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SUBMITTED BY EMAIL

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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.