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Improving the International Agency for Research on Cancer's consideration of mechanistic evidence

Julie Goodman *, Heather Lynch

Gradient, 20 University Road, Cambridge, MA 02138, United States

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ABSTRACT

Background: The International Agency for Research on Cancer (IARC) recently developed a framework for evaluating mechanistic evidence that includes a list of 10 key characteristics of carcinogens. This framework is useful for identifying and organizing large bodies of literature on carcinogenic mechanisms, but it lacks sufficient guidance for conducting evaluations that fully integrate mechanistic evidence into hazard assessments.
Objectives: We summarize the framework, and suggest approaches to strengthen the evaluation of mechanistic evidence using this framework.
Discussion: While the framework is useful for organizing mechanistic evidence, its lack of guidance for implementation limits its utility for understanding human carcinogenic potential. Specifically, it does not include explicit guidance for evaluating the biological significance of mechanistic endpoints, inter- and intra-individual variability, or study quality and relevance. It also does not explicitly address how mechanistic evidence should be integrated with other realms of evidence. Because mechanistic evidence is critical to understanding human cancer hazards, we recommend that IARC develop transparent and systematic guidelines for the use of this framework so that mechanistic evidence will be evaluated and integrated in a robust manner, and concurrently with other realms of evidence, to reach a final human cancer hazard conclusion.
Conclusions: IARC does not currently provide a standardized approach to evaluating mechanistic evidence. Incorporating the recommendations discussed here will make IARC analyses of mechanistic evidence more transparent, and lead to assessments of cancer hazards that reflect the weight of the scientific evidence and allow for scientifically defensible decision-making.

1. Introduction

The International Agency for Research on Cancer (IARC) published its first *Monographs on the Evaluation of Carcinogenic Risks to Humans* in 1971. Since that time, more than 900 agents have been evaluated for human carcinogenic potential (IARC, International Agency for Research on Cancer, 2015a). The monograph is intended to be a hazard evaluation, i.e., the first step in risk assessment. That is, IARC's goal is to identify whether a substance is associated with the development of cancer, regardless of the dose or exposure level at which an increased risk may occur. As a result, IARC states explicitly that it may identify an agent as a cancer hazard even when risks are very low at the exposure levels in the population of interest (IARC, International Agency for Research on Cancer, 2015b).

Each IARC monograph is written by a Working Group comprised of experts selected on the basis of knowledge and experience and the absence of "real or apparent conflicts of interest" (IARC, International Agency for Research on Cancer, 2015b). Invited experts with critical knowledge who have potential conflicts of interest may also be brought in to assist the Working Group and draft text on non-influential issues. The general roles of the Working Group members are outlined in the Preamble and Author Instructions. The Preamble summarizes scientific principles that govern the IARC *Monographs*; and the Author Instructions, which are intended to be used along with the Preamble, provide additional specifications to members of the Working Group writing the IARC monograph (IARC, International Agency for Research on Cancer, 2015b, 2016a). The instructions provide guidance on the literature search process, the organization of search results, the level of detail required for study summaries, the information to be provided in tables, and some brief considerations regarding animal and epidemiology study quality. Neither of these documents provide a step-by-step framework for reviewing studies, assessing quality, and integrating the evidence within or across each discipline.

While the Preamble and Author Instructions provide a general guide to the monograph evaluation process, the specific methodology varies by *Monograph*. In addition to the general Author Instructions, IARC provides monograph-specific instructions to the Working Group; these documents are not released publicly. Further, IARC explicitly states that, while the Preamble provides the overarching principles of the

* Corresponding author.
E-mail address: jgoodman@gradientcorp.com (J. Goodman).

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process, "The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous monograph meetings but remain, predominantly, the prerogative of each individual Working Group" (IARC, International Agency for Research on Cancer, 2015b).

The main charge of the Working Group is to determine how an agent or group of agents should be classified within the IARC carcinogen classification framework (Table 1). IARC specifies that the categorization is a matter of scientific judgment that reflects the strength of evidence across the realms of evidence (IARC, International Agency for Research on Cancer, 2015b). Information on exposure levels in workers and the general population is summarized, but not generally factored into causal classifications, because IARC evaluates hazard and not risk. In some cases, dose-response data are summarized in an evaluation, though IARC provides no explicit guidance with regard to how these data should be interpreted in the context of causal conclusions (IARC, International Agency for Research on Cancer, 2015b). To arrive at a classification, Working Groups have historically focused their reviews on epidemiology and animal bioassays deemed relevant and appropriate.

Table 1
IARC carcinogenicity classification system[a].

