Historical Article

The Monographs Programme of the International Agency for Research on Cancer: A Brief History of its Preamble

Robert A. Baan and Kurt Straif

The IARC Monographs Programme, International Agency for Research on Cancer, Lyon, France (retired)

Abstract

Since the early 1970s, the Monographs published by the International Agency for Research on Cancer (IARC) apply rigorous procedures for the scientific review and evaluation of carcinogenic hazards. The Preamble to the IARC Monographs describes the objective and scope of the Monographs Programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered, and the scientific criteria that guide the evaluations. This article presents an overview of the historical development of the Preamble from the time it began to take shape in the late 1970s up to and including the most recent update in 2019. Over the years, the IARC Monographs Programme has taken account of scientific and procedural advances in identifying, reviewing, evaluating, and integrating evidence to define causes of human cancer. Since the previous edition of the Preamble in 2006, the new developments include a stronger emphasis on mechanistic evidence based on key characteristics of carcinogens; greater consideration of exposure assessment methods in epidemiological studies; and integration of the streams of evidence on cancer in humans, cancer in experimental animals, and mechanisms in reaching the overall evaluations. Thus, the Preamble now allows an evaluation process in the absence of data from animal studies, and the evidence on key characteristics of cancer may be contributed by new approach methodologies, thus potentially reducing or avoiding the use of experimental animals.

1 Introduction

The International Agency for Research on Cancer (IARC) is an intergovernmental institute within the World Health Organization (WHO) of the United Nations. As the semi-autonomous cancer research arm of the WHO, its role is to conduct and coordinate research into the causes of cancer. It also collects and publishes surveillance data regarding the occurrence of cancer worldwide. The IARC Monographs Programme is a core element of the IARC's portfolio of activities, with international expert working groups identifying carcinogenic hazards and evaluating the evidence of the carcinogenicity of specific exposures[1].

1.1 The origin of the IARC

"*The IARC is the outcome of an initiative by a group of French intellectuals in 1963, who succeeded in persuading President Charles de Gaulle of France to adopt a project to help reduce humanity's ever-growing burden of cancer. De Gaulle took it upon himself to convince the world's policy-makers that they should devote a fraction of national defence budgets to a project aimed at reducing human suffering. Although the generosity of the project as initially conceived was scaled back to much more modest proportions when faced with the realities of the world, it remains clear that on this occasion, humanitarian considerations took priority over self-interest and power politics*" (adapted from the Foreword by Dr Lorenzo Tomatis in Sohier and Sutherland, 1990; English version 2015). The IARC was created on May 20, 1965, by a resolution of the 18th World Health Assembly, as the specialized cancer agency of the WHO. The IARC's main building was provided by its host and is located in Lyon, France.

1.2 The origin of the IARC Monographs Programme

Soon after the IARC was established, it received frequent requests for advice on the carcinogenic risk of chemicals, includ-

This content is part of the *Special Issue* Development of an Evidence-Based Risk Assessment Framework. doi:10.14573/altex.22S2

Received April 8, 2020; Accepted January 22, 2021;
Epub June 16, 2021;

ALTEX 39(3), 443-450. doi:10.14573/altex.22S2

Correspondence: Robert A. Baan, PhD
The IARC Monographs Programme
International Agency for Research on Cancer, Lyon, France
(robert.baan@69lyon03.org)

[1] see https://www.iarc.fr/about-iarc-mission/ and https://monographs.iarc.fr/

ing inquiries about lists of known and suspected human carcinogens. Since it would not be a simple task to summarize adequately the complexity of the available information, the IARC began to consider means of obtaining international expert opinion. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended "*...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented*." The IARC Governing Council adopted a resolution concerning the role of the IARC in providing government authorities with expert, independent scientific opinion on environmental carcinogenesis and recommended that the IARC should prepare "Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man", which became the initial title of the series.

In the succeeding years, the scope of the project broadened as Monographs were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents, and lifestyle factors. The objective of the Monographs Programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human hazard with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed. In 1988, the phrase "of chemicals" was dropped from the title, which assumed its present form (until recently, see below): "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans".

Through the Monographs, the IARC seeks to identify the causes of human cancer by evaluating cancer hazards, despite the historical presence of the word "risks" in the title. A cancer hazard is defined by the Preamble as an agent that is capable of causing cancer, whereas a cancer risk is an estimate of the probability that cancer will occur given some level of exposure to a cancer hazard. Hazard identification is the first step in cancer prevention, which is needed as much today as when the IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and was expected to reach 15 million by 2020 (Stewart and Kleihues, 2003), but more recent estimates indicated 18 million new cases in 2018 (Bray et al., 2018). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and middle-income countries. As a result of Monographs evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and the environment.

The criteria established in 1971 to evaluate carcinogenic hazards to humans were adopted by the Working Groups, whose deliberations resulted in the first 16 volumes of the Monographs series. These criteria were compiled in the Preamble to the Monographs, which was refined and updated a dozen times since.

