Small Business Administration Office of Advocacy
Comments on the Interagency Science Consultation Draft
IRIS Assessment of Formaldehyde (Inhalation) December 2021
(Date Received January 5, 2022)

Interagency Science Consultation Step 3) on the Draft IRIS Toxicological Review of Formaldehyde – Inhalation

SBA Advocacy Comments: [MAIN TEXT, Appendices and Peer Review Questions]

1. Cancers of the lymphohematopoietic system
    1. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the upper respiratory tract to distal tissues). Table ES-2, footnote e) more in section 1.3.3
        a. Section 1.3.3 –
            i. Pg. 1-417 – "Expert review panels have determined that there is sufficient evidence to conclude that formaldehyde inhalation increases the risk for myeloid leukemia based on the results of epidemiological studies alone (NTP, 2011), or additionally supported by mechanistic research (NRC, 2014b; IARC, 2012a)."
            ii. Pg. 1-417 – "Two European Union scientific bodies were not in agreement with those conclusions, noting that although there is evidence of associations between formaldehyde exposure and LHP cancers in the epidemiological literature, the observations are not biologically plausible since formaldehyde is not distributed to distal tissues preventing direct interactions in the bone marrow (SCOEL, 2017; ECHA, 2012)."
            iii. Pg. 1-417 – "In human studies, robust evidence for myeloid leukemia and moderate evidence for multiple myeloma supported a causal association with inhalation of formaldehyde based on epidemiology studies of occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies."
            iv. Pg. 1-417 – "Aneuploidy in chromosomes 1, 5, and 7 in circulating myeloid progenitor cells, considered a potential primary target for LHP carcinogenesis, was associated with occupational formaldehyde exposure."
            v. Pg. 1-417 – " The type of aneuploidies observed in the formaldehyde exposed asymptomatic human workers are also found in patients with leukemia, as well as in other worker cohorts at increased risk of developing leukemias, which provides support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis."

Commented [A1]: What does the EPA's cancer guideline and IRIS handbook require about making conclusions without being able to establish a MOA or without knowledge of mechanism(s) leading to cancer formation.

Have there been other risk assessments making definitive conclusions about causes based on evidence that only demonstrates association and without identifying a mode of action.

Commented [A2]: Please, include a footnote for reference or include citations in the text to the expert review panels.

Commented [A3]: EPA seems to be recognizing the same in this assessment since no established MOA and no observed distribution in distal tissues, but the agency is concluding that there is biological plausibility. Might be useful to note EPA's distinction here and explain why.

Commented [A4]: Explain what a causal association means here.

Commented [A5]: Does this association mean causation?

Commented [A6]: What human workers is this referring to? Which study?

Commented [A7]: What is a 'plausibility of an association'? Does that mean the same as plausibility of causation?

vi. Pg. 1-417 – "Moreover, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans, specifically chromosomal aberrations (CA), and micronucleus (MN) formation, provides additional evidence of biological plausibility for these cancer types."

vii. Pg. 1-418 – "Taken together, based on the robust and moderate human evidence for these cancers from studies that reported increased risk in groups exposed to occupational formaldehyde levels, the evidence demonstrates that formaldehyde inhalation causes myeloid leukemia in humans, given the appropriate exposure circumstances, and medium confidence that formaldehyde inhalation causes multiple myeloma in humans, given the appropriate exposure circumstances."

viii. Pg. 1-418 –" Only primary epidemiological studies of specific cancer endpoints with identified or inferred formaldehyde exposure were included."

ix. Pg. 1-423 – "Evidence describing the association between formaldehyde exposure and the risk of myeloid leukemia was available from 13 epidemiological papers reporting on 10 different study populations…"

x. Pg. 1-433- "The available epidemiological studies provide robust evidence of an association consistent with causation between formaldehyde exposure and increased risk of myeloid leukemia."

xi. Tables 1-61 and 1-62

xii. Pg. 1-451 – "The available epidemiological studies provide indeterminate evidence to assess the carcinogenic potential evidence of an association between formaldehyde exposure and an increased risk of lymphatic leukemia."

Commented [A8]: What studies are being referenced here? Consider providing references/citations.

Commented [A9]: The evidence summarized above only established an association (i.e. did not use 'cause') but the agency seems to be using "cause" in the conclusion without any explanation.

Commented [A10]: This should read "in occupation settings."

Commented [A11]: The evidence summarized above only established an association (i.e. did not use the word "cause") but the agency seems to be using "cause" in the conclusion without any explanation.

