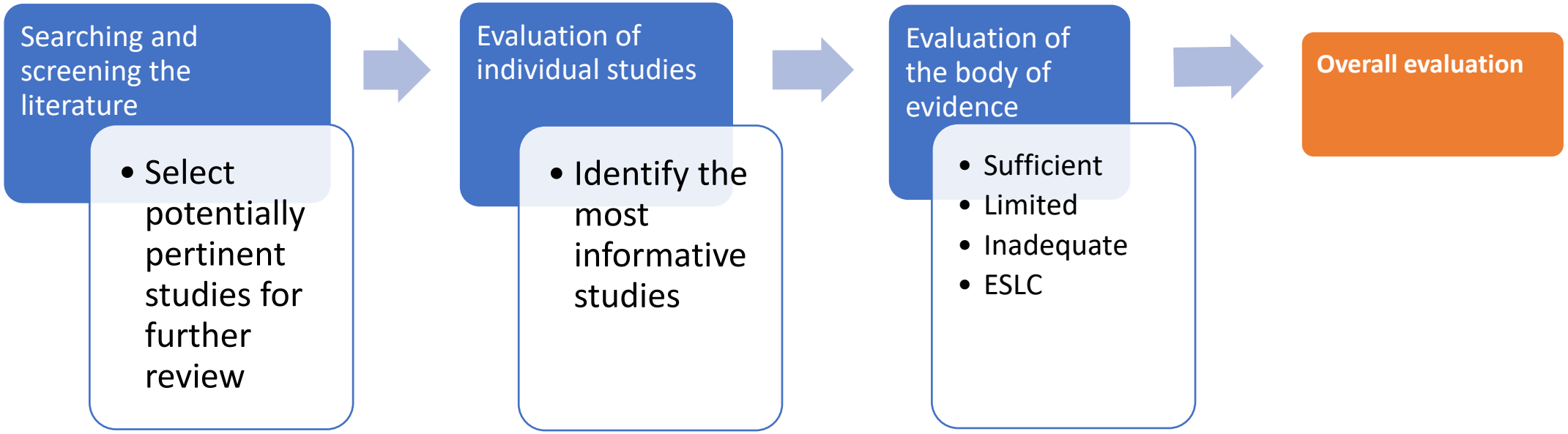
Dana Loomis, PhD

University of Nevada, USA

Declaration of Interests

- I have no financial interest related to the topic of this presentation or to the IARC Monographs
- I previously served as Senior Epidemiologist for the Monographs and Head of the IARC Monographs Group

Evaluation of evidence from epidemiologic studies



Evaluating epidemiologic studies: the purpose

- Why evaluate study quality?
  - To identify the most informative studies as a basis for hazard identification

- Other considerations
  - To assure the public that the informative studies have been considered and that strengths and limitations have been taken into account
  - To provide an trustworthy, understandable record of Working Groups' assessments of the evidence

Current practice: study selection

- Guidance from the Preamble
  - Only published/accepted reports are eligible (A.4)
  - “relevant sources of…data are gathered by IARC from recognized sources…including PubMed”
  - Working Groups “are expected to supplement IARC searches with their own searches” (A.6)
  - Studies of all types may be reviewed (B.2(a))
- Other procedures
  - IARC Secretariat conducts electronic searches, screens studies and documents results in HAWC
  - WGs may (or may not) conduct additional searches and add studies
  - Further inclusion/exclusion decisions are made in drafting and revision

Current practice: study quality

- Quality is formally evaluated and reported in the Monographs
- The Preamble gives specific guidance
- Consider ”bias, confounding and chance” (B.2(b), specifically:
  - Definition of disease and exposure; potential for differential classification
  - Control of confounding; appropriate comparison groups in cohort studies
  - Presentation of “basic data” (numbers exposed & unexposed, observed & expected, etc)
  - Reporting of statistical methods
- Use square brackets to highlight any “important aspect of a study that directly impinges on its interpretation” (A.4, B)
- Further comments may be made in narrative descriptions or summaries

Liabilities of current practice

- Working Groups have wide discretion in study selection, evaluation and documentation
- However, the state of the art has evolved: transparency & accountability are expected
- The Preamble gives little guidance on how pertinent studies are found and none on documenting inclusion and exclusion; the term "*systematic review*" is not used
- IARC and WG search strategies and results are not published
- Inclusion/exclusion decisions are not consistently documented
- Evaluation of some key elements of quality (e.g., exposure assessment) is not specifically required
- Use of square brackets to note study limitations is inconsistent
- The studies found most influential are not always clearly identified

Alternatives: checklists, scores and algorithms

- Developed for reviews of RCTs, but increasingly adopted for environmental studies, notably by US government agencies
- Provide a formal structure:
  - Specifying which elements study quality are evaluated
  - Documenting how each element was assessed
- Some produce quality or ”confidence” scores
- May be useful for non-expert reviewers
- Appearance of objectivity, yet many arbitrary elements
- Judgment still required
- “One-size-fits-all” approach
- Time consuming for reviewers

Alternatives: enhanced guidance and documentation

- Current practices and procedures usually provide robust results, but increased transparency would enhance public confidence
- Clarity and consistency also benefit the WG process
- Liabilities can be greatly reduced through improved instructions to Working Groups and clear, consistent documentation of study selection and evaluation
- Existing procedures (e.g., systematic searches) can be formalized by adoption into the Preamble

Recommendations

Study selection

- Amend the Preamble to specify systematic review methodology
- Publish search strategies (including WG searches) and numbers of studies included/excluded at each stage
- Document WG decisions to include/exclude studies within Monograph narratives
- Consider requiring explicit justification to include non-analytic studies, e.g., ecologic studies, case series, case reports

Recommendations

Study evaluation

- Revise Preamble language to clarify that potential for selection bias, information bias and confounding must be evaluated for every study
- Document specific concerns **or** absence of concern for every study in Monograph narratives
- Consider amending Preamble instructions to explicitly require evaluation of exposure assessment quality
- Amend Preamble instructions for study descriptions or summaries to ensure definitive studies are clearly identified
- *Do not adopt checklists, algorithms or scoring procedures*