2 Evolution in evaluation: The history of the IARC Monographs Preamble

The Preamble to the IARC Monographs describes the objective and scope of the Programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered, and the scientific criteria that guide the evaluations. From the very beginning, there have been two criteria for consideration of an agent for evaluation by the Programme: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity, i.e., from observations in animals and/or humans (IARC, 1972, 1987, 1992a, 2006).

2.1 The early years

Volume 1 of the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man" was published in 1972 as the outcome of the meeting of an IARC Working Group that convened in Geneva in December 1971. The carcinogenic hazard of some inorganic substances, chlorinated hydrocarbons, aromatic amines, N-nitroso compounds, and natural products was evaluated (IARC, 1972). Among these agents, auramine production, 4-aminobiphenyl, and benzidine were recognized as human carcinogens (the formal classification of these agents in "Group 1, *carcinogenic to humans*" followed several years later (IARC, 1979)).

During this first meeting, the Working Group faced the problem of the interpretation of results of cancer studies in animals, in the absence of human data, in terms of possible human cancer risk. At the time, since there were no objective criteria for such an extrapolation, the Group did not give an opinion on the significance of these animal data to humans, although some members felt that "*an educated guess with respect to the degree of carcinogenic potential would have been desirable*". The IARC announced the elaboration of guiding principles for the extrapolation from animals to humans in subsequent Monograph volumes, which might, therefore, be revised at a later date in light of such new principles. The criteria proposed by this first Working Group in 1971 to evaluate the carcinogenic hazard of chemicals were essentially adopted by all the Working Groups involved in the preparation of the first 16 volumes of the Monographs series.

In 1977 and 1978 (IARC, 1977, 1978a), two IARC *ad hoc* Working Groups met to re-evaluate these guiding criteria. The Preamble in Monograph Volume 17 (IARC, 1978b), where this term appears for the first time, reflects the results of their discussions. Volume 17 was also the first with the new title of the Series, "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans", which was adopted by the IARC Secretariat (Huff, 2002), presumably under the (erroneous) assumption that the old title (see above) would only pertain to the male half of the population. Over the years, the scope of the Programme broadened, and Monographs were developed for complex mixtures, occupational exposures, physical agents, biological factors, pharmaceuticals, and other exposures. Volume 43 (IARC, 1988) was the first for which "of chemicals" was dropped from the title and "risk" became "risks", and with the recently revised Preamble (IARC, 2019), "evaluation of carcinogenic risks" finally became

"identification of carcinogenic hazards", which had been the objective of the Programme all along. This distinction between hazard and risk (see definitions above) was confirmed in the risk assessment/risk management paradigm proposed by the US National Research Council (NRC, 1983). It is interesting to note the complications that arise from the use of these terms in other languages: in French, the new name of the Programme is "Monographies du CIRC[2] sur l'identification des dangers cancérogènes pour l'homme", although "hazard" would be better translated as "risque".

In the first 16 Monograph Volumes, the assessments of carcinogenicity in humans and experimental animals were made separately. No attempt was made to infer carcinogenic hazard to humans based on data from experimental animals. However, most of the chemicals considered only had data from animal studies: More than 350 substances were evaluated in Volumes 1-16, and human data were available for only 48 (14%) of these. When information from studies in humans was lacking, the IARC was asked to consider making an assessment of the carcinogenic hazard for humans based only on animal data (IARC, 1979). As a guiding principle, it was recommended that in the absence of adequate data in humans "*it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity (i.e. a causal association) in animals as if they presented a carcinogenic risk for humans*." Likewise, although no adequate criteria were available to interpret experimental carcinogenicity data directly in terms of carcinogenic potential for humans, the Working Group for Volume 18 (IARC, 1978c) considered that, nonetheless, "*positive extrapolations to possible human risk could reasonably be approximated*" by use of data collected solely from appropriate tests in animals. This led to evaluation statements such as "*although no epidemiological data are available, N-nitroso-N-ethylurea should be regarded for practical purposes as if it were carcinogenic to humans*" (and likewise for several other nitrosamines). The use of the expressions "for practical purposes" and "as if they presented a carcinogenic risk" indicated that – at the time – a correlation between carcinogenicity in animals and possible human risk was not made on a scientific basis, but rather pragmatically, with the intent of helping regulators in making decisions on the primary prevention of cancer. It took another ten years before this issue was finally resolved in Supplement 7 (IARC, 1987), where *N*-ethyl-*N*-nitrosourea was placed in Group 2A, *probably carcinogenic to humans*, with sufficient evidence of carcinogenicity in animals in the absence of human epidemiological data, but supported by mechanistic evidence (see below). Over the years, this important guiding principle has been qualified as "reasonable", "biologically plausible and prudent", and "biologically plausible" (IARC, 2006, 2019).

