Commentary

The *IARC Monographs*: Updated procedures for modern and transparent evidence synthesis in cancer hazard identification

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Running head: Updated Preamble to the *IARC Monographs*

List of abbreviations

IARC: International Agency for Research on Cancer

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Abstract

The *Monographs* produced by the International Agency for Research on Cancer (IARC) apply rigorous procedures for the scientific review and evaluation of carcinogenic hazards by independent experts. The Preamble to the *IARC Monographs*, which outlines these procedures, was updated in 2019, following recommendations of a 2018 expert Advisory Group. This article presents the key features of the updated Preamble, a major milestone that will enable IARC to take advantage of recent scientific and procedural advances made during the 12 years since the last Preamble amendments. The updated Preamble formalizes important developments already being pioneered in the *Monograph*s Programme. These developments were taken forward in a clarified and strengthened process for identifying, reviewing, evaluating and integrating evidence to identify causes of human cancer. The advancements adopted include strengthening of systematic review methodologies; greater emphasis on mechanistic evidence, based on key characteristics of carcinogens; greater consideration of quality and informativeness in the critical evaluation of epidemiological studies, including their exposure assessment methods; improved harmonization of evaluation criteria for the different evidence streams; and a single-step process of integrating evidence on cancer in humans, cancer in experimental animals and mechanisms for reaching overall evaluations. In all, the updated Preamble underpins a stronger and more transparent method for the identification of carcinogenic hazards, the essential first step in cancer prevention.

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For nearly 50 years, the *Monograph*s Programme of the International Agency for Research on Cancer (IARC) has been a premier global resource for identifying agents that can cause cancer. The identification of carcinogenic hazards is a necessary initial step in cancer prevention. National and international authorities and organizations use information on causes of cancer to support actions to reduce human exposure to carcinogens.

More than 1000 agents have been evaluated in the *Monographs* Programme. These evaluations have addressed chemical, physical, and biological substances, working conditions, dietary constituents, and other exposures of everyday life. Slightly more than half of all agents evaluated have been classified as possibly carcinogenic, probably carcinogenic or carcinogenic to humans (https://Monographs.iarc.fr/agents-classified-by-the-iarc/).

The *IARC Monographs* embody principles of scientific rigour, impartial evaluation, transparency, and consistency. Long-standing hallmarks of *Monograph*s evaluations include the transparent synthesis of different streams of evidence and their integration into uniform classifications of the strength of evidence for causation[12,13,1]. Three streams of scientific evidence are considered: studies of human cancer, studies of cancer in experimental animals, and mechanistic evidence. Human exposure is also characterized. The evaluation process has evolved since the Programme's inception, in 1971, in parallel with the evolution of the scientific evidence on causation and experience gained over the decades of the Programme's existence. Starting in 1982, it has been possible to "upgrade" overall evaluations based on results from short-term genotoxicity assays. In 1991, a Working Group proposed principles and procedures for use of mechanistic evidence for overall evaluations, specifying criteria for mechanistic upgrades to a higher hazard category, as well as criteria for downgrades to a lower category based on the extent of mechanistic understanding. The update of the Preamble[2] described here reflects the changing mix of scientific evidence considered by *Monograph*s Working Groups, notably the predominance of mechanistic evidence for some agents[3]. Advances in the assessment of

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mechanistic data include the identification of "key characteristics of carcinogens", which provide a framework for organizing mechanistic data and assessing strengths as well as gaps in evidence[4–7]. The revisions to the Preamble reflect these advances and describe a harmonized process for integrating evidence from epidemiological studies, experimental animal bioassays, and mechanistic data to reach a carcinogenicity classification.

While IARC Working Groups have always conducted comprehensive reviews of evidence of carcinogenicity, advances in systematic review methods[8–12] provide a basis for more specific guidance to Working Group members, thereby enhancing consistency and transparency. IARC has embraced these methods and incorporated them into its procedures for assembling and assessing evidence[13]. Rather than relying on specific checklists and scoring methodologies for evaluating studies, the revised Preamble specifies review procedures to formally consider the quality of the studies that are tailored to each stream of evidence and the types of studies available.

Given the potential importance and impact of the classification of an agent, consideration has long been given to managing conflicts of interest on the part of all participants in a Working Group meeting. For enhanced transparency, the 2006 Preamble strengthened conflict of interest management and delineated the distinct roles of different participants (Working Group Members, Invited Specialists, Representatives, Observers, IARC Secretariat)[14,15]. The revised Preamble maintains a robust process for identifying, evaluating and disclosing conflicts of interest. Commitments to transparency are extended, including in the area of engagement with the public and in broadening of the admissible data sources, while maintaining the requirement that the information used be publicly available.

