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Letter to the Editor

LETTER TO THE EDITOR

Re: 'Application of the key characteristics of carcinogens in cancer hazard evaluation': response to Goodman, Lynch and Rhomberg

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Guyton *et al.* (1) reviewed feasibility and limitations of applying the 10 key characteristics (KCs) of carcinogens, as identified by Smith *et al.* (2), to the comprehensive search, screening and evaluation of mechanistic evidence in cancer hazard identification. To do so, we compiled methods and results of mechanistic data evaluations from eight recent IARC Monograph meetings in which a range of more than 30 diverse chemicals and complex exposures were classified into Group 1, 2A, 2B or 3 by expert Working Groups (3–12). For most of the 16 carcinogens classified in Group 1 or 2A in these meetings, a broad literature encompassing multiple KCs was identified. Mechanistic data were used as part of the overall evaluation to classify two substances (tetrabromobisphenol A and tetrachloroazobenzene) in Group 2A, both of which modulate receptor-mediated effects in combination with other KCs (7,9). Fewer studies were available for the 17 agents classified in Group 2B or 3, and only one Group 2B carcinogen (1-bromopropane (7)) had strong evidence of more than one KC. In all, an approach based on the KCs of carcinogens had several strengths for addressing the recognized challenges in assembling and evaluating mechanistic studies, as well as identifying data gaps, but we also identified opportunities for improvement.

A letter by Goodman, Lynch, and Rhomberg raises some issues with our article, asserting that there is a lack of validation of the approach and a lack of consideration of the quality and relevance of the mechanistic studies. We are pleased for the opportunity to provide clarifications in response.

We regret that our article was misunderstood as a validation exercise; instead, it intended to review all recent IARC Monograph evaluations (Meetings 112–119 (3,12)), encompassing mechanistically diverse agents, as an opportunity to explore strengths and limitations of the described approach. We also find their proposal for validation of the methodology questionable, as it appears to consider mechanistic data in isolation as able to differentiate carcinogens from non-carcinogens. In contrast, three distinct lines of relevant evidence—on cancer in humans, cancer in experimental animals, as well as data from mechanistic studies—are first evaluated individually and then brought together through a formal process of synthesis and characterization by the IARC Monographs (13). Furthermore, although data on cancer mechanisms form an important stream of evidence for any IARC Monographs Working Group, they are only able to play a key role in determining the overall evaluation when the evidence on cancer in humans is less than sufficient (13). Moreover, as we report, the extent of available evidence on cancer mechanisms was variable, with very few mechanistic studies identified for most agents evaluated as Group 2B or 3 (in contrast to most agents classified in Group 2A or 1) (1). This clear disparity in the adequacy of the mechanistic database across agents of differing classifications further undermines their proposal for validation. However, it does support the utility of an approach based on the KCs to not only uniformly search for and identify relevant mechanistic studies, but also reveal when coverage is incomplete.

We further wish to clarify that consideration of quality and relevance of the evidence, whether human, animal or mechanistic, is paramount in IARC Monograph evaluations, in contrast to any claims to the contrary. In the Methods section of

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our article (1), we summarize factors considered in evaluating study strengths and weaknesses, citing the IARC Monographs Preamble (13) and the online Instructions to Authors (14), where these topics are further elaborated. We also address the basis of expert strength-of-evidence judgments, highlighting the extent of evidence available as well as the important roles of consistency and coherence (i.e. external validity) (1). Moreover, our article at multiple points stresses the assessment of whether the mechanism can operate in humans, emphasizing the particular value of human-relevant studies. In this regard, we give specific mention to human biomarker studies while also citing examples of mechanisms that lack relevance to humans (i.e. due to precipitates in the bladder or α2u-globulin in the kidney). Thus, we find these criticisms to be unfounded.

Several additional misconceptions are also noteworthy. The authors wrongly assert that IARC evaluations are 'of the carcinogenic potency of chemicals and other agents'. To the contrary, the IARC Monographs are hazard classifications, of all forms of carcinogenic agents including viruses and occupations, but do not evaluate potencies of these hazards nor undertake potency comparisons (13). The letter authors go on to mischaracterize the KCs, showing that these authors may have misunderstood the approach. We wish to clarify that the KCs are not similar to the hallmarks of cancer and were not informed by them. KCs are the chemical and biological properties of carcinogens and therefore reflect the properties of cancer-causing agents (2). The KCs are distinct from the hallmarks of cancer, which are the biological properties of cancer cells (15,16). We also disagree with the claim that the KCs are generic or common attributes. They are generic only in that they relate to a class of similar agents, i.e. known human carcinogens, and are common to this class of agents (2).

In conclusion, our article acknowledges the considerable challenges of comprehensively and efficiently organizing, analyzing and interpreting the diverse and often voluminous mechanistic data in cancer hazard evaluation (1). To address these challenges, we describe a transparent and uniform approach that can advance systematic consideration of relevant mechanistic information. We report on its utility in cancer hazard evaluations, a utility underscored by the fact that agencies throughout the world, including at the Environmental Protection Agency and the National Toxicology Program's Report on Carcinogens in the USA, are beginning to apply it. In parallel, development of KCs for other toxicological hazards is similarly underway, in line with recommendations of the National Academy of Sciences of the US report on 'Using 21st Century Science to Improve Risk-Related Evaluations' (17). These related efforts could be informed by the experience of IARC Monographs. Our report, inclusive of 34 sequentially evaluated chemicals and complex exposures, reveals a variable extent of mechanistic information available, even for carcinogens with widespread human exposures (1). Moreover, for most agents, few studies of biomarker endpoints relevant to the KCs in exposed humans were available. Especially when mechanistic data are sparse, high-throughput testing systems such as ToxCast and Tox21 can aid as an additional or supportive mechanistic data source (18,19). However, our experience of applying an approach based on KCs to this data stream, as further elaborated elsewhere (18), demonstrated their usefulness for the KC 'modulates receptor-mediated effects' while also revealing significant gaps in coverage for several other KCs. These and other challenges have hampered carcinogenicity prediction, which, as we and others have discussed, remains imprecise (20,21). Altogether, these limitations underscore the need for a testing battery with greater relevance to cancer hazard identification. In parallel, the National Academy of Science of the USA in the report 'Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment' (22) has encouraged human biomarker studies to improve hazard prediction; endpoints related to the KCs could be applied in such studies to better forecast carcinogenic activity in humans (23). In summary, we show that application of the KCs to hazard identification is a robust new approach that complements other efforts to advance identification of the causes of human cancer, the first step in cancer prevention.

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