2.2 Levels of evidence; categorization in Groups 1, 2, 3

In Volume 17 of the Monographs (IARC, 1978b), the terms "sufficient" and "limited" were used for the first time to define the evidence from human and animal studies. The term "inadequate evidence" was introduced in Supplement 4 (IARC, 1982a) and Volume 29 (IARC, 1982b). An ad-hoc group convened in 1978 to review all chemicals evaluated in Volumes 1-19 of the Monographs (IARC, 1979) and proposed the following categories for the overall evaluation:

Group 1: The chemical or group of chemicals is *carcinogenic for humans*. This category was used only when there was sufficient evidence to support a causal association between exposure and cancer.

Group 2: The chemical or group of chemicals is *probably carcinogenic for humans*. This category includes chemicals for which the evidence of human carcinogenicity is "almost sufficient" as well as those for which it is only suggestive. To reflect this range, this category was divided into higher (group A) or lower (group B) degrees of evidence. The data from experimental animal studies played an important role in assigning chemicals to category 2, and particularly to those in group B.

Group 3: The chemical or group of chemicals *cannot be classified as to its carcinogenicity for humans*.

However, this classification scheme was only fully implemented in Supplement 7 (IARC, 1987), which also proposed the designation of agents in Group 2A as *probably carcinogenic* and in Group 2B as *possibly carcinogenic*.

In all subsequent Monographs, the evaluation scheme with categories 1, 2A, 2B, 3, and 4 (the agent is probably not carcinogenic to humans) was applied. More than three decades later, i.e., during the recent revision of the Preamble (IARC, 2019), the somewhat anomalous Group 4 was eliminated to finally confirm that the IARC Monographs do not evaluate agents for which there is no evidence or suspicion of carcinogenicity. The orphan compound caprolactam, which had been the sole chemical in Group 4 since 1987, was moved to Group 3.

2.3 Tasks of the Working Group

An interesting aspect of the developing Monographs Programme from the early years to the present can be found in the list of tasks of the Working Group, which were described in Volume 7 (IARC, 1974) as follows:

(1) to verify that as far as feasible all data have been collected;
(2) to select the data relevant for the evaluation;
(3) to determine whether the data, as summarized, will enable the reader to make his own judgement concerning the adequacy of the experiment and the effect observed;
(4) to judge the significance of the experimental results;
(5) to make an evaluation.

Because task (3) would seem to be a tall order – with the average reader in mind – the text was modified already in Volume 8 (IARC, 1975) to read: to determine whether the data, as summarized, will enable the reader to follow the reasoning of the committee. Also, an omission in the text of task (4) was corrected in Volume 10 (IARC, 1976): (4) to judge the significance of results of experimental and epidemiological studies. And, finally, the summaries (IARC, 1990) and the consideration of mechanistic data (IARC, 1992b) were introduced. In subsequent Preamble

[2] CIRC, Centre international de Recherche sur le Cancer

documents, the tasks have been defined and extended as follows (IARC, 1986, 1992a, 2006):

(i) to ascertain that all appropriate data have been collected;
(ii) to select the data relevant for the evaluation based on scientific merit;
(iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group;
(iv) to evaluate the results of experimental and epidemiological studies on cancer;
(v) to evaluate data relevant to the understanding of the mechanism of carcinogenesis;
(vi) to make an overall evaluation of the carcinogenicity of the exposure to humans.

2.4 Section 4 of the Monograph

The title of Section 4 of a Monograph has evolved over the years from "Other relevant data" in Monograph Volume 53 and earlier volumes, to "Other data relevant to an evaluation of carcinogenicity and its mechanisms" in Volumes 54-92, and "Mechanistic and other relevant data" in Volume 93 and beyond, reflecting the increasing prominence of mechanistic considerations in the evaluations. A revised Preamble (version 1991) appeared in Volume 54 (IARC, 1992a) with the following outline of the Summary for Section 4:

"*For the agent, mixture or exposure circumstance being evaluated, the available data on endpoints or other phenomena relevant to mechanisms of carcinogenesis from studies in humans, experimental animals and tissue and cell test systems are summarized within one or more of the following descriptive dimensions: (i) Evidence of genotoxicity (i.e., structural changes at the level of the gene): for example, structure-activity considerations, adduct formation, mutagenicity (effect on specific genes), chromosomal mutation/aneuploidy; (ii) Evidence of effects on the expression of relevant genes (i.e., functional changes at the intracellular level): for example, alterations to the structure or quantity of the product of a proto-oncogene or tumour suppressor gene, alterations to metabolic activation/inactivation/DNA repair; (iii) Evidence of relevant effects on cell behaviour (i.e., morphological or behavioural changes at the cellular or tissue level): for example, induction of mitogenesis, compensatory cell proliferation, pre-neoplasia and hyperplasia, survival of premalignant or malignant cells (immortalization, immunosuppression), effects on metastatic potential; (iv) Evidence from dose and time relationships of carcinogenic effects and interactions between agents: for example, early/late stage, as inferred from epidemiological studies; initiation/promotion/progression/malignant conversion, as defined in animal carcinogenicity experiments; and toxicokinetics. These dimensions are not mutually exclusive, and an agent may fall within more than one of them. Thus, for example, the action of an agent on the expression of relevant genes could be summarized under both the first and second dimension, even if it were known with reasonable certainty that those effects resulted from genotoxicity.*" (Note: the "dimensions" as defined above show analogies or similarities with some of the "Key characteristics of human carcinogens" introduced in the recently updated Preamble, see below).

