

## REVIEW

# The IARC monographs: critics and controversy

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## Abstract

The monograph program of the International Agency for Research on Cancer (IARC), which relies on the efforts of volunteer Working Groups, uses a transparent approach to evaluate the carcinogenicity of agents for which scoping has determined that there is sufficient evidence to warrant a review. Because of the potentially powerful implications of the conclusions of the monographs and the sometimes challenging nature of the evidence reviewed, the monographs and the IARC process have been criticized from time to time. This commentary describes the IARC monograph process and addresses recent criticisms of the program, drawing on a recent defense of the program authored by 124 researchers. These authors concluded that the IARC processes are robust and transparent and not flawed and biased as suggested by some critics.

Most readers of *Carcinogenesis* are familiar with the International Agency for Research on Cancer (widely known as 'IARC'), the World Health Organization element concerned with cancer. Now approaching its 50th anniversary, IARC has multiple component units to achieve its overall objective: '...to promote international collaboration in cancer research'. One of the units is the IARC Monograph Section, operating since 1971, which produces the IARC monographs on the Evaluation of Carcinogenic Risks to Humans. This program, which relies on the efforts of volunteer Working Groups, evaluates the carcinogenicity of agents for which scoping has determined that there is sufficient evidence to warrant a review. There is an established IARC methodology for evidence review, described in the preamble to each monograph, and for characterizing the strength of evidence for causation. For each agent, subgroups within the overall Working Group evaluate evidence related to exposure, mechanisms, animal studies and human studies. The classification schema for the strength of evidence for causation brings together the findings from the animal and human studies, while also giving consideration to mechanistic understanding (Figure 1) (1). The IARC monographs have global reach and are relied on by diverse parties throughout the world, including governmental regulators and risk managers, industry, non-governmental organizations, public health agencies, lawyers and the general public. Since its start in 1971, the monograph program has reviewed >900 agents and classified over 400 as carcinogenic, probably carcinogenic

or possibly carcinogenic (Figure 1). For some agents, e.g. tobacco smoking and radon, the body of evidence considered was definitive and classification in Group 1, carcinogenic to humans, was indisputable. For others, the evidence reviewed was mixed and uncertain, leading to classification as probably (Group 2A) or possibly carcinogenic (Group 2B), e.g. radiofrequency electromagnetic radiation.

Some agents reviewed are of broad societal interest and the classifications of IARC may be of concern to many stakeholders and have policy, regulatory and legal implications. Recent examples of such agents include ambient air pollution, radiofrequency electromagnetic radiation (the type emitted by mobile phones), the organophosphate pesticide glyphosate and diesel exhaust, and a review of 'red meat and processed meat' is scheduled. Consequently, causal conclusions, as reached by the IARC Working Groups, may have powerful implications (2). Quoting the 2004 report of the United States Surgeon General on smoking and health: 'The statement that an exposure "causes" a disease in humans represents a serious claim, but one that carries with it the possibility of prevention (3). Causal determinations may also carry substantial economic implications for society and for those who might be held responsible for the exposure or for achieving its prevention'. Not surprisingly, given the potential implications of its monographs, the IARC monograph program has been criticized from time to time, both generally and in regard to

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## Abbreviations

IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System

		EVIDENCE IN EXPERIMENTAL ANIMALS			
		Sufficient	Limited	Inadequate	ESLC*
EVIDENCE IN HUMANS	Sufficient	Group 1 (carcinogenic to humans)			
	Limited	Group 2A (probably carcinogenic)	Group 2B (possibly carcinogenic) (exceptionally, Group 2A)		
	Inadequate	Group 2B (possibly carcinogenic)	Group 3 (not classifiable)		
	ESLC*				Group 4

Figure 1. Modified version of the IARC Classification Scheme for Carcinogenicity. Source: IARC Monograph-PREAMBLE (1). \*ESLC: Evidence Suggesting Lack of Carcinogenicity

specific conclusions. The more recent criticisms fall into four groups: (i) reliance on epidemiological evidence that may be limited; (ii) limitations of the IARC process and reluctance to participate in it; (iii) issues related to specific evaluations and (iv) issues related to the composition of the Working Groups (4). Previously, the monograph program was criticized for not maintaining sufficient distance from industrial stakeholders and the associated potential for conflict of interest (5). Steps were taken to increase transparency (6).

