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Formaldehyde and Lymphopoietic Cancers

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A 501c3 nonprofit research organization with the mission to ensure that the **best science** is used in making Public Health, Risk Analysis, Policy, and Legal Decisions.



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- How did the EPA determine that inhaled formaldehyde *causes* myeloid leukemia and other blood cancers?
- The reasoning explained and approved by NASEM in their review of the EPA process is that because no biologically plausible mechanism for inhaled formaldehyde to enter the blood or bone marrow has to date been identified, the causal inference can be based on the association evidence found in some epidemiological studies.

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- The Center for Truth in Science put out a call for proposals in 2023 to conduct a State-of –the Science Systematic Review of the literature on the relationship between inhaled formaldehyde and lymphogenic cancers, including myeloid leukemia.
- After a review of applications conducted by independent toxicologists, epidemiologists, and risk analysts, an award was made to a team at Tox Strategies led by Daniele Wikoff and Melissa Vincent, to assess the likelihood of a causal relationship between formaldehyde and LHP cancers , integrating components recommended by NASEM.
- The review was published this past Spring:
M J Vincent, S Fitch, L Bylsma, C Thompson, S Rogers, J Britt, D Wikoff, **Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility**, *Toxicological Sciences*, 2024;, kfae039, <https://doi.org/10.1093/toxsci/kfae039>

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The Center asks EPA to consider the following findings:

- Four experimental rodent bioassays and 16 observational studies in humans were included following the implementation of the a priori protocol (Published on the Center for Open Science in July, 2023 [DOI 10.17605/OSF.IO/2FJAH](https://doi.org/10.17605/OSF.IO/2FJAH))
- All studies were assessed for risk of bias (RoB), and meta analyses were conducted on epidemiological studies, followed by a structured assessment of causation based on GRADE and the Branford Hill criteria..

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- RoB analysis identified systematic limitations precluding confidence in the epidemiological evidence due to inadequate characterization of formaldehyde exposure and a failure to adequately adjust for confounders or effect modifiers suggesting that the effect estimates are likely to be impacted by systematic bias.
- Mixed findings were reported in individual studies.
- Meta-analyses did not identify significant associations between formaldehyde inhalation (when measured as never/ever exposure) and LHP outcomes.
- No associations with LHP-related lesions were reported in reliable animal bioassays
- No biologically plausible explanation linking the inhalation of Formaldehyde and LHP was identified, supported primarily by the lack of systemic distribution and in vivo genotoxicity.

In conclusion

The inconsistent associations reported in a subset of the evidence were not considered causal when integrated with the totality of the epidemiologic evidence, toxicological data, and considerations of biological plausibility.

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Another recent study funded by the Center uses advanced causal analysis methods that are applied in a case study of inhaled Formaldehyde and acute myeloid leukemia.

- Results were presented at the Society for Risk analysis annual meeting in December 2023.
- The article with a description of the methods and findings has recently been published in *Critical Reviews in Toxicology* as open access:

Cox, L. A., Thompson, W. J., & Mundt, K. A. (2024). **Interventional probability of causation (IPoC) with epidemiological and partial mechanistic evidence: benzene vs. formaldehyde and acute myeloid leukemia (AML)**. *Critical Reviews in Toxicology*, 54(4), 252–289.

<https://doi.org/10.1080/10408444.2024.2337435>

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- The causal analysis case study using advanced methods found **no causal pathway** leading from formaldehyde exposure to increased risk for myeloid leukemia.



Thank you!

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