In the previous versions of the Preamble (IARC, 1991, 2006), the detailed outlines of Section 4 contained approximately 800 and 1700 words, respectively. This reflects the increasingly prominent place of mechanistic considerations during that period.

2.5 Use of mechanistic data

The aim of the IARC Monographs Programme has been, from its inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Initially, there was insufficient information to implement classification of agents according to their mechanism of action (IARC, 1983, 1989), but a decade later it was stated that "*information on mechanisms may be used in making the overall evaluation*" (IARC 1992c; Vainio et al., 1992). The IARC has allowed an agent to be classified as carcinogenic to humans if there is "sufficient evidence" in animal models and "strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity" (IARC 1992a). The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism was evaluated and expressed by the use of terms such as "weak", "moderate" or "strong" (and not with the evaluation-specific terms "inadequate", "limited" and "sufficient"). The Working Group then assessed whether that particular mechanism was likely to be operative in humans and whether this would warrant a deviation from the "default" evaluation (see below).

2.6 The evaluations, then and now

Traditionally, IARC Monograph evaluations were developed through a series of distinct steps, as illustrated in Figure 1.

Separate evaluations were made of the evidence of cancer in humans and cancer in experimental animals, each choosing one of the four descriptors: "sufficient", "limited", "inadequate" evidence, or "evidence suggesting lack of carcinogenicity". These two partial evaluations were then combined into a preliminary default evaluation that the agent is carcinogenic (Group 1), probably carcinogenic (Group 2A), possibly carcinogenic to humans (Group 2B), not classifiable (Group 3), or probably not carcinogenic to humans (Group 4). Then the mechanistic and other relevant data were considered to determine whether the default evaluation should be modified given the strength of the mechanistic evidence and whether or not the mechanism operates in humans. The current list of IARC evaluations mentions 62 agents that were so "upgraded" and six that were "downgraded".

2.7 The 2018 revision of the Preamble

Apart from the introduction of a new title for the IARC Monographs Programme (see above), an important change in the revised Preamble (IARC, 2019) is the elimination of Group 4 (probably not carcinogenic to humans) from the list of evaluation categories (see above). Furthermore, the two criteria for consideration of an agent to review have been modified to read "*there is potential human exposure and there is evidence for assessing its carcinogenicity*". Other changes made in the Preamble during the revision in November 2018 comprise specific instructions on the critical review of exposure assessment methods in key epidemiological studies, which has now become a specific task of the experts

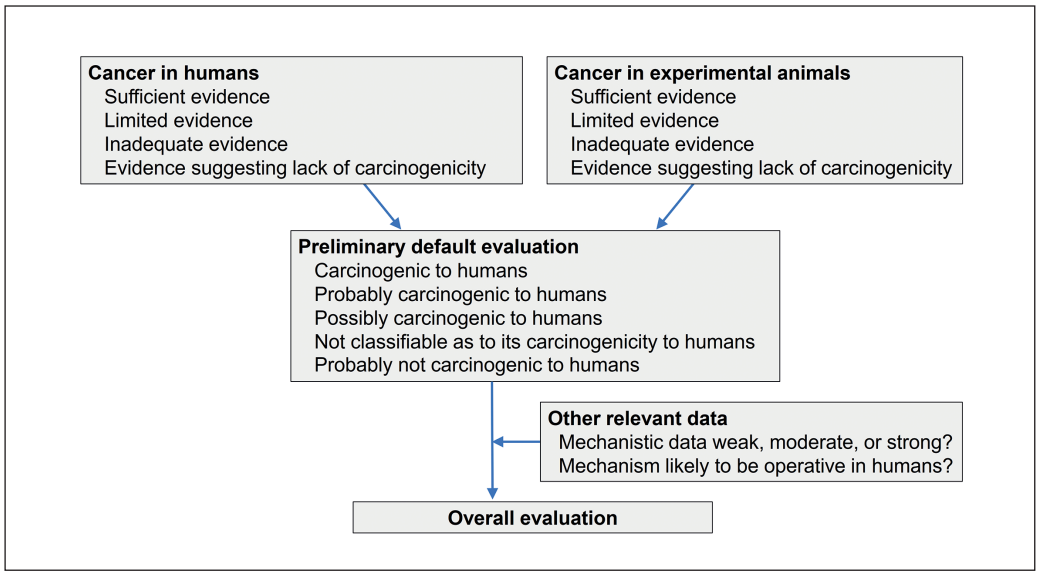

Fig. 1: The evaluation process used in the IARC Monographs before the revision of the Preamble in 2006 (IARC, 2006)
From Cogliano et al. (2004).

