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Editorial

EDITORIAL

The Hazards of Assessing the Carcinogenicity of Agents

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For more than four decades, the *International Agency for Research on Cancer (IARC) Monograph* series has provided the world with the most comprehensive, systematic evaluation of potentially carcinogenic agents. The *Monograph* series has focused on assessing the hazard of an exposure by providing a detailed analysis of existing literature to determine if an agent causes cancer. Public health officials or other stakeholders often use the scientific assessments of the *IARC Monographs* to independently evaluate the carcinogenic risks of an agent in relation to their local jurisdiction. The *IARC Monographs* series content is also an invaluable resource for researchers and governmental agencies that rely on them for public health decision making on the primary prevention of cancer.

This issue of the Journal includes a commentary on the recently revised Preamble to the *IARC Monographs* that was the product of an international panel convened by IARC to review the process for evaluation of potentially carcinogenic agents (1). The commentary describes the motivation and methodology for the recent update to the Preamble and highlights changes in the evaluation processes focusing on scientific rigor, impartial evaluation, transparency, and consistency. Reassessment of procedures for evidence synthesis, evaluation, and recommendations are always important, as exemplified by the Institute of Medicine report on the development of trustworthy clinical practice guidelines (2). In the future, there will be added emphasis assigned to the quality and informational content of the studies under evaluation. The highlighting of this point provides an important signal to the community as to how the relative quality of published studies will be factored into the decision making of future *IARC Monographs*.

Similarly, critical review of the strengths and limitations of the exposure assessment methods used in key studies represents an important revision. The new Preamble points out that the value of an epidemiologic study might be weighted based on the quality of its exposure assessment and the potential for confounding. The defining principles for admissible data sources are broader and require that the data be publicly available. However, it will be important to protect against selective reporting of findings, which can be a slippery slope toward biased conclusions.

The inclusion of mechanistic data and its integration with data from epidemiologic and experimental studies is an important addition to the Preamble. When epidemiologic and experimental evidence is sufficient, strong mechanistic data will add to the weight of evidence supporting a group 1 classification. If epidemiologic evidence is limited and experimental evidence is sufficient, strong mechanistic data can result in classification as a probable (group 2A) or possible (group 2B) carcinogen. If an exposure is newly introduced (eg, inadequate latency for the development of cancer), strong mechanistic data will be important and will add to the weight of evidence for possible carcinogenicity.

Use of mechanistic data in the evaluation process also focuses attention on the emerging importance of mutational signatures of somatic alterations in exposed tumors. If an agent is a group 1 carcinogen and the evidence is driven by one specific cancer, it will be important to evaluate whether the association extends to other cancer sites. If tumors of exposed individuals display a comparable mutational signature, this observation could add weight to the evidence of carcinogenicity, particularly for those likely to be determined as a group 2A or 2B carcinogen. Evidence can be strengthened when the observation that a mutational signature seen for one cancer is also detected in a second cancer, especially when it occurs in relation to the same exposure. It is important to point out that traditional methods, namely evaluation in a cohort study, can strengthen the case for an agent.

The publication of the revised Preamble is very timely, as an expert panel recently convened by the *IARC Monograph* program recommended review of a broad range of old and new agents in the next five years (3,4). The expert panel considered more than 170 unique candidate agents nominated by the scientific community and general public, and those agents recommended for review are wide ranging, including breast implants, cannabis

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smoking, e-cigarettes, and disinfection by-products. This highlights how many emerging hazards will require assessment in the coming years.

One of the thorniest issues addressed in the Preamble relates to a long-standing problem of conflict of interest, for which there is now a clear policy statement. It is notable that the Preamble directly addresses the emerging issue of careerism, namely, the tendency to promote one's own published work in the working discussions of an *IARC Monograph*. To avoid Working Group members attempting to advance their own findings or careers, study summaries will be drafted or peer reviewed by a Working Group member who is not associated with the study. Although this is clearly a step in the right direction, the question is, does it go far enough?

The new Preamble of the *IARC Monograph* presents suitable revisions for future monographs. Although the Preamble has been revised periodically, it was particularly important to do so given the rise in criticisms (5). Because this is a dynamic process, we can anticipate that further revisions will be prepared to provide continuous improvement of the value of the output of the *IARC Monograph* program. In conclusion, the Preamble outlines a modern and forward-thinking approach toward the determination of the hazard for an agent to cause cancer based on systematic review of the published literature. In the commentary, the authors underscore the value of the *IARC Monograph* program, namely, to assess the carcinogenic hazard of an agent. It should be emphasized that the determination of risk must continue to fall on the shoulders of those who will incorporate the findings of *IARC Monographs* into strategies that require additional information and, at times, the need to make hard decisions.

Notes

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