Submitted Via Email

October 25, 2022

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Board on Environmental Studies and Toxicology
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RE: Procedural Deficiencies in Developing the 2022 Draft IRIS Formaldehyde Assessment

Dear Dr. Guyton,

On behalf of the American Chemistry Council ("ACC") Formaldehyde Panel ("Panel"), I am writing to underscore EPA's procedural deficiencies in developing the 2022 draft IRIS formaldehyde assessment ("2022 draft assessment") that inexplicably ignored or truncated key steps in the 7-step IRIS assessment process and consequently limited both federal agency and public input on the 2022 draft assessment.[1]

EPA's IRIS process for developing human health assessments consists of seven steps including: 1) draft development/scoping and problem formulation, 2) agency review, 3) interagency science consultation, 4) public comment/external peer review, 5) revision of assessment, 6) final agency review and interagency science discussion, and 7) finalization of the assessment.[2] These steps are intended to provide a degree of predictability and transparency to the IRIS assessment process. These steps also provide multiple opportunities for public input. As described below, in developing the 2022 draft assessment, EPA either ignored or truncated steps one, three, and four of the 7-step IRIS process.

Step 1: Draft Development/Scoping and Problem Formulation

The first step in the IRIS assessment process is Scoping and Problem Formulation/Draft Development, which EPA describes as follows:

> Beginning an assessment, EPA's Office of Research and Development (ORD) undertakes scoping and problem formulation to ensure that the product meets the scientific needs of the EPA program or regional office(s) requesting the assessment. These activities help focus the assessment by describing the routes of exposure, potential health effects, types of studies, and key science issues to be considered in the assessment. EPA ORD also develops an assessment protocol which presents the systematic review and dose-response methods being used to develop the draft assessment. EPA releases these preliminary

assessment materials to obtain input from the scientific community and general public. A public science meeting may be held to obtain additional input.[3]

In developing the 2022 draft assessment, however, EPA failed to implement Step 1 of the IRIS process; EPA never released an IRIS assessment plan, which would have included scoping and problem formulation materials. Inexplicably, formaldehyde is the only one of the eighteen chemicals under review by the IRIS Program for which EPA **has not** developed an IRIS Assessment Plan or Systematic Review Protocol. [4] Perhaps most significantly, five chemical assessments were suspended in 2019 and then reprioritized in 2021 (formaldehyde, chloroform, ethylbenzene, naphthalene, and uranium). Yet all of them, except formaldehyde, have involved public comment on an IRIS assessment plan and systematic review protocol.

At the October 12, 2022, NASEM public meeting[5] on the 2022 draft assessment, the EPA staff asserted that political leadership suspended all work on a complete formaldehyde draft assessment in 2017 and that work restarted in 2021. This characterization is at odds with the Agency's own statements about the process announced in April 2019 to prioritize assessments identified by program offices, in which EPA suspended the formaldehyde assessment (among other assessments) because it was not identified as a priority. [6] Indeed, no EPA program office identified the formaldehyde assessment as priority.[7]

The significant deficiencies of the current 2022 draft assessment, discussed in the Panel's extensive comments [8], are due in part from EPA's failure to fully follow the IRIS process. EPA excluded scores of key peer-reviewed studies and reviews, along with other relevant information, from the 2022 draft assessment (see Appendix A). Many of these references were presented to EPA by the Panel in correspondence and presentations since 2010. In addition, although several key peer-reviewed studies and reviews are cited by EPA in the 2022 draft assessment, EPA cursorily dismisses each one with a footnote, parenthetical, or a single sentence.

Step 3: Interagency Science Consultation

At Step 3 of the IRIS process, Interagency Science Consultation, EPA solicits input from other federal agencies. For the 2022 draft assessment, EPA provided other federal agencies only 30 days to review and comment on the extensive 2022 draft assessment.[9] Compounding the truncated review period, the 30-day period extended over the Christmas and New Year holidays, a time when many in the federal government are out of the office. This may have accounted for some federal agencies not providing comments on the 2022 draft assessment. Nonetheless, the federal agencies that did review at least some portions of the 2022 draft assessment raised important issues, including:

