Submitted Via Email

October 7, 2022

Dr. Jonathan M. Samet
Committee Chair
Committee on Review of EPA's 2022 Draft Formaldehyde Assessment
National Academies of Science Engineering and Medicine
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Dear Dr. Samet,

On behalf of the American Chemistry Council ("ACC") Formaldehyde Panel ("Panel"), I would like to thank you for your willingness to serve as committee chair of the National Academies of Sciences, Engineering, and Medicine ("NASEM") ad hoc committee ("Committee") that will review EPA's 2022 draft formaldehyde assessment. The Panel welcomes the chance to be a technical resource to the Committee through written and oral comments, workshops, information-gathering sessions, and other opportunities to provide information to inform the review.

As you are aware, in 2011, the NASEM committee that reviewed an earlier EPA draft formaldehyde assessment found significant deficiencies in how EPA's assessment organized and considered the existing science. As a result, the 2011 committee acknowledged that key sections of the assessment did not align with the available scientific information. The 2011 committee also identified areas where additional scientific information would be informative to the revised formaldehyde assessment. Even before the public release of the 2022 draft assessment, the Panel identified key issues related to the peer review process, including the scientific and legal need to fully resolve 2011 NASEM recommendations[1] and the scope of the committee task and charge questions,[2] which are critical to ensure the same rigor is applied to the updated draft.

ACC Formaldehyde Panel members took those recommendations seriously and launched numerous investigative research projects to fill perceived data gaps. Subsequently, since 2010 over 50 peer reviewed publications on various key topics have been added to the literature to inform the formaldehyde hazard and dose-response assessment. All this information has been made available and discussed with EPA IRIS staff over that time. A list of those publications to EPA are attached for your background and understanding.[3] It is our understanding that all the materials we have submitted to the EPA docket have also been shared with NASEM committee members.[4]

Unfortunately, a large majority of the research and studies undertaken, specifically to respond to the recommendations and questions raised by the 2011 NASEM committee, have not been appropriately considered in the EPA's 2022 draft formaldehyde assessment.[5] Due to flaws in EPA's literature search approach, including a flawed PECO statement which allowed EPA to subjectively pick "impactful" studies, some of these studies are not even mentioned in the assessment. Other studies that are mentioned, are then summarily dismissed or discounted. For instance, we look forward to having the NASEM committee look closely at how EPA interpreted critical data regarding genotoxicity in a manner that is inconsistent with the findings of the primary study authors.[6] These interpretations have lent support to EPA's determination to conduct linear dose-response modelling, when a threshold approach would be more appropriate.

Most importantly, EPA's stated approach to evidence integration in the draft assessment allows EPA to ignore critical information that informs mode of action. EPA's failure to consider this critical information contradicts EPA's own guidelines[7], internationally accepted approaches[8], and the draft IRIS handbook, which emphasize the importance of considering ***all*** lines of evidence[9]. The approach in the draft assessment excludes mechanistic and mode of action "evidence against" the conclusions reached in the draft assessment. Failure to integrate mechanistic data, as well as important toxicokinetic data and dosimetry information has led to an assessment which is inconsistent with the best available scientific information.

We have requested that the NASEM allow more time for public comment or consider a targeted information gathering session where scientists who have been studying formaldehyde science for decades can provide you and the committee with an in-depth understanding of the literature. We would welcome such an opportunity.[10]

In addition, the Panel intends to provide additional electronic resources to the Committee in the coming weeks, including distilled materials to address key issues. These include: the applicability of key studies and comments for EPA's charge questions; key recommendations from the 2011 NASEM review that are not fully addressed or resolved in the new draft assessment; key comments from other federal agencies; and comments by authors of important studies.

Formaldehyde is a critical chemical building block for hundreds of key sectors and essential items including affordable housing, sustainable wood products, agriculture, medical devices, and electric vehicles. The public health consequences of an incorrect IRIS value, including a value that is overly restrictive, warrant a robust and comprehensive review.

Thank you again for your willingness to chair this important review. ACC Panel members are prepared to provide you and the committee with any assistance and information that may be helpful. Should you have any questions, 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), Kathryn Guyton (NASEM), Audrey Mosley (NASEM), Elizabeth Eide (NASEM), Clifford Duke (BEST), Public Comment Docket: formaldehyde@nas.edu

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

[1] Formaldehyde Panel Letter to EPA Administrator Michael Regan, March 10, 2022: https://www.americanchemistry.com/industry-groups/formaldehyde/resources/formaldehyde-panel-follow-up-letter-to-epa.

[2] ACC Comments to EPA Administrator Michael Regan and Dr. Clifford Duke with the Board on Environmental Studies and Toxicology (BEST) on the Charge Questions and Committee Task for Peer Review of Draft Formaldehyde Assessment, April 13, 2022: https://www.americanchemistry.com/industry-groups/formaldehyde/resources/acc-comments-on-the-charge-questions-and-committee-task-for-peer-review-of-draft-formaldehyde-assessment

[3] See Appendix A on pages 107-114 in the Panel comments available at https://www.regulations.gov/comment/EPA-HQ-ORD-2010-0396-0103 for a list of important studies, reviews, or responses which are not referenced in the external review draft for EPA's toxicological review or supplemental information. This document is also attached for your reference.

