June 12, 2022

Submitted to regulations.gov Docket ID: EPA-HQ-ORD-2010-0396
Wayne Cascio,
Director, Center for Public Health & Environmental Assessment.

Re: Availability of the Draft IRIS Toxicological Review of Formaldehyde (Inhalation). 87 Fed. Reg. 22208 (April 14, 2022).

Dear Dr. Cascio:

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments to EPA regarding the draft IRIS Toxicological Review of Formaldehyde via the inhalation route of exposure. Our comments focus on the science policy aspects of the draft Formaldehyde Review and complement the comments submitted by ACC's Formaldehyde Panel that is part of ACC's Chemical Products and Technology Division (CPTD).

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

Sincerely,

Jessica Ryman-Rasmussen, PhD, DABT
Senior Director, Chemical Management

[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.

1. **EPA should evaluate carcinogenicity entirely under its 2005 Guidelines for Carcinogen Risk Assessment (2005 Guidelines). The 2005 Guidelines and descriptors have not been harmonized with the re-purposed GRADE framework and descriptors used in the IRIS Handbook.**

ACC recognizes that the GRADE framework, which was included in the draft IRIS Handbook, has been published in the peer-reviewed scientific literature[2] and reviewed by the National Academies (NAS). However, the GRADE framework was re-purposed from medicine, public health, and public policy, and was not developed as fit-for-purpose for EPA, for environmental chemicals, or for cancer causality. In contrast, EPA's 2005 Guidelines for Carcinogen Risk Assessment (2005 Guidelines) were developed as fit-for-purpose for cancer causality for environmental chemicals for EPA. To our knowledge, the re-purposed GRADE framework and the 2005 Guidelines have not been harmonized for cancer classification and evaluation.

In Section 1.1.4 of the Assessment Overview, Evidence Integration,[3] EPA describes how the draft Formaldehyde Review incorporated the principles of the 2005 Guidelines into hazard evaluation. However, the criteria listed in "Table 9. Criteria for applying cancer descriptors to evidence integration judgments for cancer types"[4] differ from the criteria in the 2005 Guidelines for the "*carcinogenic to humans*" descriptor. Specifically, Table 9 states:

6 Table 9. Criteria for applying cancer descriptors to evidence integration judgments for
7 cancer types

Cancer descriptor	Criteria
Carcinogenic to humans	• This descriptor was used if the evidence demonstrates that, for at least one cancer type, formaldehyde inhalation exposure caused the increase in cancer incidence or mortality. • This descriptor could also be used in rare instances if for the evidence indicates that formaldehyde inhalation exposure likely causes different cancer types across evidence bases (e.g., when one type of cancer is based on human evidence and tumors at another site is supported by animal evidence, consistent with EPA

Cancer descriptor	Criteria
	guidelines (U.S. EPA, 2005a) that site-concordance is not required). Such a decision would depend on mechanistic understanding (i.e., in this example, the decision would consider differences in tumor types or ADME across species).

The 2005 Guidelines, however, state:

[2]Morgan et al. GRADE: Assessing the quality of evidence in environmental and occupational health. Environment International. Volumes 92–93, July–August 2016, Pages 611-616.
[3] Assessment Overview for the Toxicological Review of Formaldehyde (Inhalation), pages 14-25.
[4] Id., pages 24-25.

"Carcinogenic to Humans"

This descriptor indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.
- Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when all of the following conditions are met: (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and (b) there is extensive evidence of carcinogenicity in animals, and (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information. In this case, the narrative includes a summary of both the experimental and epidemiologic information on mode of action and also an indication of the relative weight that each source of information carries, e.g., based on human information, based on limited human and extensive animal experiments.

The 2005 Guidelines state that "*The following descriptors can be used as an introduction to the weight of evidence narrative. The examples presented in the discussion of the descriptors are illustrative. The examples are neither a checklist nor a limitation for the descriptor. The complete weight of evidence narrative, rather than the descriptor alone, provides the conclusions and the basis for them.*" Nevertheless, it is unclear why it would be necessary to include separate criteria for the cancer descriptor under the re-purposed GRADE framework in the draft Formaldehyde Review and why the criteria are so different from the 2005 Guidelines. It is evident that the re-purposed GRADE framework is not harmonized with the 2005 Guidelines.

The applied science policy (e.g., re-purposed GRADE framework or 2005 Guidelines) could impact the cancer classification and dose-response assessment for cancer endpoints. Since the re-purposed GRADE framework and descriptors have not, to our knowledge, been harmonized with the 2005 Guidelines and descriptors, the re-purposed GRADE framework should not be applied in any way to cancer classification and dose-response assessment and EPA should re-evaluate these entirely under its own, fit-for-purpose, 2005 Guidelines.