- The White House Office of Management and Budget: "[W]e are concerned with EPA's judgement of 'evidence demonstrates' for myeloid leukemia. Given the inconsistencies in the epidemiologic data and the lack of proposed MOA, it is not clear that this determination is, as EPA indicates (Overview, page 4), based on "robust human evidence […]. Claiming 'evidence demonstrates' while the confidence in the unit risk estimate is low and the data are limited may result in an overly conservative appreciation of the degree of hazard for myeloid leukemia, particularly considering no MOA has been established to explain how

formaldehyde inhalation can cause myeloid leukemia, a disease that results from systemic exposure. The mechanistic information considered by EPA may support associations with local, route-of-exposure, tumors associated with epithelial cells, but does not support the tumorigenesis or carcinogenesis of disease related to systemic exposures."[10]

- The Small Business Administration: "EPA states that it is evaluating the extra risks associated with exogenous formaldehyde from being added to endogenous formaldehyde---does endogenous formaldehyde pose risks by itself? What is the mechanism by which exogenous formaldehyde create "extra" risks by adding to the endogenous formaldehyde?"[11]

Step 4 – Public Comment/External Peer Review

With respect to Step 4, Public Comment/External Peer Review, EPA did not seek meaningful comment on draft charge questions[12] and the NASEM Committee task despite the clear language of Step 4 of the IRIS process: "a draft assessment and charge questions are released for public comment and peer review."[13]

EPA describes the 2022 draft assessment as "an entirely new draft developed de novo using systematic review methods and in a manner responsive to NAS [NASEM] comment on the prior draft."[14] If the 2022 draft assessment is in fact a de novo assessment, we question why EPA opted against following each step of the 7-step IRIS process including public comment on the IRIS assessment plan and systematic review protocol prior to draft development.

EPA also failed to fully document in drafting the 2022 draft assessment NASEM's 2011 peer review recommendations on the 2010 draft assessment. In a March 2022 letter to EPA, the Panel noted that EPA policies require full documentation of Agency resolution, implementation, and incorporation of previous NASEM findings and recommendations, including those related to the IRIS program and the 2010 draft assessment, as well as other relevant peer review comments received by EPA and that failure to do so was inconsistent with Congressional direction. [15] We also noted that by ignoring congressional direction and EPA policy, EPA could seriously diminish the utility of a final formaldehyde assessment in future EPA regulatory actions.[16]

In a subsequent April 2022 letter to EPA, the Panel provided the Agency with a robust set of recommended peer review charge questions, many of which correspond to direction provided in EPA's Peer Review Handbook as well as statutory provisions in TSCA and the Clean Air Act which govern Agency use of an IRIS assessment in support of rulemaking.[17] The Panel, however, neither received any response to this correspondence nor do EPA's draft charge questions[18] incorporate any of the Panel's recommendations. In particular, the charge questions for the NASEM peer review do not include questions focused on whether EPA fully addressed the NASEM 2011 recommendations.

Moreover, EPA provided only a 60-day comment period on the 2022 draft assessment despite requests from stakeholders and Members of Congress for additional time. In contrast, for the 2010 draft assessment, EPA provided a 90-day public comment period **and** a public listening session. Thus, stakeholders were denied adequate opportunities to fully review and comment on the 2022 draft assessment, despite EPA's past practice and the voluminous size - nearly 2000

pages - and complexity of the 2022 draft assessment. EPA has offered no explanation for deviating from either past practice or the 7-step IRIS process in developing the 2022 draft assessment.

The October 12, 2022, public meeting[19] included a briefing from the Chair of the NASEM Review of EPA's IRIS Assessment Handbook, which identified numerous Tier 1 recommendations which have not been implemented to the draft Handbook or applied to any IRIS assessment including formaldehyde. Several comments from the NASEM Committee and the American Chemistry Council identified numerous examples of deviations and inconsistencies between the draft formaldehyde assessment and the NASEM review of the draft Handbook.[20] ACC comments and letters have also identified inconsistencies between EPA's draft formaldehyde assessment and requirements related to the Toxic Substances Control Act, Information Quality Act, Clean Air Act, Federal Advisory Committee Act, and several Agency regulations, guidance documents, and other directives.[21]

We would welcome the opportunity to share more information on these legal and procedural defects relevant to the Committee's work. Should you have any questions regarding this submission, I can be reached at sahar_osman-sypher@amerianchemistry.com.