preparing Section 1, Exposure data. Also, the Preamble now prescribes that information on the conduct of the literature searches be specified or referenced, including search terms and inclusion or exclusion criteria that were used for each stream of evidence (epidemiological information, animal cancer data, mechanistic evidence). Identification, screening, selection, quality assessment, reporting, synthesis, and evaluation of the studies selected should be described in detail. In the section on exposure, a particular effort may be directed towards finding data on production of an agent in low- and middle-income countries, where rapid economic development may lead to higher exposures than those in high-income countries.

In the new Preamble (IARC, 2019), mechanistic evidence, epidemiological evidence, and evidence from animal studies receive equal attention. Mechanistic studies have gained in prominence and have increased in volume, diversity, and relevance to cancer hazard evaluation. The major change in the new Preamble is the introduction of a systematic review of mechanistic data facilitated by the organization into "Key characteristics of human carcinogens" (see below), which is now common practice since Monograph Volume 112. On the other hand, the relevance of epidemiological studies in the evaluation of, e.g., occupational carcinogens has been emphasized in a recent review (Loomis et al., 2018).

A schematic overview of the modernized and transparent evidence synthesis for cancer hazard identification is given in Figure 2. A written account, prepared by the members of the Advisory Group and the IARC Secretariat, was published recently (Samet et al., 2019).

The concept of "Key characteristics of human carcinogens" was introduced to facilitate systematic consideration of mechanistic evidence in IARC Monographs evaluations (Baan et al., 2019; Guyton et al., 2018; Smith et al., 2016). These ten key characteristics – similar to the descriptive dimensions mentioned above – 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.

The key characteristic properties of human carcinogens are:

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

In the new Preamble, a prominent new paragraph in Section 4 on "Mechanistic evidence" deals with "*evidence relevant to key characteristics of carcinogens*". The strength of the mechanistic evidence is to be expressed as "strong", "limited", or "inadequate" (in contrast to "strong, moderate, weak" mentioned above). And finally, in the Section on "Evaluation and rationale", one of the elements that contribute to the classification "strong mechanistic evidence" is the finding of "Strong evidence that the agent exhibits key characteristics of carcinogens." However, the new Preamble does not specify criteria for evaluating mechanistic evidence, including how many and which of the ten characteristics constitute "strong evidence" in this case. This is left to the judgement of the Working Group.

3 The future of the two-year rodent bioassay to assess cancer hazard and risk

The two-year rodent bioassay identifies chemicals that are carcinogenic to rodents. As such, it has been an important tool in IARC's hazard identification process, since it is biologically