Commented [A12]: What are these "appropriate exposure circumstances?"

Commented [A13]: What qualifies as inferred exposure?

Commented [A14]: EPA continues to discuss association in describing the evidence rather than causation.

Commented [A15]: What does this mean i.e. 'evidence of an association consistent with causation'? Has this been used for other assessments?

Commented [A16]: Many of the studies noted that coexposure to other chemicals (including other carcinogen chemicals) was not evaluated.

Commented [A17]: Is evidence that leads to an indeterminate conclusion usually included in risk assessments?

b. No mode of action established

i. NAS comment/EPA response:

1. NAS comment: The committee agrees that EPA's choice of NPC, Hodgkin lymphoma, and leukemia data from the NCI studies to estimate a unit risk is appropriate given that the analysis of Hodgkin lymphoma and leukemia primarily supports the assessment of uncertainty and the magnitude of potential cancer risk. However, the mode of action for formaldehyde-induced Hodgkin lymphoma and leukemia has not been clearly established. Moreover, the highly limited systemic delivery of

formaldehyde draws into question the biologic feasibility of causality between formaldehyde exposure and the two cancers. Thus, substantial uncertainties in using Hodgkin lymphoma and leukemia for consensus cancer risk estimation remain.

2. Response: The integration of evidence from the epidemiology studies provided the rationale for EPA's finding there is sufficient epidemiologic evidence of a causal association between formaldehyde exposure and increased risks of NPC, sinonasal cancer, and myeloid leukemia and that there is suggestive epidemiologic evidence of a causal association between formaldehyde exposure and increased risks of oro/hypopharyngeal cancer and multiple myeloma. The MOA discussion for myeloid leukemia and multiple myeloma concluded that the mechanisms for these cancers is not known, although evidence was discussed that supported the biological plausibility for the conclusion. The cancer hazard section discusses in depth the uncertainties associated with the causality conclusions, and the dose-response section (see Section 2) discusses the uncertainties associated with the derived unit risk estimate.

Commented [A18]: This remains true and is not addressed in the agency's response. The agency does not have a mode of action or mechanistic evidence for formaldehyde-induced LHP cancers. The phrase "evidence of a casual association" is used for noting conclusions for the hazards but it is not defined.

c. Studies- These recent studies have not been included in EPA's assessment, they were submitted to EPA's docket and should be considered.
    i. Albertini, R. J., & Kaden, D. A. (2016). Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. Critical Reviews in Toxicology, 1-40. *Reviewed and integrated the mechanistic data; reports of genetic changes in circulating blood cells and hematopoietic precursor cells; and relevant animal studies to conclude that the genetic changes in circulating blood cells do not provide convincing support to classify formaldehyde as leukemogenic.*
    ii. Andersen, M.E., Gentry, P.R., Swenberg, J.A., Mundt, K.A., White, K.W., Thompson, C., Bus, J. et al. (2019) "Considerations for refining the risk assessment process for formaldehyde: Results from an interdisciplinary workshop." Regulatory Toxicology and Pharmacology 106: 210-223. *Published key points from a 2017 interdisciplinary workshop on the epidemiology, toxicology and mechanistic studies regarding the carcinogenicity of formaldehyde in humans. The expert participants concluded that the toxicological, mode of action, formaldehyde-DNA adduct, computational fluid dynamics, biological based dose response and pharmacokinetic modeling studies were consistent in supporting a conclusion that formaldehyde does not reach sites distant from the front of the nose and would not be expected to cause cancer or any other endpoints in tissues other than directly at the portal of entry.*
    iii. Gentry, R., Thompson, C.M., Franzen, A., Salley, J., Albertini, R., Lu, K., and Greene, T. (2021). "Using mechanistic information to support evidence integration and synthesis: a case study with inhaled formaldehyde and leukemia." Critical Reviews in Toxicology, 1-34. *The authors concluded that none of the four postulated MOAs was biologically plausible, using the IPCS MOA framework, and the weight of evidence did not support the postulated MOAs.*

iv. Checkoway, H., Lees, P. S.J., Dell, L.D., Gentry, P.R., and Mundt, K.A. "Peak exposures in epidemiologic studies and cancer risks: considerations for regulatory risk assessment." Risk Analysis 39, no. 7 (2019): 1441-1464. *The authors found little compelling evidence that any peak exposure metric was predictive of increased leukemia (or LHM) risk, and especially in the absence of demonstrable increased risks with cumulative exposure. The authors concluded, that when peak exposure metrics drive epidemiological cancer hazard determinations, the dose response assessment should not be based on cumulative exposures and linear extrapolations.*