Sincerely,

Sahar Osman-Sypher
Senior Director
Chemical Products & Technology Division
American Chemistry Council
On Behalf of the ACC Formaldehyde Panel

Cc: Marcia McNutt (NASEM), Audrey Mosley (NASEM), Elizabeth Eide (NASEM), Clifford Duke (BEST), Jonathan Samet (NASEM Committee Chair)

Attachment: Appendix A of ACC Formaldehyde Panel Comments to EPA on Draft IRIS Formaldehyde Assessment, June 13, 2022

[1] In a September 20, 2022, letter to Dr. Kathryn Guyton, the Panel requested that the NASEM Committee reviewing EPA's 2022 draft IRIS formaldehyde assessment convene a public information gathering session and designate at least 4 hours of oral public comments during the NASEM committee public meetings. The Panel believes that these additional opportunities to provide information will allow the Committee to better understand the deficiencies regarding the 2022 draft assessment.

[2] Basic Information about the Integrated Risk Information System | US EPA

[3] See Endnote 2

[4] IRIS Program Outlook June 2022; The reviews of the other 17 chemicals have already released (or have plans to release prior to assessment development) a chemical-specific systematic review protocol for at least 30 days of public comment. For the 12 assessments with expected dates for release of a public comment draft, the date of issuing the draft assessment averages 3.5 years after EPA solicited public comment on a systematic review protocol. EPA Response to ACC Stakeholder Letter on NASEM Review of Draft IRIS Assessment_Feb 2022; ACC Formaldehyde Panel Follow-up Letter to EPA_March 2022

[5] October 12, 2022 NASEM Public | National Academies

[6] "In April 2019, the IRIS Program announced under the Program Outlook that in an effort to modernize its workflow, IRIS has moved away from one-size-fits-all assessments to a portfolio of chemical evaluation products to meet specific decision needs. This approach optimizes the application of best practices of systematic review in the IRIS Program." (EPA IRIS Program Outlook April 2019-Suspended/Discontinued Assessment); "The IRIS assessment of formaldehyde (inhalation) announced as suspended in April 2019 has recently been unsuspended." (EPA History/Chronology of IRIS Toxicological Review of Formaldehyde).

[7] EPA Response to ORD Solicitation: OCHP Nominations for IRIS Risk Assessment Chemicals_August 2018; EPA Memo to Assistant Administrators and Deputies Soliciting Requests for IRIS Assessments_August 2018; EPA Internal Communications Regarding Solicitation of IRIS Nominations_October-November 2018; EPA Email to Assistant Administrators and Deputies Regarding Updated Priorities for IRIS Assessments_December 2018.

[8] Comments submitted to EPA Docket ID No. EPA-HQ-ORD-2010-0396 on the draft formaldehyde assessment include: ACC Formaldehyde Panel and ACC Formaldehyde TSCA Risk Evaluation Consortium

[9] Comments from Federal Agencies Submitted to EPA on the 2010 Draft IRIS Assessment for Formaldehyde

[10] White House Office of Management and Budget Comments to EPA December 2021

[11] Small Business Administration Comments to EPA _December 2021

[12] In denying an extension of the comment period, EPA noted that public commenters on the 2022 draft assessment could provide comments on the charge questions. But EPA's request for public comment was clarified only toward the end of the already truncated 60-day comment period and thus did not cure the lack of serious public engagement on development of the charge questions.

[13] See Endnote 2

[14] EPA Contract with NASEM For Review of Draft 2022 Formaldehyde IRIS Assessment

[15] ACC Formaldehyde Panel Letter to EPA Administrator Regan March 2022

[16] ACC Formaldehyde Panel Letter to EPA_April 2022

[17] ACC Comments on the Charge Questions and Committee Task for Peer Review of Draft Formaldehyde Assessment April 2022

[18] Draft EPA External Peer Review Charge Questions, December 2021

[19] See Endnote 5

[20] Comments Submitted by ACC on Draft Formaldehyde IRIS Assessment_June 2022 (pg. 7-13); Comments Submitted by ACC Formaldehyde Panel (pg. 7-26); Comments Submitted by ACC Formaldehyde TSCA Risk Evaluation Consortium.

