

# TOP TAKEAWAYS

**New systematic review finds no credible explanation for how inhalation of formaldehyde could cause lymphohematopoietic (LHP) cancers**



A team of epidemiologists and toxicologists from the firm ToxStrategies has just released a state-of-the-science systematic review of studies that focus on the relationship between inhaled formaldehyde and lymphohematopoietic cancers (LHP's), including myeloid leukemia. The paper has been accepted for publication in *Toxicological Sciences*, the official journal of the Society of Toxicology.

This new review takes advantage of advances in the field of systematic review methodology to assess the likelihood of a causal relationship between formaldehyde and LHP cancers.

**It found no evidence of systemic delivery of inhaled formaldehyde to bone marrow – where LHP cancers are formed – or blood, following inhalation of formaldehyde. Therefore, causation is unlikely.**

Meanwhile, U.S. EPA and the World Health Organization's cancer research group, The International Association for Research on Cancer, IARC (2018) have concluded that formaldehyde is a cause of LHP cancers. Other groups, including the US National Toxicology Program stop short of doing so.

## DIFFERENT RISK REVIEWS

The reason for the different conclusions between ToxStrategies and EPA is that, although both used systematic reviews, EPA did not use formal integration of evidence, and risk of bias analysis. In addition, ToxStrategies addressed the National Academy of Sciences Engineering and Medicine's (NASEM) review of EPA's formaldehyde analysis (2022). NASEM made 40 recommendations to increase the scientific rigor of their process, particularly concerning the systematic review process, evidence integration and transparency. ToxStrategies both incorporated new studies and included new methodologies that EPA had not used including:

1. Determining the research question a priori (before beginning the search for relevant studies).
2. Making the study protocol publicly available on the Center for Open Science platform to allow transparency and comments from the scientific community before work on the review began.
3. Placing emphasis on rigorous appraisal of epidemiological studies using established criteria including GRADE, Bradford Hill and RoB (Risk of Bias) analysis. and integrating experimental animal and mechanistic evidence with the epidemiology findings to inform the assessment of causality.

Although formaldehyde has been recognized as a carcinogen when humans are exposed at high levels, this systematic review has shown that it cannot be concluded that formaldehyde causes LHP cancers.

### Why It Matters

Formaldehyde is made naturally in the human body and is a by-product of forest fires, cooking and automobile exhaust. It is also widely used in industries such as composite wood products (plywood, pasteboard), embalming fluid, vaccines, medicine, adhesives, paper towels, makeup, insulation, cars, computers, furniture, cabinets and textiles.

Regulatory or legal decisions based on old or weak science can have devastating effects on these industries - including on workers and consumers.

*“The Center for Truth in Science believed a rigorous systematic review of the existing research, using the most advanced methods available, would help resolve discrepancies over the effects of inhaled formaldehyde. And the publication in Toxicological Sciences this week shows it has.”*

*“Daniele Wikoff, Ph.D., and her excellent team of experts on systematic review, toxicology, epidemiology, and formaldehyde, thoroughly assessed the quality of each selected study using scientifically established guidelines, and provided clear answers on what is known about causality, using the most rigorous research protocols.”*

*– Jacob Traverse, President & CEO, Center for Truth in Science*

## RESEARCH METHODS

Methods used in the systematic review of associations between inhaled formaldehyde and lymphohematopoietic cancers:

- The analysis of a causal relationship between inhaled formaldehyde and LHP cancers was completed using systematic review methodology from international recommendations developed by the World Health Organization and the U.S. National Toxicology Program.
  - These included AMSTAR2 (a critical appraisal tool for systematic reviews) as well as both PRISMA-P (protocol reporting checklist) and PRISMA (systematic review and meta-analyses reporting checklist), and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Details related to the assessment methods are described fully in the published paper and its supplementary material.
- The review integrates components recommended to EPA by the National Academies of Science Engineering and Medicine in their August 2023 report.
- An integration of four experimental rodent bioassays and 16 human epidemiological (observational) studies were included after a rigorous quality assessment of all available literature.
- This review follows transparency recommendations in developing its conclusions and demonstrates the importance of appropriately applying critical appraisal tools and considering biological credibility in systematic reviews that look at risk for health effects from exposures.

## Additional Facts and Findings from the Review

The ability of a toxic substance to reach a target tissue is fundamental when assessing the ability of an exposure to cause a health effect. A substantial body of evidence collected over previous decades, and involving increasingly sophisticated and accurate methods, has demonstrated that inhaled formaldehyde does not travel beyond the portal of entry. It does not reach the blood or bone marrow.

Use of modern systematic review methodology to evaluate any causal association between formaldehyde inhalation and potential LHP outcomes offered a robust and rigorous approach to evaluating and summarizing the scientific evidence from multiple data streams – human, animal, and mechanistic studies.

Results from the integration of these three streams found that genotoxicity (which has been theorized in some papers as the way formaldehyde might cause LHP cancers) is not a plausible mode of action for development of LHP cancers following inhalation of formaldehyde by humans.

Inconsistent associations reported in some earlier worker studies (a subset of all available evidence) were not found to be evidence of a causal relationship between formaldehyde exposures and LHPs, when integrated with the total epidemiological evidence (including meta-analyses), toxicological data, and considerations of biological plausibility.

This scientific review was funded by the [Center for Truth in Science](#), an independent non-profit organization dedicated to exploring the intersection of science, justice and the economy.

“This research brings clarity to the ongoing debate and rule-making process around formaldehyde exposure and myeloid leukemia,” said Jacob Traverse, President and CEO of Center for Truth in Science. “The findings of this comprehensive and transparent review should ensure that upcoming decisions will be based on validated science, and produce regulatory decisions that foster innovation, benefit consumers and protect public health.”

The research plan and summary were prepared by Margaret Murray, Ph.D., Research Director of Center for Truth in Science, and performed by a highly qualified group of toxicologists and epidemiologists from April 2023 to November 2023.

To view the full independent systematic review:

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>