2. **EPA's 2005 Guidelines indicate that meta-analysis can follow systematic review and can be helpful when varying degrees of risk or conflicting results are present. A meta-analysis by Mundt et al. (2021) indicates the descriptor "*Inadequate information to assess carcinogenic potential*" should be used until a meta-analysis that separately analyzes AML (with control for tobacco smoking) and CML is conducted by EPA solely under its 2005 Guidelines.**

EPA's 2005 Guidelines indicate that meta-analysis can follow systematic review and can be helpful when varying degrees of risk or conflicting associations are present:

> ***2.2.1.6.3 Combining statistical evidence across studies***. Meta-analysis is a means of integrating the results of multiple studies of similar health effects and risk factors. This technique is particularly useful when various studies yield varying degrees of risk or even conflicting associations (negative and positive). It is intended to introduce consistency and comprehensiveness into what otherwise might be a more subjective review of the literature. The value of such an analysis is dependent upon a systematic review of the literature that uses transparent criteria of inclusion and exclusion.

Mundt et al. (2021)[5] (described in an ACC docket submission[6]) stated that "Some analyses evaluated myeloid malignancies separately from the lymphocytic neoplasms, but still combined AML and CML, despite evidence of different mutations in genes and other risk factors that indicate different etiologies." These differences in etiology indicate that AML and CML should not be combined.

Mundt et al. (2021) also conducted a meta-analysis for formaldehyde stated that "Overall, the updated cohort study analyses demonstrate no clear or consistent excess risk of myeloid leukemia or AML or CML." A meta-analysis was also conducted for tobacco, which stated that "...the evidence on the risk of specific leukemia subtypes from tobacco smoking indicates an association with AML, but not with CML." This provides evidence that studies investigating AML alone and/or that combine AML and CML should be controlled for tobacco smoking to avoid the potential for confounding.

Together, 1) indications by EPA's 2005 Guidelines that meta-analysis can be helpful and can follow systematic review; 2) lack of supporting animal data; 3) lack of a mode of action (MOA); 4) a meta-analysis showing no clear or consistent excess risk for myeloid leukemia, AML, or CML; and 5) evidence of potential for confounding of AML and combined AML/CML by tobacco smoking indicate the descriptor "*Inadequate information to assess carcinogenic potential*" should be used unless and until a meta-analysis that separately analyzes AML (with control for tobacco smoking) and CML is conducted by EPA. Furthermore, and as mentioned above, unless and until the re-purposed GRADE framework is harmonized with EPA's 2005 Guidelines, all analyses and cancer classifications should be solely under EPA's 2005 Guidelines.

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[5] Mundt, K. A., L. D. Dell, P. Boffetta, E. M. Beckett, H. N. Lynch, V. J. Desai, C. K. Lin, and W. J. Thompson. (2021) "The importance of evaluating specific myeloid malignancies in epidemiological studies of environmental carcinogens." BMC cancer, 21(1), 1-22.

[6] EPA-HQ-OPPT-2018-0438-0067.

3. The 2005 Guidelines provide that while a linear extrapolation would generally be the default for DNA-reactive chemicals, a threshold approach would be allowed given sufficient evidence. The descriptor "Not likely to be carcinogenic to humans at concentrations that do not cause nasal tumors in rodents" should be used, as should a threshold approach for deriving a toxicity value.

EPA's 2005 Guidelines state:

A *nonlinear approach* should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses. Special attention is important when the data support a nonlinear mode of action but there is also a suggestion of mutagenicity. Depending on the strength of the suggestion of mutagenicity, the assessment may justify a conclusion that mutagenicity is not operative at low doses and focus on a nonlinear approach, or alternatively, the assessment may use both linear and nonlinear approaches.

Previously, ACC's Formaldehyde TSCA Risk Evaluation Consortium submitted the following information to the docket for the TSCA risk evaluation of formaldehyde:[7]

> Thompson et al. (2020)[12] updated the mode of action (MOA) framework for nasal tumors and found there are exposure concentrations below which there are no detectable biomarkers of exposure in rats. Exposure to several ppm formaldehyde was required to increase exogenous N_2-hydroxymethyldeoxyguanosine (HmdG) adducts to and above endogenous levels in the rat nasal cavity, and the genotoxic potential of exogenous HmdG levels at and above endogenous levels appears to be weak or nil (up to 15 ppm). The only tumors unequivocally associated with formaldehyde exposure in animals were nasal tumors in rats following inhalation exposure to ≥ 6 ppm formaldehyde. An exposure threshold for nasal tumors, the reactivity with proteins and DNA, and inconclusive *in vivo* evidence of genotoxicity indicates the potential for inhaled formaldehyde to cause nasal tumors through genotoxic mechanisms but does not lend support to a mutagenic MOA. Covalent binding of labeled formaldehyde to DNA was observed at ≥ 2 ppm with evidence for significant nonlinearities occurring between 2 and 6 ppm, where metabolism is saturated and exogenous formaldehyde adducts become more prevalent than endogenous adducts.