[21] See Endnote 20

Appendix A

EPA has excluded or dismissed a number of key studies, reviews, responses, and presentations, with a majority having been presented in correspondence and presentations by the ACC Formaldehyde Panel to the Agency since 2011.

Important studies, reviews, or responses which are not referenced in the external review draft for EPA's toxicological review (789 pp) or supplemental information (1058 pp):[231]

Albertini, R.J. and Kaden, D.A., 2017. Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. *Critical Reviews in Toxicology*, *47*(2), pp.145-184.

Albertini, R.J. and Kaden, D.A., 2020. Mutagenicity monitoring in humans: global versus specific origin of mutations. *Mutation Research/Reviews in Mutation Research*, *786*, p.108341.

Allegra, A., Spatari, G., Mattioli, S., Curti, S., Innao, V., Ettari, R., Allegra, A.G., Giorgianni, C., Gangemi, S. and Musolino, C., 2019. Formaldehyde exposure and acute myeloid leukemia: a review of the literature. *Medicina*, *55*(10), p.638.

Andersen, M.E., Gentry, P.R., Swenberg, J.A., Mundt, K.A., White, K.W., Thompson, C., Bus, J., Sherman, J.H., Greim, H., Bolt, H. and Marsh, G.M., 2019. Considerations for refining the risk assessment process for formaldehyde: Results from an interdisciplinary workshop. *Regulatory Toxicology and Pharmacology*, *106*, pp.210-223.

Bachand, A.M., Mundt, K.A., Mundt, D.J. and Montgomery, R.R., 2010. Epidemiological studies of formaldehyde exposure and risk of leukemia and nasopharyngeal cancer: a meta-analysis. *Critical reviews in toxicology*, *40*(2), pp.85-100.*

Bosetti, C., McLaughlin, J.K., Tarone, R.E., Pira, E. and La Vecchia, C., 2008. Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006. Annals of Oncology, 19(1), pp.29-43.*

[231] * denotes studies, reviews, or responses referenced in supplemental information but not the main text; ** denotes studies, review, or responses briefly referenced in the main text but not the supplemental information; *** denotes studies miscited in the main text but not referenced in the supplemental information.

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Catalani, S., Donato, F., Madeo, E., Apostoli, P., De Palma, G., Pira, E., Mundt, K.A. and Boffetta, P., 2019. Occupational exposure to formaldehyde and risk of non hodgkin lymphoma: a meta-analysis. *BMC cancer*, *19*(1), pp.1-9.

Chang, E.T., Ye, W., Zeng, Y.X. and Adami, H.O., 2021. The evolving epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiology and Prevention Biomarkers*, *30*(6), pp.1035-1047.

Checkoway, H., Boffetta, P., Mundt, D.J. and Mundt, K.A., 2012. Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies. *Cancer Causes & Control*, *23*(11), pp.1747-1766.

Checkoway, H., Lees, P.S., Dell, L.D., Gentry, P.R. and Mundt, K.A., 2019. Peak exposures in epidemiologic studies and cancer risks: considerations for regulatory risk assessment. *Risk Analysis*, *39*(7), pp.1441-1464.

Cole, P., Adami, H.O., Trichopoulos, D. and Mandel, J., 2010. Formaldehyde and lymphohematopoietic cancers: a review of two recent studies. *Regulatory Toxicology and Pharmacology*, *58*(2), pp.161-166.

Cole, P., Adami, H.O., Trichopoulos, D. and Mandel, J.S., 2010. Re: Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. Journal of the National Cancer Institute, 102(19), pp.1518-1519.

Cole, P. and Axten, C., 2004. Formaldehyde and leukemia: an improbable causal relationship. *Regulatory Toxicology and Pharmacology*, *40*(2), pp.107-112.

Collins, J.J. and Lineker, G.A., 2004. A review and meta-analysis of formaldehyde exposure and leukemia. *Regulatory Toxicology and Pharmacology*, *40*(2), pp.81-91.*

Collins, J.J., Ness, R., Tyl, R.W., Krivanek, N., Esmen, N.A. and Hall, T.A., 2001. A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies. *Regulatory Toxicology and Pharmacology*, *34*(1), pp.17-34.