This Commentary describes the motivation and methodology for the recent update to the Preamble for the *Monograph*s Programme of IARC, and highlights the key changes adopted. In doing so, the methodology and utility of the hazard identifications provided by the *Monographs*

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are communicated more broadly. The Preamble offers a well-established framework for evidence integration and, as such, the new approach to considering mechanistic evidence is of broad interest.

Motivation and Process for Preamble Revision

Since 2006, substantial growth has occurred in the scientific understanding of factors contributing to carcinogenicity as well as in the development of methods for information gathering, evidence assessment, and integration. In 2018, IARC convened an *Advisory Group to Recommend an Update to the Preamble*, with broad expertise across multiple disciplines to consider scientific progress and the views of different stakeholders on these important developments. IARC solicited input through a six-month public comment period, during which more than 30 individuals or institutions responded (https://Monographs.iarc.fr/wp-content/uploads/2018/11/Preamble_PublicComments.pdf). In addition, IARC sought expert input during a scientific webinar held in advance of the Advisory Group meeting (https://Monographs.iarc.fr/wp-content/uploads/2018/11/Webinar-presentations.pdf).

The Advisory Group comprised 21 members from 9 countries, with a range of expertise including exposure characterization, epidemiology, cancer bioassays, carcinogen mechanisms, risk assessment, systematic review, and philosophy of science. From 12–14 November 2018, the Advisory Group met to finalize recommendations to update the Preamble. Other meeting participants included two Invited Specialists, seven Representatives of national and international health agencies, three Observers from interested organizations, and 16 members of the IARC/WHO Secretariat. The Advisory Group carefully considered written comments from the public, scientific webinar presentations, and input from all meeting participants.

The Advisory Group made specific recommendations for revising the Preamble and prepared a report to IARC highlighting key deliberations[16]. In early 2019, IARC considered and

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accepted these recommendations, and authorised the updated Preamble for immediate use in the *Monograph*s Programme.

Key changes in the revised Preamble

General procedures

The Advisory Group encouraged IARC to clarify the purpose and scope of the *Monographs* evaluations. In this regard, the name of the *Monographs* series has been changed to the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*. This change, while semantic in nature, reflects the important distinction between hazard and risk: "hazard" refers to the strength of the evidence that an agent is a carcinogen, while "risk" refers to the probability that a given exposure to a carcinogen will result in cancer. From the onset of the program, the *Monograph*s have evaluated the potential cancer hazard of an agent. Hazard identification as conducted within the *Monograph*s is distinct from risk assessment, in which exposure-response characterization is used to estimate cancer risk for a given scenario and level of exposure.

The collective application of informed judgment by experts is an integral and critical component of the *Monograph* development process. The updated Preamble, incorporating recommendations from the Advisory Group, emphasizes the necessity of relying on international experts who are free from conflicts of interest and clearly describes current procedures for evaluating conflicts of interest. Such conflicts are largely financial in nature, but public statements and positions related to the subject of the meeting are also considered. Furthermore, while the use of WHO's Declaration of Interests to identify conflicting interests is a long-term strength of the Programme, the Advisory Group recommended that IARC go further and communicate its expectation that Working Group members not use their participation in IARC meetings for later financial gain. In this regard, the updated Preamble specifies that the Working

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Group should not engage in consulting or other activities involving the agents under review, until after publication of the Monograph volume.

Rationales for IARC practices in convening expert groups were also clarified. For example, IARC's reliance on subject-matter experts who have published studies on the agents under review has shown value borne out by decades of experience in the *Monographs* Programme. This experience has shown that the vast majority of Working Group members are committed to a fair and objective evaluation of the evidence according to the scientific principles and criteria set forth in the Preamble, and not to advancement of their own research findings or careers. Nevertheless, the Preamble recommends several steps to minimize the undue influence of any such "careerism", should it occur, on a *Monograph* evaluation. First, in inviting experts, consideration is given to diversity in scientific approaches and views. Second, study summaries are drafted or peer reviewed by a Working Group member who is not associated with the study and by members of the IARC Secretariat. Third, the identification, screening, organization, and data extraction from the literature are standardized and are executed by several individuals, including the Secretariat. The peer review explicitly addresses whether inclusion and exclusion, data extraction, and summarization of strengths and limitations for each study were carried out in an unbiased manner. Fourth, the peer review expands during the meeting to include the subgroup evaluating individual evidence streams, e.g., studies of cancer in humans, and then to the entire Working Group. Within subgroups, studies are presented for discussion by independent experts and undergo scrutiny by the whole subgroup (including experts who have not worked directly with the agent). The entire body of evidence is synthesized through discussion first within subgroup and then in Plenary sessions. Lastly, to transparently document the process, the Working Group is asked to lay out clear reasoning for its decisions, describe the role of expert judgement in those decisions, and explain the basis for those judgements. Through this rigorous

