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Submitted by email to:

Carcinogen Identification Committee
California EPA
Office of Environmental Health Hazard Assessment (OEHHA)
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Sacramento, CA 95812-4010
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Dear Carcinogen Identification Committee:

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments on the **Key Characteristics of Carcinogens**.

Please contact Jessica Ryman-Rasmussen at 202-249-6406 or jessica_ryman-rasmussen@americanchemistry.com if you have any questions.

Sincerely,

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American Chemistry Council (ACC)

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the multibillion-dollar business of chemistry. ACC members apply the science of chemistry to make innovative products, technologies and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health, safety and security performance through Responsible Care®; common sense advocacy addressing major public policy issues; and health and environmental research and product testing. ACC members and chemistry companies are among the largest investors in research and development, and are advancing products, processes and technologies to address climate change, enhance air and water quality, and progress toward a more sustainable, circular economy.

The Carcinogen Identification Committee (CIC) is discussing the Key Characteristics of Carcinogens (KCCs) . However, unlike the specificity of silicosis from silica dust, not all of the KCCs are specific to the endpoint of carcinogenesis. "Induces chronic inflammation"[2] could be said to be a 'key characteristic' for acne vulgaris,[3] while "induces oxidative stress" and "alters cell proliferation, cell death, or nutrient supply" could be said to be 'key characteristics' of exercise[4] and wound repair,[5] respectively. Therefore, it is not clear that the KCCs should be used for regulatory decisions.

Seven years ago, the KCCs were proposed as a basis for organizing mechanistic data.[6] However, since that time, key characteristics for other endpoints have been proposed and use of the key characteristics has expanded (in some cases) to directly informing hazard identification.[7]

Becker et al. (2017) evaluated whether key characteristics of carcinogens could distinguish carcinogens from non-carcinogens in a study entitled "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?"[8]. This study used EPA's ToxCast data of effects of chemicals in mechanistic assays (bioactivity data) and mapped these assays and data to 7 of the 10 KCCs. They compared the results to EPA's previously derived cancer classifications for the same chemicals, conducted extensive statistical analyses, and used machine learning algorithms to evaluate the predictiveness of KCCs to distinguish / predict EPA-designated carcinogens from EPA-designated non-carcinogens. The results clearly showed that bioactivity corresponding to the so-called Key Characteristics of Carcinogens was no better than chance alone in predicting cancer classifications. Since that time,

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[4] Kawamura T, Muraoka I. Exercise-Induced Oxidative Stress and the Effects of Antioxidant Intake from a Physiological Viewpoint. Antioxidants (Basel). 2018 Sep 5;7(9):119. doi: 10.3390/antiox7090119. PMID: 30189660; PMCID: PMC6162669.
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[6] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. Environ Health Perspect. 2016 Jun;124(6):713-21. doi: 10.1289/ehp.1509912. Epub 2015 Nov 24. PMID: 26600562; PMCID: PMC4892922.
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[8] Becker RA, Dreier DA, Manibusan MK, Cox LAT, Simon TW, Bus JS. How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? Regul Toxicol Pharmacol. 2017 Nov;90:185-196. doi: 10.1016/j.yrtph.2017.08.021. Epub 2017 Sep 1. PMID: 28866267.

studies by Bus (2017)[9] and Goodman and Lynch (2017)[10] have raised concern with using the KCCs as a tool for assessing cancer hazards and Smith et al. (2021)[11] recently affirmed that the KCCs are too broad and non-specific for evaluating the potential cancer hazards of chemicals.

These findings raise legitimate questions about the value of the KCCs. The KCCs have no value in hazard identification, as evidenced by the 2017 study by Becker et al. showing they predict cancer classification no better than a coin toss. The KCCs also have no value for "just" organizing information because of the potential risk of anchoring errors. The Merk Manual describes anchoring errors as "when clinicians steadfastly cling to an initial impression even as conflicting and contradictory data accumulate."[12] Here, the name itself "key characteristics of carcinogens" (instead of, for example, "key characteristics of potential carcinogens") contains a conclusion, even though some of the KCCs are not specific to carcinogenicity.

Interestingly, some of the KCCs (e.g., oxidative stress, sustained receptor activation (which is a type of 'modulates receptor mediated effects'), and cell proliferation) had been proposed as key events in modes of action (MOAs)[13,14] published before the KCCs. However, because some in the scientific community regard KCCs as new and different, use of the KCCs is not necessarily subject to the formal causality criteria of the IPCS Mode of Action framework for Carcinogens[15] or the OCED AOP Guidance,[16] which were developed for regulatory use.

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[9] Bus JS. IARC use of oxidative stress as key mode of action characteristic for facilitating cancer classification: Glyphosate case example illustrating a lack of robustness in interpretative implementation. Regul Toxicol Pharmacol. 2017 Jun;86:157-166. doi: 10.1016/j.yrtph.2017.03.004. Epub 2017 Mar 6. PMID: 28274811.
[10] Goodman J, Lynch H. Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. Toxicol Appl Pharmacol. 2017 Mar 15;319:39-46. doi: 10.1016/j.taap.2017.01.020. Epub 2017 Feb 3. PMID: 28162991.
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https://www.merckmanuals.com/professional/special-subjects/clinical-decision-making/cognitive-errors-in-clinical-decision-making
[13] Borgert CJ, Wise K, Becker RA. Modernizing problem formulation for risk assessment necessitates articulation of mode of action. Regul Toxicol Pharmacol. 2015 Aug;72(3):538-51. doi: 10.1016/j.yrtph.2015.04.018. Epub 2015 Apr 27. PMID: 25929618.
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[15] Sonich-Mullin C, Fielder R, Wiltse J, Baetcke K, Dempsey J, Fenner-Crisp P, Grant D, Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice JM, Younes M; International Programme on Chemical Safety. IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. Regul Toxicol Pharmacol. 2001 Oct;34(2):146-52. doi: 10.1006/rtph.2001.1493. PMID: 11603957.
[16] Guidance Document for developing and assessing Adverse Outcome Pathways (AOPs) [ENV/JM/MONO(2013)6].

These concerns raise questions about how KCCs should be used, if at all. Meek and Wickoff (2023)[7] propose good practice that assimilates KCCs into an integrated AOP and MOA pathway construct, essentially using KCCs as a means to identify Key Events. This is consistent with earlier conclusions in Becker et al. (2017):

> For incorporating mechanistic data into cancer hazard evaluations, we specifically recommend adoption of the AOP (OECD, 2016) or MOA framework (Meek et al., 2014) that articulates toxicity pathways comprised of sequences of key events, starting with an initial molecular event, followed by a series of key events linked to one another, ultimately resulting in a specific adverse outcome (Meek et al., 2013, Meek et al., 2014).

In closing, we encourage the CIC to conduct its own risk/benefit assessment of the regulatory use of the KCCs, given the limitations and concerns we have noted.

ACC appreciates the opportunity to comment.