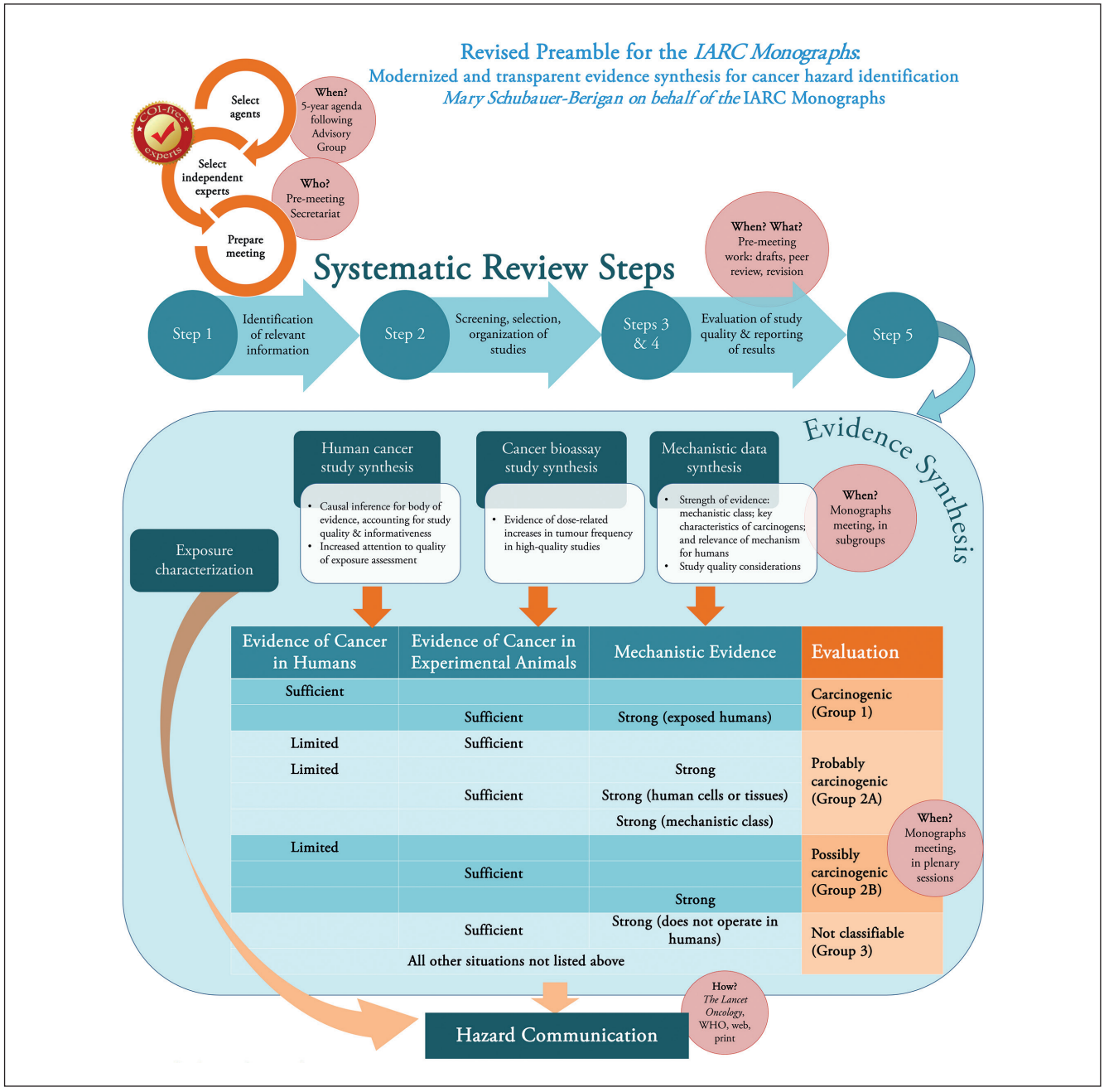

Fig. 2: The making of IARC Monographs: Evidence synthesis for cancer hazard identification
See: https://monographs.iarc.fr/wp-content/uploads/2019/07/2019-SR-001-Revised_Preamble.pdf

plausible that animal carcinogens present a carcinogenic hazard to humans: Most of the currently 313 agents in Group 2B (possibly carcinogenic to humans) were classified based on sufficient evidence of carcinogenicity in experimental animals. In the past decade, alternatives for the two-year bioassay have been proposed (Cohen, 2010, 2018; Tsuda et al., 2010). These may involve a combination of *in vitro* assays aimed at the screening of chemicals for DNA reactivity, immunosuppressive effects, estrogenic activity, and short-term (up to 13 weeks) bioassays in rodents to assess potentially increased cell proliferation. The emphasis is on mechanistic understanding, evaluation of the dose-response, and relevance to humans. The high-throughput and high-output methods proposed in programs like ToxCast and Tox21 (Dix et al., 2007; Tice et al., 2013) aim at developing new ways to rapidly test whether substances adversely affect human health. These methods have the potential advantage that they require greatly reduced numbers of animals. However, their predictive value awaits validation.

4 The IARC Monographs Preamble and the 3R concept; contributions from NAMs

For half a century, the two-year rodent bioassay has been a major element in IARC's cancer hazard evaluation process. At the same time, the 3R concept – replacement, reduction and refinement of animal use – has become an important principle in biomedical research (Russell and Burch, 1959; Tannenbaum and Bennett, 2015). As indicated above, efforts have been made in the past decade to develop short-term animal test systems that might replace the long-term bioassays, thus reducing the number of experimental animals. The term "new approach methodologies" (NAMs) has been adopted to refer to any non-animal technology or methodology that can be used to assess chemical hazards and risks, also from putative carcinogens. The Preamble of the IARC Monographs allows an evaluation process in the absence of data from animal studies. This is especially relevant in cases where information from human epidemiology is less than sufficient. An overall evaluation in Group 2A can be based on "*limited evidence of carcinogenicity*" in humans and "*strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens*". If there is "*inadequate evidence of carcinogenicity*" in humans, there should be "*strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*". Likewise, an overall evaluation in Group 2B can be based solely on "*strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens*". In each case, the evidence on key characteristics may come from NAMs, thus potentially reducing or avoiding the use of experimental animals.

In a retrospective analysis of IARC Group-1 agents (Krewski et al., 2019), *in vitro* data were found to be widely used in the mechanistic evaluations of these agents, providing results that were generally consistent with *in vivo* data. With mechanistic considerations within the IARC Monographs Programme now focused on the ten key characteristics of human carcinogens, mechanistic data derived from NAMs may be expected to play a prominent role in defining the key characteristics in future evaluations.