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process, the entire volume becomes the collective consensus product of the Working Group and the influence of any individual is minimized.

The revised Preamble also clarifies the responsibilities of the expert Working Groups in strengthening the use and documentation of systematic review methodology in the evaluations of cancer in humans, cancer in experimental animals, and mechanistic evidence. In particular, the Working Group is responsible for assuring that the relevant studies have been identified and selected, for assessing the methods and quality of individual studies, and for accurately reporting the study characteristics and results. Steps related to systematically searching for evidence, screening, data extraction, and study quality evaluation are clearly outlined.

Considerations of study quality are tailored to each evidence stream. The revised Preamble describes in greater detail the thorough peer review undertaken throughout the evaluation process, including during identification of relevant information, study review, and data extraction, as well as *Monograph* drafting, revision, and discussion. The Advisory Group considered whether the Preamble should discuss the use of specific quality assessment and systematic review tools but recognized that these tools are rapidly evolving and are more appropriately discussed in the Instruction for Authors (https://monographs.iarc.fr/instructions-for-authors/) that IARC provides for Working Group members. As the Programme keeps abreast of pertinent methodological developments, this allows flexibility for experimentation with new procedures, which can then be adopted once empirically demonstrated to improve the validity of the carcinogenicity evaluation.

Scientific Review and Evaluation

The revised Preamble defines how the principles of systematic review – e.g., formal consideration of quality of the studies (e.g., design, methodology), and reporting of results that are tailored to each stream of evidence and the types of studies available – apply to IARC assessments and how evaluations are reached, to clearly articulate the rationales for expert

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judgements. At the same time, it is designed to be flexible enough to enable incorporation of further scientific advances as these arise.

Exposure characterization: The revised Preamble retains the primary aims and methodology of the exposure characterization section: to identify the agent, to describe its occurrence, main uses, and production (when relevant), and to summarize exposure measurement methods and the prevalence and concentrations in affected human populations. In relation to its enhanced description of these concepts, the revised Preamble re-emphasizes the importance of summarizing data on exposure circumstances in low- and middle-income countries whenever feasible. A critical review of the strengths and limitations of the exposure assessment methods used in key studies of cancer or cancer mechanisms in humans is an important addition to this section. This review is integral in considering study quality and informativeness in the evaluations of the human cancer and mechanistic evidence.

Studies of cancer in humans: The revised Preamble maintains and builds on many aspects of earlier versions to promote a synthetic review of human cancer studies that focuses on the most informative studies, while including a detailed evaluation of their quality. The scope of the review and inclusion criteria, consisting of all pertinent epidemiological studies evaluating the association between exposure to the agent and human cancer as an outcome, are retained. Greater detail is given on the most critical aspects of study quality considered by the Working Group, including those related to the study description, study population (including evaluation of selection bias), exposure assessment methods, outcome measurement, assessment of the potential for and likely impact of confounding, and statistical methods. In addition, the revised Preamble adds the explicit consideration of study informativeness (described elsewhere as "study sensitivity"[17]). An informative study is one that is likely to detect a true association. Considerations include whether the study population is of sufficient size to obtain precise estimates of effect; whether sufficient time has elapsed between exposure occurrence to

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measurement of outcome for an effect to be observable; the presence of adequate exposure contrast; the use of biologically relevant definitions of exposure; and the inclusion of relevant and well-defined time-windows for exposure and outcome[18]. The Advisory Group recommended against mandating the use of any specific checklists and scoring systems in favor of using procedures aligned with the principles outlined in the Preamble that are tailored to the evidence reviewed[19]. While the revised Preamble has been designed to accommodate flexibility as evaluation methods evolve, each Monograph Working Group is encouraged to lay out clear reasoning for its decisions, describing the basis of expert judgment in those decisions. Further, the approach to synthesizing epidemiological evidence for causal inference as applied to cancer hazard identification continues to include consideration of the strength, consistency, and temporality of the association, assessment of any exposure-response gradients, and evaluation of the coherence with physiological and biological knowledge related to exposure to the target tissue or organ, latency and timing of exposure. Through this synthetic review process, the Working Group characterizes the body of evidence of cancer in humans as showing *sufficient*, *limited*, or *inadequate* evidence of carcinogenicity (**Table 1**), or *evidence suggesting lack of carcinogenicity*. The evidence is evaluated by organ or tissue site.