[7] EPA-HQ-OPPT-2018-0438-0067, reference 12 in this submission is Thompson, C. M., Gentry, R., Fitch, S., Lu, K., & Clewell, H. J. (2020). "An updated mode of action and human relevance framework evaluation for Formaldehyde-Related nasal tumors." Critical Reviews in Toxicology, 50(10), 919-952.

The draft Formaldehyde Review does not mention the MOA evaluation by Thompson et al. (2020). This analysis of the dose-response indicates there is a threshold for genotoxicity and that it is higher than the threshold for nasal tumors. As such, a threshold approach based on nasal tumors in rats would be protective for any tumors resulting from genotoxicity. The MOA information, together with the robust toxicity database for formaldehyde, provides ample evidence to "justify a conclusion that mutagenicity is not operative at low doses and focus on a non-linear approach," in accordance with the 2005 Guidelines.

In addition to the updated MOA by Thompson et al. (2020), authoritative sources have concluded there is a threshold for both nasal tumors and genotoxicity:

i. **ECHA Committee for Risk Assessment (RAC). 13 March 2020. Opinion on an Annex XV Dossier Proposing Restrictions on Formaldehyde and Formaldehyde Releasers.**

> It is agreed in accordance with the RAC conclusion on FA carcinogenicity (2012) that experimental results and mechanistic data support "the existence of a threshold type dose-response for induction of nasal tumours, with regenerative cell proliferation being the predominant feature in the carcinogenic process. The genotoxicity of formaldehyde is also expected to play a role above this threshold." However, RAC further reflected the uncertainties that "the data does not allow a firm conclusion on a threshold-mode of action or the identification of a threshold", while SCOEL (2016) considered that "the apparent NOAEC of 1 ppm [1.24 mg/m^3] can be considered a mode-of-action based NOAEC for carcinogenic effects at the portal-of-entry" (SCOEL 2016). In line with the DS RAC concludes that formaldehyde is a locally acting genotoxic carcinogen for which a mode-of-action based limit value for its carcinogenic effect in the nose is very likely. Whether the WHO threshold value of 0.1 mg/m^3 can be considered sufficiently conservative for formaldehyde risk assessment is discussed in the next section.

ii. **WHO. 2010. WHO Guidelines for Indoor Air Quality: Selected Pollutants. World Health Organization, Regional Office for Europe.**

> Increased cell proliferation due to cell damage is considered a key mechanism for the development of nasal malignancies following exposure to formaldehyde. Overall, indoor air effects of formaldehyde are expected to be limited to the site of contact, generally the nasal and upper airways. Increasing cell proliferation in the nasal mucosa of rats occurs at concentrations at and above 2.5

mg/m^3 formaldehyde. The NOAEL for cell proliferation is 1.25 mg/m^3 for long-term exposures.
Thus a threshold approach to setting a guideline for cancer effects is appropriate.

4. The systematic review methods used in the draft Formaldehyde Review need further improvements to fully address the 2011 recommendations from the NASEM and the guidance in the IRIS Handbook.

In 2011, a NASEM Committee reviewed an earlier draft IRIS assessment for formaldehyde (2011 report).[8] The 2011 report included evaluation of the general methodology used in the assessment and provided recommendations for improvement of the assessment and the general IRIS process. Overall, the committee found that EPA's draft assessment was not prepared in a logically consistent fashion, lacked clear links to an underlying conceptual framework and did not sufficiently document methods and criteria used to identify evidence for selecting and evaluating studies. Notably, the Committee devoted a full chapter in the final NASEM report to a roadmap for revising the IRIS assessment process.

Further NASEM reviews of the IRIS Program include the 2014 review of the IRIS program (2014 report),[9] and the 2018 review of the IRIS program (2018 report).[10] Taken together, these reviews identified important areas for improvement with respect to several critical areas, including problem formulation, evaluation of study quality, and evidence integration. Perhaps the most important recommendation was for EPA to develop an IRIS Handbook to provide detailed guidance for developing IRIS assessments. In November 2020, EPA released a draft IRIS Handbook (the Handbook) for public comment and review by NASEM.[11] This was a long-awaited step toward meeting the NASEM recommendations for the IRIS Program and providing a transparent framework for how IRIS assessments are developed. ACC provided substantive comments on the Handbook, and we incorporate those by reference.[12]

The 2022 draft Formaldehyde Review needs further improvement to fully meet the recommendations from both the NASEM reviews and EPA's own guidance for the IRIS assessment process contained in the Handbook. We highlight several key areas below.

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[8] National Research Council. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press. https://doi.org/10.17226/13142.
[9] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.
[10] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086.
[11] U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). U.S. EPA Office of Research and Development, Washington, DC, EPA/600/R-20/137, 2020.
[12] Docket ID EPA-HQ-ORD-2018-0654-0022.