5 Concluding remarks

For more than four decades, the IARC Monographs Programme has provided evaluations of cancer hazards to humans from many different exposures and agents. The IARC Monographs are prepared according to principles of scientific rigor, impartial evaluation, transparency, and consistency. The criteria defining those principles have evolved during the first years of the Programme and are outlined in the first Preamble to the Monographs (IARC 1978b), which has been refined and updated a dozen times since, as described in the present paper. IARC Monographs evaluations are widely respected and used by many organizations, institutions, companies, and government agencies worldwide to improve public health. They also serve as reference documents summarizing the literature on many different agents.

References

Baan, R. A., Stewart, B. W. and Straif, K. (eds.) (2019). *Tumour Site Concordance and Mechanisms of Carcinogenesis*. IARC Scientific Publication No. 165. Lyon, France: International Agency for Research on Cancer. http://publications.iarc.fr/578

Bray, F., Ferlay, J., Soerjomataram, I. et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin 68*, 394-424. doi:10.3322/caac.21492

Cogliano, V. J., Baan, R. A., Straif, K. et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect 112*, 1269-1274. doi:10.1289/ehp.6950

Cohen, S. M. (2010). An enhanced 13-week bioassay: An alternative to the 2-year bioassay to screen for human carcinogenesis. *Exp Toxicol Pathol 62*, 497-502. doi:10.1016/j.etp.2009.06.011

Cohen, S. M. (2018). Screening for human urinary bladder carcinogens: Two-year bioassay is unnecessary. *Toxicol Res (Camb) 23*, 565-575. doi:10.1039/c7tx00294g

Dix, D. J., Houck, K. A., Martin, M. T. et al. (2007). The ToxCast program for prioritizing toxicity testing of environmental chemicals. *Toxicol Sci 95*, 5-12. doi:10.1093/toxsci/kfl103

Guyton, K. Z., Rieswijk, L., Wang, A. et al. (2018). Key characteristics approach to carcinogenic hazard identification. *Chem Res Toxicol 31*, 1290-1292. doi:10.1021/acs.chemrestox.8b00321

Huff, J. (2002). IARC monographs, industry influence, and upgrading, downgrading, and under-grading chemicals: A personal point of view. *Int J Occup Environ Health 8*, 261. Afterword. doi:10.1179/107735202800338795

IARC (1972). Some inorganic substances, chlorinated hydrocarbons, aromatic amines, N-nitroso compounds and natural products. *IARC Monogr Eval Carcinog Risk Chem Man 1*, 1-184. http://publications.iarc.fr/19

IARC (1974). Some anti-thyroid and related substances, nitrofurans and industrial chemical. *IARC Monogr Eval Carcinog Risk Chem Man 7,* 1-326. http://publications.iarc.fr/25

IARC (1975). Some aromatic azo compounds. *IARC Monogr Eval Carcinog Risk Chem Man 8*, 1-357. http://publications.iarc.fr/26

IARC (1976). Some naturally occurring substances. *IARC Monogr Eval Carcinog Risk Chem Man 10,* 1-342. http://publications.iarc.fr/28

IARC (1977). IARC Monographs Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Preamble. IARC intern. tech. Rep. No. 77/002.

IARC (1978a). Chemicals with Sufficient Evidence of Carcinogenicity in Experimental Animals – IARC Monographs Volumes 1-17. IARC intern. tech. Rep. No. 78/003.

IARC (1978b). Some N-nitroso compounds. *IARC Monogr Eval Carcinog Risk Chem Hum 17*, 1-349. http://publications.iarc.fr/35

IARC (1978c). Polychlorinated biphenyls and polybrominated biphenyls. *IARC Monogr Eval Carcinog Risk Chem Hum 18*, 1-124. http://publications.iarc.fr/36

IARC (1979). Chemicals and industrial processes associated with cancer in humans. IARC Monographs, Volumes 1 to 20. *IARC Monogr Eval Carcinog Risks Hum, Suppl 1*, 1-71. http://publications.iarc.fr/133

IARC (1982a). Chemicals, industrial processes and industries associated with cancer in humans (an updating of IARC Monographs, Volumes 1 to 29). *IARC Monogr Eval Carcinog Risks Hum, Suppl 14*, 1-292. http://publications.iarc.fr/136

IARC (1982b). Some industrial chemicals and dyestuffs. *IARC Monogr Eval Carcinog Risk Chem Hum 29*, 1-398. http://publications.iarc.fr/47

IARC (1983). Approaches to Classifying Chemical Carcinogens According to Mechanism of Action. IARC intern. tech. Rep. No. 83/001.