Studies of cancer in experimental animals: The revised Preamble retains most aspects of the evaluation of studies of cancer in experimental animals. The particular attributes that are considered for evaluating quality include agent characterization, dose monitoring, dosing regimen, appropriateness of experimental animal model, sample sizes, exposure effects on survival and body weight, group allocation and randomization, histopathological review, data reporting, and data analysis. For certain exposures (e.g., viruses specific to humans), it is emphasised that studies using genetically modified animals may provide particularly important experimental evidence. Statistical considerations are described for different test conditions, such as the use of survival-adjusted methods when survival is affected by exposure to the agent.

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Guidance is provided on the use of concurrent versus historical control groups. After reviewing study quality and findings, a determination is made of whether there is *sufficient*, *limited*, or *inadequate* evidence of carcinogenicity (**Table 1**), or *evidence suggesting lack of carcinogenicity.* It is noteworthy that new criteria have been added for the determination of *limited evidence*, e.g., the agent causes cancer in observational studies in non-laboratory animals, or increases tumour multiplicity or decreases tumour latency in experimental animals.

Studies of carcinogen mechanisms: Both the availability and utility of mechanistic evidence to inform the evaluation of carcinogenicity have increased substantially since the Preamble was last updated. On the other hand, epidemiological studies of cancer and lifetime cancer bioassays in rodents may be available for only a fraction of agents to which humans are currently exposed[4,20]. Several reports from the US 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 mechanistic data[10,11,21]. Additionally, IARC's review of Group 1 carcinogens[22], as well as recent experience of IARC Working Groups, has shown how mechanistic data can play a role in evaluations of carcinogenicity[4–6]. In particular, human carcinogens often exhibit one or more key characteristics that are related to how they cause cancer, and different carcinogenic agents exhibit different spectra of these key characteristics. The key characteristics described by Smith and colleagues[5] (see **Box 1**), such as "is genotoxic", "is immunosuppressive", or "modulates receptor-mediated effects", are based on empirical observations of the chemical and biological properties associated with the human carcinogens identified by the *IARC Monographs* Programme up to and including Volume 100. Key characteristics are distinct from the "hallmarks of cancer", which relate to the properties of cancer cells[23,24]. Key characteristics are also distinct from hypothesized mechanistic pathways, which describe a sequence of biological events postulated to occur during carcinogenesis. As such, the evaluation approach based on key characteristics adopted in the revised Preamble "avoids a

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narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence"[11].

Given the increasing emphasis on mechanistic data, the Preamble also recognized the importance of evaluating the quality of study design, exposure assessment methods, and biologic assay validity and reliability for human studies that evaluate potential mechanisms relevant to carcinogenesis. This evaluation is in line with the review of epidemiologic studies of cancer, and takes into consideration issues relevant to the assessment of mechanistic endpoints[25,26]. Similarly, quality considerations are emphasized in the review of mechanistic studies conducted in other species and experimental systems (e.g., the suitability of the endpoint, the dosing range, and of the test article for in vitro studies, as well as completeness of reporting).

The evidence that the agent exhibits key characteristics of carcinogens is categorized according to one of three distinct terms (*strong, limited, inadequate),* the latter two aligning with terms used for the human and animal evidence (**Table 1**). When the mechanistic evidence is *strong*, further specification (i.e., from exposed humans, human primary cells or tissues, or experimental systems) is used to guide the overall evaluation.

A substantial part of the evaluation of mechanistic evidence is organized around the key characteristics of carcinogens as initially identified[5]. However, it is recognized that the set of key characteristics of carcinogens may evolve with additional experience and scientific understanding[6]. This may occur as new carcinogens with new characteristics are identified in the future. Progress in understanding the differences in the relative importance among key characteristics, and the assays providing evidence of them, is also anticipated[6,7,8]. As noted in the Preamble, some human carcinogens exhibit a single or primary key characteristic, while for others, evidence for a group of key characteristics may be needed to strengthen mechanistic conclusions. For instance, non-carcinogens can also induce oxidative stress, and the Preamble accordingly notes that evidence of this key characteristic should be interpreted with caution

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unless found in combination with other key characteristics. Further development and mapping of toxicological and biomarker endpoints and pathways relevant to the key characteristics can advance understanding of the evidence and assays most informative for carcinogen hazard identification[6,7].