Collins, J.J., Esmen, N.A. and Hall, T.A., 2001. A review and meta-analysis of formaldehyde exposure and pancreatic cancer. *American journal of industrial medicine*, *39*(3), pp.336-345.*

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European Food Safety Authority, 2014. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. *EFSA Journal*, *12*(2), p.3550.

Gaylor, D.W., Lutz, W.K. and Conolly, R.B., 2004. Statistical analysis of nonmonotonic dose-response relationships: Research design and analysis of nasal cell proliferation in rats exposed to formaldehyde. *Toxicological Sciences*, *77*(1), pp.158-164.

Gentry, R., Thompson, C.M., Franzen, A., Salley, J., Albertini, R., Lu, K. and Greene, T., 2020. Using mechanistic information to support evidence integration and synthesis: a case study with inhaled formaldehyde and leukemia. *Critical reviews in toxicology*, *50*(10), pp.885-918.

Golden, R., 2011. Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. *Critical reviews in toxicology*, *41*(8), pp.672-721.

Golden, R. and Holm, S., 2017. Indoor air quality and asthma: has unrecognized exposure to acrolein confounded results of previous studies?. *Dose-Response*, *15*(1), p.1559325817691159.

Golden, R. and Valentini, M., 2014. Formaldehyde and methylene glycol equivalence: critical assessment of chemical and toxicological aspects. *Regulatory Toxicology and Pharmacology*, *69*(2), pp.178-186.

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Heck, H.D.A. and Casanova, M., 2004. The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regulatory Toxicology and Pharmacology*, *40*(2), pp.92-106.**

Just, W., Zeller, J., Riegert, C. and Speit, G., 2011. Genetic polymorphisms in the formaldehyde dehydrogenase gene and their biological significance. *Toxicology letters*, *207*(2), pp.121-127.

Lu, K., Hsiao, Y.C., Liu, C.W., Schoeny, R., Gentry, R. and Starr, T.B., 2021. A Review of Stable Isotope Labeling and Mass Spectrometry Methods to Distinguish Exogenous from Endogenous DNA Adducts and Improve Dose–Response Assessments. *Chemical Research in Toxicology*.

Lu, K., Ye, W., Zhou, L., Collins, L.B., Chen, X., Gold, A., Ball, L.M. and Swenberg, J.A., 2010. Structural characterization of formaldehyde-induced cross-links between amino acids and deoxynucleosides and their oligomers. *Journal of the American Chemical Society*, *132*(10), pp.3388-3399.**

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[232] Included in main text references but not in text nor in appendices.

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Zeller, J., Ulrich, A., Mueller, J.U., Riegert, C., Neuss, S., Bruckner, T., Triebig, G. and Speit, G., 2011. Is individual nasal sensitivity related to cellular metabolism of formaldehyde and susceptibility towards formaldehyde-induced genotoxicity?. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *723*(1), pp.11-17.

In addition, several important studies and reviews, while briefly cited by EPA in the main text of the assessment, are summarily dismissed by the Agency (in several cases devoting a sentence or less, or a single footnote to the content). Examples include:

Gentry, P.R., Rodricks, J.V., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A.M., Albertini, R.J. and Irons, R., 2013. Formaldehyde exposure and leukemia: critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. *Critical reviews in toxicology*, *43*(8), pp.661-670.

Lu, K., Boysen, G., Gao, L., Collins, L.B. and Swenberg, J.A., 2008. Formaldehyde-induced histone modifications in vitro. *Chemical research in toxicology*, *21*(8), pp.1586-1593.

Möhner, M., Liu, Y. and Marsh, G.M., 2019. New insights into the mortality risk from nasopharyngeal cancer in the national cancer institute formaldehyde worker cohort study. *Journal of Occupational Medicine and Toxicology*, *14*(1), pp.1-4.

Mundt, K.A., Gallagher, A.E., Dell, L.D., Natelson, E.A., Boffetta, P. and Gentry, P.R., 2017. Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells? *Critical Reviews in Toxicology*, *47*(7), pp.598-608.