IARC (1986). Preamble in: Some chemicals used in plastics and elastomers. *IARC Monogr Eval Carcinog Risk Chem Hum 39*, 13-32. http://publications.iarc.fr/57

IARC (1987). Overall evaluations of carcinogenicity: An updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum, Suppl 7*, 1-440. http://publications.iarc.fr/139

IARC (1988). Man-made mineral fibres and radon. *IARC Monogr Eval Carcinog Risks Hum 43*, 1-300. http://publications.iarc.fr/61

IARC (1989). Occupational exposures in petroleum refining; crude oil and major petroleum fuels. *IARC Monogr Eval Carcinog Risks Hum 45*, 1-322. http://publications.iarc.fr/63

IARC (1990). Pharmaceutical drugs. *IARC Monogr Eval Carcinog Risks Hum 50*, 1-415. http://publications.iarc.fr/68

IARC (1991). Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, International Agency for Research on Cancer. https://monographs.iarc.fr/wp-content/uploads/2018/06/PreambleMonographs1991.pdf

IARC (1992a). Preamble (1991 version). *IARC Monogr Eval Carcinog Risks Hum 54*, 13-32. http://publications.iarc.fr/72

IARC (1992b). Occupational exposures to mists and vapours from strong inorganic acids and other industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum 54*, 1-310. http://publications.iarc.fr/72

IARC (1992c). Solar and Ultraviolet Radiation. *IARC Monogr Eval Carcinog Risks Hum 55*, 1-316. http://publications.iarc.fr/73

IARC (2006). Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, International Agency for Research on Cancer. https://monographs.iarc.fr/wp-content/uploads/2019/05/Preamble_updated2015.pdf

IARC (2019). Preamble to the IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Lyon, International Agency for Research on Cancer. https://monographs.iarc.fr/wp-content/uploads/2019/07/Preamble-2019.pdf

Krewski, D., Bird, M., Al-Zoughool, M. et al. (2019). Key characteristics of 86 agents known to cause cancer in humans. *J Toxicol Environ Health B Crit Rev 22,* 244-263. doi:10.1080/10937404.2019.1643536

Loomis, D., Guha, N., Hall, A. L. et al. (2018). Identifying occupational carcinogens: An update from the IARC Monographs. *Occup Environ Med 75*, 593-603. doi:10.1136/oemed-2017-104944

NRC (US) Committee on the Institutional Means for Assessment of Risks to Public Health (1983). *Risk Assessment in the Federal Government: Managing the Process*. Washington (DC), USA: National Academy Press (US).

Russell, W. M. S. and Burch, R. L. (1959). *The Principles of Humane Experimental Technique*. London, UK: Methuen and Co. Ltd.

Samet, J. M., Chiu, W. A., Cogliano, V. et al. (2019). The IARC Monographs: Updated procedures for modern and transparent evidence synthesis in cancer hazard identification. *J Natl Cancer Inst 112*, 30-37. doi:10.1093/jnci/djz169

Smith, M. T., Guyton, K. Z., Gibbons, C. F. et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect 124*, 713-721. doi:10.1289/ehp.1509912

Sohier, R. and Sutherland, A. G. B. (1990). The Origin of the International Agency for Research on Cancer. IARC Technical Report No. 6 (in French; translated by Cheney, J., 2015). https://publications.iarc.fr/_publications/media/download/3765/da829bb6bc17748f4c7f624dae17e11af7e40f6c.pdf

Stewart, B. W. and Kleihues, P. (eds.) (2003). World Cancer Report, Lyon, IARC. https://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2003

Tannenbaum, J. and Bennett, B. T. (2015). Russell and Burch's 3Rs then and now: The need for clarity in definition and purpose. *J Am Assoc Lab Anim Sci 54*, 120-132.

Tice, R. R., Austin, C. P., Kavlock, R. J. et al. (2013). Improving the human hazard characterization of chemicals: A Tox21 update. *Environ Health Perspect 121*, 756-765. doi:10.1289/ehp.1205784

Tsuda, H., Futakuchi, M., Fukamachi, K. et al. (2010). A medium-term, rapid rat bioassay model for the detection of carcinogenic potential of chemicals. *Toxicol Pathol 38*, 182-187. doi:10.1177/0192623309356451

Vainio, H., Magee, P., McGregor, D. and McMichael, A. (eds.) (1992). *Mechanisms of Carcinogenesis in Risk Identification.* IARC Scientific Publication No. 116. Lyon, France: International Agency for Research on Cancer. https://publications.iarc.fr/Book-And-Report-Series

Acknowledgements

The thoughtful comments and useful suggestions received from Drs Jerry Rice, Bernard Stewart and Vincent Cogliano are gratefully acknowledged. We thank the Working Groups of expert scientists and the successive Monographs teams for preparing and producing the IARC Monographs during nearly five decades, and the respective Advisory Groups for their guidance in revising and updating the Preamble at regular intervals since 1978. We are grateful to Dr M. Schubauer-Berigan and Mrs Solène Quennehen for creating Figure 2 and for granting permission to reproduce it here. The IARC Monographs Programme receives funding since 1982 from the US National Cancer Institute, since 1986 from the European Commission/European Union, and since 1992 from the US National Institute of Environmental Health Sciences.