In addition, evidence that falls outside of the recognized key characteristics of carcinogens, reflecting emerging knowledge or important novel scientific developments on carcinogen mechanisms, may also be included. Moreover, the revised Preamble retains the option to assess the strength of evidence for mechanistic classes; these considerations can go beyond chemical similarity and quantitative structure-activity relationships to include common biological activities across dissimilar chemicals. Also retained is consideration of the strength of evidence based on authoritative criteria for determining that tumours in experimental animals are induced by mechanisms that do not operate in humans. *Strong* evidence in each of these circumstances can be influential in the overall evaluation.

Overall evaluation: A major revision in the overall evaluation process was to allow for mechanistic data to be explicitly considered simultaneously along with evidence from studies of cancer in humans and in experimental animals. Previously, integration of mechanistic evidence usually occurred after the evaluation of human and experimental animal cancer evidence. In the revised Preamble, all three bodies of evidence are considered together, and integrated according to the procedure in **Table 2**.

Another revision is that the evaluation categories were simplified to encompass one of four "Groups" (Group 1, 2A, 2B or 3; see **Box 2**), rather than five (Group 1, 2A, 2B, 3 or 4), as previously. The *IARC Monographs* Programme selects agents for review only if there is evidence of human exposure and some evidence suggesting carcinogenicity. Therefore, the previous Group 3 (*not classifiable*) and Group 4 have been combined, and Working Groups are encouraged to add the statement that an agent is "*probably not carcinogenic to humans*" when warranted. For

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instance, this statement may be appropriate when multiple well-conducted and highly precise epidemiological studies did not find a positive association between the agent and cancer in humans. However, a definitive determination of an absence of any carcinogenic hazard to humans based on epidemiological studies requires assurances that all susceptible populations, exposure circumstances, cancer outcomes, and relevant variables be captured adequately in the body of available studies, which in practice is nearly impossible to attain. An evaluation as Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent has unknown carcinogenic potential and that there are prominent gaps in research.

The option of merging Groups 2A and 2B was also considered, to address the concern expressed by some stakeholders that these groups did not appear to be well distinguished. However, because Group 2A and Group 2B are based on distinctly different levels of strength of evidence, combining the groups would reduce the utility of the past and future evaluations. Recognizing the concern raised, the revised Preamble was enhanced with respect to the clarity and transparency for distinguishing between Groups 2A and 2B, particularly with respect to how they differ in their indication of strength of evidence.

While these modifications will clarify the bases of future evaluations, past evaluations will remain in effect. For example, Group 2A evaluations that are based solely on *limited* evidence of carcinogenicity in humans according to the 2006 Preamble will not change. Agents may be re-evaluated under the most recent Preamble when important additional scientific evidence becomes available.

Conclusion

Overall, the revised Preamble will enable IARC to leverage recent scientific and procedural advancements in carcinogenesis and systematic review methodology. The Advisory Group recommended increased emphasis on mechanistic evidence, continued critical evaluation of

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epidemiological studies, including their exposure assessment methods, as well as strengthening of the systematic review methodology. These developments, in turn, were taken forward in their recommendations to clarify and strengthen the process for integrating the three streams of evidence – human cancer studies, studies of cancer in experimental animals, and mechanistic studies and data – in order to reach an overall evaluation of carcinogenic hazard.

Looking to the future, implementing the updates in the revised Preamble will allow IARC to transparently and consistently apply important advancements in carcinogen hazard identification pioneered in the *Monograph*s Programme, with the ultimate aim of more effectively serving the public health goal of cancer prevention.

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Notes

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Table 1. Definitions of strength-of-evidence descriptors for the evidence streams

Strength-of-Evidence descriptor	Evidence stream		
	Cancer in humans	**Cancer in experimental animals**	**Mechanistic evidence**
Sufficient (or Strong for mechanistic evidence)	A causal association has been established: a positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.	A causal relationship has been established between exposure to the agent and cancer in experimental animals based on an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories and/or under different protocols or (c) in both sexes of a single species in a well-conducted study.	Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. Further support can be provided by studies that demonstrate experimentally that the suppression of key mechanistic processes leads to the suppression of tumour development. Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species*
Limited	A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.	The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) evidence of carcinogenicity is restricted to a single experiment; (b) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; (c) the agent increases tumour multiplicity or decreases tumour latency but does not increase tumour incidence; (d) the evidence of carcinogenicity is restricted to initiation–promotion studies.	The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.
Inadequate	No data are available, or the available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and cancer.	The studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data are available on cancer in experimental animals.	Few or no data are available; there are unresolved questions about the adequacy of the design, conduct, or interpretation of the studies; and/or the available results are negative.