v. Morgan, DL, Dixon, D, King, DH, Travlos, GS, Herbert, RA, French, JE, Tokar, EJ, Waalkes, MP, Jokinen, MP, (2017) National Toxicology Program (NTP) Research Report on Absence of Formaldehyde-Induced Neoplasia in Trp53 - Haploinsufficient Mice Exposed by Inhalation. NTP RR 3. Research Triangle Park, NC: National Toxicology Program (3): 1-29 – *The results of this study results demonstrate that formaldehyde reached the nasal epithelium but did not induce any DNA lesions leading to neoplasia contradicting the hypothesis that hematopoietic stem cells in the nasal epithelium or in circulation undergo formaldehyde-induced mutations that result in loss of Trp53 and acquisition of the capacity for self-renewal, one of the initial steps in cancer.*

vi. Mundt, K., Gentry, PR., Dell, L., Rodricks, J., 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, Vol 92:472-490. *Nearly all the recently available evidence from the multiple lines of inquiry have increased the weight of evidence favoring a conclusion of a lack of causal association between formaldehyde exposure and LHM. Reanalysis of cohort data provided no support for the original study conclusions or that formaldehyde causes AML.*

vii. Checkoway, H., Boffetta, P., Mundt, D., and Mundt, K. (2012). Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies." Cancer Causes & Control 23, no. 11: 1747-1766. *Critically reviewed the epidemiological evidence on formaldehyde exposure and the risk of leukemia and other lymphohematopoietic malignancies (LHMs) and found there was little to no evidence indicating excess risks overall or exposure-response associations between formaldehyde and any of the LHM, including leukemias, myeloid leukemias and acute myeloid leukemias.*

viii. Rhomberg, L., Bailey, L., Goodman, J., Hamade, A., 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, no. 7: 555- 621. *Concluded the studies provide little evidence to support the conclusion that formaldehyde exposure is causally associated with leukemia. Based on the epidemiological evidence and endpoint-by-endpoint analysis, the authors determined there were no lymphohematopoietic cancers or groups of*

lymphohematopoietic cancers for which associations with formaldehyde were found consistently within or across studies.

2. Nasal cancer
    a. Appendix D –
        i. Pg. D-18- "The assessment notes that the assessment is evaluating the extra risk associated with inhaled formaldehyde adding to endogenous concentrations in nasal tissues and is not estimating the risk associated with the endogenous formaldehyde concentration. The revised assessment draft concludes that the background rates of nasal cancers and the background cellular concentration of endogenous formaldehyde are not inconsistent with the draft assessments estimates of the extra risk associated with difference inhaled doses of formaldehyde"

Commented [A19]: 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?

    b. Studies - These recent studies have not been included in EPA's assessment, they were submitted to EPA's docket and should be considered.
        i. 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. *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 N2 - 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 ≥ 6ppm formaldehyde.*
        ii. Marsh, G., Morfeld, P., Collins, J., Symons, JM. (2014). Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. Journal of Occupational Medicine and Toxicology 9, no. 1:1. *Concluded that the link between nasopharyngeal cancer (NPC) mortality and formaldehyde exposure in one of ten factories reported in the 2004 follow-up of the National Cancer Institute (NCI) formaldehyde cohort study was neither consistent with the available data nor with other research findings based on this group of US formaldehyde workers.*
        iii. Marsh, G., Morfeld, P., Zimmerman, S., Liu, Y., and Balmert, L. (2016). An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study." Journal of Occupational Medicine and Toxicology 11, no. 1: 1. *Re-analyzed the mortality risk from nasopharyngeal cancer (NPC) in the updated National Cancer Institute (NCI) formaldehyde worker cohort study and found there was little or no evidence to support NCI's suggestion of a persistent association between formaldehyde exposure and mortality from NPC.*
3. Peer Review Questions

a. Pg. 6 - Formaldehyde is genotoxic in several test systems and operates, at least in part, through a mutagenic MOA. Specifically, a mutagenic MOA was identified in association with the development of nasal (including nasopharyngeal and sinonasal) cancers, while a mutagenic MOA was not identified for other cancer types. The mechanistic evidence was sufficient to conclude that both mutations and cellular proliferation play a role in nasal carcinogenesis

Commented [A20]: It should say "lymphohematopoietic (LHP) cancers" instead of "other cancer types". In addition, a sentence should be added to acknowledge that there is no established MOA for LHP cancers.