[4] Key comments submitted to EPA Docket ID No. EPA-HQ-ORD-2010-0396 on the draft formaldehyde assessment include: ACC Formaldehyde Panel; ACC Formaldehyde TSCA Risk Evaluation Consortium; as well as comments by: Rory Connolly; Gary Marsh; Peder Wolkoff and Debra Kaden; Thomas Starr; Chad Thompson; Kun Lu; Robinan Gentry; Richard Albertini and Debra Kaden; Pamela Dalton; Kenneth Mundt; Harvey Checkoway, Kenneth Mundt and Linda Dell; Leslie Recio; and Robert Golden and Stewart Holm.

[5] See Footnote 3

[6] See for instance Thompson, CM, Gentry, R, Fitch, S, Lu, K, Clewell, HJ (2020) An updated mode of action and human relevance framework evaluation for Formaldehyde-Related nasal tumors. Critical Reviews in Toxicology 50(10): 919-952; and Leslie Recio, Susan Sisk, Linda Pluta, Edilberto Bermudez, Elizabeth A. Gross, Zhuchu Chen, Kevin Morgan, Cheryl Walker (1992) p53 Mutations in Formaldehyde-induced Nasal Squamous Cell Carcinomas in Rats. Cancer Res 52 (21): 6113-6116.

[7] The EPA Guidelines for Carcinogen Risk Assessment (2005) state at page 2-1: "The purpose of the assessment is not simply to assemble these separate evaluations; its purpose is to construct a total analysis examining what the biological data reveal as a whole about carcinogenic effects and mode of action of the agent, and their implications for human hazard and dose-response evaluation. Conclusions are drawn from weight-of-evidence evaluations based on the combined strength and coherence of inferences appropriately drawn from all of the available information." These Guidelines are available at: https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf.

[8] The WHO IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans (2007) was developed to extend the mode of action framework to bring transparency to the analysis and promote confidence in conclusions through a defined process that evaluates the available data. The Framework, which provides a systematic means of considering the weight of evidence for a mode of action is available at: https://www.who.int/publications/i/item/9789241563499.

[9] The ORD Staff Handbook for Developing IRIS Assessments (2020), at page 11-20 discusses how overall evidence integration judgements must consider "the animal and human evidence while also considering mechanistic information on the human relevance of the findings in animals and relevance of the mechanistic evidence to humans along with coherence across bodies of evidence, and information on susceptible populations and lifestages." The Handbook is available at: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086#tab-3.

[10] Formaldehyde Panel Letter to Dr. Kathryn Guyton, requesting NASEM convene a public information gathering session and designate at least 4 hours of oral public comments during the public meetings, September 20, 2022: https://www.americanchemistry.com/industry-groups/formaldehyde/research/letter-to-nasem-on-information-gathering-session

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.

Brüning, T., Bartsch, R., Bolt, H.M., Desel, H., Drexler, H., Gundert-Remy, U., Hartwig, A., Jäckh, R., Leibold, E., Pallapies, D. and Rettenmeier, A.W., 2014. Sensory irritation as a basis for setting occupational exposure limits. *Archives of toxicology*, *88*(10), pp.1855-1879.

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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.*

Doty, R.L., Cometto-Muñiz, J.E., Jalowayski, A.A., Dalton, P., Kendal-Reed, M. and Hodgson, M., 2004. Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans. *Critical reviews in toxicology*, *34*(2), pp.85-142.

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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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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Monticello, T.M., Morgan, K.T. and Hurtt, M.E., 1990. Unit length as the denominator for quantitation of cell proliferation in nasal epithelia. *Toxicologic Pathology*, *18*(1), pp.24-31.[232]

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

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

Mundt, K.A., Gentry, P.R., Dell, L.D., Rodricks, J.V. and Boffetta, P., 2018. Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. *Regulatory Toxicology and Pharmacology*, *92*, pp.472-490.

Mundt, K.A., Gallagher, A.E., Dell, L.D., Natelson, E.A., Boffetta, P. and Gentry, P.R., 2018. Response to Dr. Bernard D. Goldstein's Letter to the Editor. *Critical Reviews in Toxicology*, *48*(5), pp.341-343.

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Pira, E., Romano, C., Vecchia, C.L. and Boffetta, P., 2017. Hematologic and cytogenetic biomarkers of leukemia risk from formaldehyde exposure. *Carcinogenesis*, *38*(12), pp.1251-1252.

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Rhomberg, L.R., Bailey, L.A., Goodman, J.E., Hamade, A.K. and Mayfield, D., 2011. Is exposure to formaldehyde in air causally associated with leukemia? A hypothesis-based weight-of-evidence analysis. *Critical Reviews in Toxicology*, *41*(7), pp.555-621.

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Speit, G., Heinz-Peter, G., Pallapies, D. and Morfeld, P., 2010. Occupational Exposure to Formaldehyde, Hematotoxicity and Leukemia-Specific Chromosome Changes in Cultured Myeloid Progenitor Cells-Letter (vol 19, pg 1882, 2010). *Cancer Epidemiology Biomarkers and Prevention*, *19*, pp.2991-2991.

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Thompson, C.M., 2018. Commentary on new formaldehyde studies in Trp53 haploinsufficient mice: further support for nonlinear risks from inhaled formaldehyde. *Dose-Response*, *16*(2), p.1559325818777931.

Van Landingham, C., Mundt, K.A., Allen, B.C. and Gentry, P.R., 2016. The need for transparency and reproducibility in documenting values for regulatory decision making and evaluating causality: The example of formaldehyde. *Regulatory Toxicology and Pharmacology*, *81*, pp.512-521.

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Zeller, J., Högel, J., Linsenmeyer, R., Teller, C. and Speit, G., 2012. Investigations of potential susceptibility toward formaldehyde-induced genotoxicity. *Archives of toxicology*, *86*(9), pp.1465-1473.

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.

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