In a recent commentary in *Environmental Health Perspectives*, these four sets of concerns were addressed by 124 scientists, many of whom had participated in IARC Working Groups (4). The authors were motivated by the continuing criticism of the IARC monograph program and the need for a countering voice, given the significance of the IARC classifications. They offer responses to criticisms in each of the four areas, which I repeat here. With regard to epidemiology, elaborations of the potential weaknesses of epidemiology have long been used to discredit observational evidence. However, as noted by Pearce *et al.* (4), researchers themselves and the peer review process give great attention to potential methodological weaknesses, and the IARC Working Groups review individual studies in detail, particularly if the findings are pivotal. Although one commenter suggests that there is reluctance on the part of scientists to participate in the IARC process, no 'hard' evidence has been offered in that regard. In fact, the IARC Working Group volunteer model functions well, even though participants spend 8 days at a monograph meeting and prepare drafts in advance. The monograph processes are overseen by an advisory group and periodically updated. With regard to particular monographs, inevitably if evidence is lacking or mixed and at equipoise, any classification can be reasonably questioned. The IARC process is particularly well suited for such scenarios, bringing a multidisciplinary group together to systematically sort through what is known and not known. The Group 2B classification (possibly carcinogenic) is particularly problematic because it reflects mixed evidence. Not surprisingly, the composition of the Working Groups and the potential for conflict of interest have also been raised as points of concern. Pearce *et al.* describe the steps taken by IARC to limit the potential for conflict of interest.

IARC is not the only authoritative entity that assesses the carcinogenicity of chemicals and other agents. In the USA, the Environmental Protection Agency's Integrated Risk Information System (IRIS) program assesses both carcinogenicity and quantitative risk, currently covering over 550 chemical substances, and the National Toxicology Program is congressionally mandated to evaluate carcinogenicity of selected agents. Beyond determining if there is a hazard, the IRIS assessments provide quantitative information on risk. The methodologies of both programs are in evolution to make them more transparent and reflective of current evidence review and evaluation methods, to enhance integration of different lines of evidence and to incorporate emerging data streams from various 'omics' approaches. A series of reports from the National Research Council has guided the Environmental Protection Agency in revising the IRIS process (7,8). The National Toxicology Program publishes its Report on Carcinogens annually, also using a standardized methodology to classify carcinogenicity (9). Globally, various governments and other agencies also provide assessments of carcinogenicity. Thus, there is a relatively robust, albeit ill-defined 'system' in place for assessment of carcinogenicity; IARC is a key entity globally, but agents of broad societal concern are likely to be evaluated by other entities. For example, formaldehyde has been evaluated by the Environmental Protection Agency's IRIS program, the National Toxicology Program, a Committee of the National Research Council and IARC (10–13). Each group concluded that formaldehyde is carcinogenic to humans.

Reports from these and other agencies are used worldwide. IARC's classifications bear the imprimatur of the World Health Organization, whereas IRIS provides quantitative risk estimates that can support risk assessment and risk management. Multiple stakeholders in the USA use the IRIS assessments in guiding decision making.

As in any area of science and policy, criticisms and stakeholder assessments of translational programs, such as the IARC monograph program, may have value and merit consideration, regardless of the motivations of those making them. For example, stakeholder concerns were one motivation for the revisions to the IRIS program that are in progress. With regard to IARC, Pearce *et al.* (4) rebutted the recent comments and used them as a platform for laying out the strengths of the IARC approach. They conclude: 'However, as a group of international scientists, we have looked carefully at the recent charges of flaws and bias in the hazard evaluations by IARC Working Groups, and we have concluded that the recent criticisms are unfair and unconstructive'.

Moreover, the types of concerns raised about the IARC monograph program are also archetypical of strategies for creating 'doubt' about scientific evidence that has policy implications. Such strategies can be traced to the 'playbook' of the tobacco industry for discrediting findings related to active and passive smoking (14,15). One tactic has been to question the processes used to draw causal inferences and the integrity and potential conflicts of interest of those doing so. The IARC processes are robust and transparent and as concluded by Pearce and his 123 colleagues, not flawed and biased.

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