Classification	Requirements
Group 1 Carcinogenic to humans	▪ Sufficient evidence in humans OR ▪ Exceptionally, sufficient evidence in animals AND **strong evidence in exposed humans that the agent acts through a relevant mechanism** OR ▪ Clearly belongs, **based on mechanistic considerations**, to a class of agents for which one or more members have been classified in Group 1[b]
Group 2A Probably carcinogenic to humans	▪ Limited in humans AND sufficient in animals ▪ Inadequate in humans AND sufficient in animals AND **strong evidence that carcinogenesis is mediated by a mechanism that also operates in humans** ▪ Exceptionally, an agent may be classified in this category solely on the basis of limited evidence in humans[c] ▪ Clearly belongs, **based on mechanistic considerations**, to a class of agents for which one or more members have been classified in Group 2A
Group 2B Possibly carcinogenic to humans	▪ Limited in humans AND less than sufficient in animals ▪ Inadequate in humans BUT sufficient in animals ▪ Inadequate in humans AND less than sufficient in animals AND **supporting evidence from mechanistic and other relevant data** ▪ An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.[c]
Group 3 Not classifiable as to its carcinogenicity in humans	▪ Inadequate in humans AND inadequate/-limited in animals. ▪ Inadequate in humans AND sufficient in animals AND **strong evidence that the mechanism of carcinogenicity in animals does not operate in humans**.
Group 4 Probably not carcinogenic to humans[d]	▪ Sufficient evidence suggesting lack of carcinogenicity in humans and animals ▪ In some instances, inadequate evidence of carcinogenicity BUT evidence suggesting lack of carcinogenicity in experimental animals, **supporting evidence from mechanistic and other relevant data**

[a] As presented in the Preamble (IARC 2015b) and Author Instructions (IARC 2016a).
[b] Does not appear in the Preamble.
[c] This is only noted in the Preamble; it does not appear in the Author Instructions.
[d] The requirements for this category are not discussed in the Author Instructions.

Although they have also considered available mechanistic evidence, this was generally considered secondary to other realms of evidence.

There has been a recent shift in focus at IARC, whereby mechanistic evidence is given more weight in cancer hazard evaluations. As discussed below, the IARC framework is useful for organizing mechanistic evidence, but its lack of guidance for implementation limits its utility for understanding human carcinogenic potential. Specifically, it does not include explicit guidance for evaluating the biological significance of mechanistic endpoints, inter- and intra-individual variability, or study quality and relevance. It also does not explicitly address how mechanistic evidence should be integrated with other realms of evidence. Because mechanistic evidence is critical to understanding human cancer hazards, we recommend that IARC develop transparent and systematic guidelines for the use of this framework, so that mechanistic evidence will be evaluated and integrated in a robust manner, and concurrently with other realms of evidence. This will result in assessments that are based on the best available science and, thus, allow for more scientifically defensible decision-making.

2. IARC's use of mechanistic data

2.1. Overall approach according to the Preamble

The goal of the monographs has historically been to determine cancer hazard regardless of underlying mechanism; however, the current Preamble (IARC, International Agency for Research on Cancer, 2015b) and associated guidance materials have shifted focus to include information on mechanisms in the overall evaluation of an agent. The Preamble specifies that the Working Group is charged with identifying possible mechanisms whereby an agent of interest may increase the risk of cancer, and when available, summarize a representative "selection of key mechanistic data"; the Preamble explicitly states that a monograph need not cite all mechanistic literature for the agent, but does not give direction on how to identify key studies (IARC, International Agency for Research on Cancer, 2015b).

In the Preamble, mechanisms are grouped into physiological changes (e.g., escape from apoptosis and/or senescence), functional changes at the cellular level (e.g., changes in gene expression), and changes at the molecular level (e.g., DNA adducts and DNA strand breaks). Mechanistic data are discussed in their own section of the monograph, and then considered within the overall Evaluation and Rationale as they relate to plausibility of effects observed in animals. The strength of evidence that any observed carcinogenic effect in animals is due to a specific mechanism is rated as "weak," "moderate," or "strong." Evidence that a mechanism operates in animals is strengthened if results are consistent in different species; data are coherent; and studies show that when the relevant mechanism is suppressed, tumor development is also suppressed (IARC, International Agency for Research on Cancer, 2015b). Specific guidelines for ranking the strength of mechanistic evidence are not detailed, however, and there is no discussion of what actually constitutes "weak," "moderate," or "strong" mechanistic evidence.

After reaching conclusions on the strength of mechanistic evidence, IARC determines whether a particular mechanism is likely to operate in humans; most often, this conclusion is made if there are measured data in humans or biological specimens from humans.

2.2. 10 key mechanism-of-action characteristics

When IARC reviewed Group 1 carcinogens in *Monograph* 100 in early 2011, it noted that many were classified before mechanistic data were available, and that these data had become available in the prior two decades. IARC also found that the agents it had listed as human carcinogens shared a number of common characteristics (Smith et al., 2016). In 2012, IARC organized two workshops to discuss the mechanisms by which Group 1 carcinogens cause cancer; the participants