*Quantitative structure–activity considerations, in vitro tests in non-human mammalian cells, and experiments in non-mammalian species may provide corroborating evidence but typically do not in themselves provide strong evidence. However, consistent findings across a number of different test systems in different species may provide strong evidence

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Table 2. Integration of streams of evidence in reaching overall classifications

Stream of evidence			Basis of the overall evaluation	Classification based on strength of evidence
Cancer in humans*	**Cancer in experimental animals**	**Mechanistic evidence**		
Sufficient	Not necessary	Not necessary	Cancer in humans	Carcinogenic to humans (Group 1)
Limited or Inadequate	Sufficient	Strong: Key characteristics of carcinogens, from exposed humans	Cancer in experimental animals and mechanistic evidence	
Limited	Sufficient	Not necessary	Cancer in humans and cancer in experimental animals	Probably carcinogenic to humans (Group 2A)
Inadequate	Sufficient	Strong: Key characteristics of carcinogens, from human cells or tissues	Cancer in experimental animals and mechanistic evidence	
Limited	Less than Sufficient	Strong: Key characteristics of carcinogens	Cancer in humans and mechanistic evidence	
Limited or Inadequate	Not necessary	Strong: The agent belongs to a mechanistic class of agents for which one or more members have been classified in Group 2A or 1	Mechanistic evidence	
Limited	Less than Sufficient	Limited or Inadequate	Cancer in humans	Possibly carcinogenic to humans (Group 2B)
Inadequate	Sufficient	Not necessary	Cancer in experimental animals	
Inadequate	Less than Sufficient	Strong: Key characteristics of carcinogens	Mechanistic evidence	
Limited	Sufficient	Strong: The mechanism of carcinogenicity in experimental animals does not operate in humans†	Cancer in humans and mechanistic evidence	

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Inadequate	Sufficient	Strong: The mechanism of carcinogenicity in experimental animals does not operate in humans†	Mechanistic evidence	Not classifiable as to its carcinogenicity to humans (Group 3)
All other situations not listed above				

* Highest strength of evidence for any cancer site(s)

† The "strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans" must specifically be for the tumour sites supporting the classification of "sufficient evidence in experimental animals".

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Box 1. The key characteristics of carcinogens described by Smith et al. (2016)[27]

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

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Box 2. Overall evaluations of the IARC *Monographs*

The agent is *carcinogenic to humans* (Group 1): This category is used whenever there is *sufficient* evidence of carcinogenicity in humans. In addition, this category may apply when there is both *strong* evidence in exposed humans that the agent exhibits key characteristics of carcinogens and *sufficient* evidence of carcinogenicity in experimental animals.

The agent is *probably carcinogenic to humans* (Group 2A): This category generally applies when the Working Group has made at least two of the following evaluations, including at least one that involves either exposed humans or human cells or tissues:

- *Limited* evidence of carcinogenicity in humans,
- *Sufficient* evidence of carcinogenicity in experimental animals,
- *Strong* evidence that the agent exhibits key characteristics of carcinogens.

Separately, this category generally applies if there is *strong* evidence that the agent 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.

The agent is *possibly carcinogenic to humans* (Group 2B): This category generally applies when only one of the following evaluations has been made by the Working Group:

- *Limited* evidence of carcinogenicity in humans,
- *Sufficient* evidence of carcinogenicity in experimental animals,
- *Strong* evidence that the agent exhibits key characteristics of carcinogens (regardless of whether from exposed humans or human cells, or from experimental systems).

The agent is *not classifiable as to its carcinogenicity to humans* (Group 3): Agents that do not fall into any other group are generally placed in this category. Typically, this category is used when there is less than *sufficient* evidence in animals and *inadequate* evidence in humans. This category is also used when there is *strong* evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans and the evidence in humans is *inadequate*. However, if other tumour sites in experimental animals support an evaluation of *sufficient* evidence in experimental animals, or if the evidence in humans is *limited*, a higher classification according to criteria listed above applies.

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