

BACKGROUND ON NEW ANALYSES OF FORMALDEHYDE CANCER RISK RESEARCH

Studies reveal critical flaws in results used by regulatory and advisory agencies

Ongoing analyses of raw data from studies widely used by chemical assessment organizations have identified problems with the current cancer-risk estimate for formaldehyde currently under development by the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) and risk assessments previously made by some other advisory groups.

These analyses are part of a growing body of scientific evidence that specifically address National Academy of Sciences (NAS) recommended improvements in the science underlying EPA's formaldehyde assessment. The full weight of evidence from several types of studies -- epidemiological, biological and animal -- fails to support a causal association between formaldehyde exposure and the risk of developing leukemia. The latest in a series of new scientific results aimed at addressing the NAS recommendations was published in the peer-reviewed journal [Critical Reviews in Toxicology \(CRT\)](#).

Understanding biological effects

The newly published study presents a compelling analysis of raw data, recently acquired from the National Cancer Institute (NCI), a part of the U.S. National Institutes of Health, from a study of the biological effects on the blood of Chinese workers occupationally exposed to formaldehyde. The original paper from which the raw data comes, published in January 2010 by Luoping Zhang and 33 co-authors in [Cancer Epidemiology, Biomarkers & Prevention](#), evaluated biological differences -- specifically chromosomal abnormalities and some blood measures -- between formaldehyde-exposed workers and an unexposed group. The original researchers concluded that the biological differences between the groups were likely due to formaldehyde exposure, which heightened the regulatory concern of potential leukemia risk from formaldehyde exposure.

The Zhang *et al.* 2010 study has long been controversial. [Significant flaws were initially pointed out by a group of researchers in 2013](#). In the newly published analysis of the raw data, lead author Kenneth A. Mundt, Ph.D., Health Science Global Practice Network Leader and Director of Applied Epidemiology for Ramboll Environ, and his co-authors, reported the following findings:

- The number of study participants is small, which warrants caution when interpreting the results. The study only included 43 formaldehyde-exposed workers and 51 controls from different industries. Of these, only 10 exposed workers were studied for chromosomal abnormalities and compared to 12 unexposed workers. Moreover, most of the workers were men; only 14 percent were women.
- The analysis of the raw data showed that Zhang *et al.* failed to use the actual measurements of formaldehyde exposure obtained for each of the exposed workers in the original analysis.
- Most importantly, the raw data showed that variations in blood parameters (e.g., counts of different types of blood cells and chromosomal abnormalities) were more correlated with gender and cigarette smoking and not correlated with formaldehyde exposure.
- The evaluated workers were all healthy and free of leukemia at the time of the study. There was no follow up to determine whether any workers later developed leukemia.
- The chromosomal abnormalities appear to arise when sampled blood cells were prepared for analysis in the laboratory -- after the blood had been drawn from the body -- and likely do not represent the condition of the blood cells in the body.

- When evaluating chromosomal abnormalities, the researchers failed to follow their own study protocol designed to ensure a sufficient number of cells within a blood sample were counted to draw valid results. The raw data show the evaluation of most individual samples counted an insufficient number of cells to meet the requirements of the study.

The authors also reviewed other recently published research on the potential health effects of formaldehyde. In combination with these new results, and based on the weight of evidence, Mundt *et al.* concluded that exposure to formaldehyde was unlikely to cause leukemia.

Understanding exposed populations

A previously published analysis of raw data from a population-based, epidemiological study of factory workers by the National Cancer Institute also challenges the conclusions of EPA's IRIS cancer assessment for formaldehyde. The research, published in the *Journal of Occupational and Environmental Medicine* (JOEM), is titled [Formaldehyde Exposure and Mortality Risks from Acute Myeloid Leukemia and Other Lymphohematopoietic Malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries](#). In it, the researchers concluded that there is no epidemiological evidence from the NCI cohort supporting an association between formaldehyde exposure and the risk of leukemia.

The study, conducted by lead author Harvey Checkoway, Ph.D., Professor of Family Medicine & Public Health at the University of California, San Diego, and others, earned the Kammer Merit in Authorship Award from the American College of Occupational and Environmental Medicine (ACOEM). The award recognizes an outstanding scientific contribution published in the academy's journal.

Checkoway and colleagues performed analyses of raw data acquired from NCI to replicate findings reported from a population mortality study of workers from 10 U.S. factories producing or using formaldehyde. This NCI study has been influential in the classification of formaldehyde as a cause of leukemia by the International Agency for Research on Cancer (IARC) and the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program (NTP).

The Checkoway *et al.* analysis disputed the cancer-risk conclusion of the original epidemiology study. Their findings included:

- No clear association between peak or cumulative formaldehyde exposure by the workers and any of the specific lymphohematopoietic malignancies (LHM), including acute myeloid leukemia (AML), the type of cancer most likely to develop from exposure to a carcinogenic chemical.
- The earlier study inappropriately treated acute myeloid leukemia and chronic myeloid leukemia as a single type of leukemia. The two forms are physiologically distinct – CML occurs when the patient makes too many mature white blood cells; AML occurs when the patient makes too many immature white blood cells. Moreover, AML and CML have different causes. CML, for example, is associated with presence of the inherited Philadelphia Chromosome which activates the oncogene *bcr-abl*. AML is associated with a range of other mutations and is the form of leukemia most associated with environmental exposures.

Understanding animal studies

In addition, recent studies conducted by the National Institute of Environmental Health Sciences (NIEHS), also part of the National Institutes of Health, examined leukemia in strains of mice susceptible



to environmental leukemogens (chemicals shown to cause leukemia) and found no increased risk of leukemia from formaldehyde exposure.

Other peer reviewed scientific studies examining how formaldehyde enters and moves through the body clearly have shown that inhaled formaldehyde fumes cannot reach the bone marrow where leukemia develops. A sophisticated series of experiments using radio-labeled formaldehyde demonstrated that inhalation of formaldehyde, even at high concentrations, does not result in detectable levels of environmental formaldehyde reaching the bone marrow.

Taken together, the new lines of evidence published over the past six years, directly challenge any conclusion that formaldehyde exposure causes leukemia.

Regulatory implications

The regulatory implications of the new research are significant. The original studies were used by chemical assessment agencies such as the U.S. Environmental Protection Agency (EPA) and the International Agency for Research on Cancer to classify formaldehyde as a carcinogen. The new research raises serious questions about the accuracy of the original studies and whether they should continue to be relied upon in both existing and future formaldehyde assessments and regulation.

A 2011 peer-review report by NAS recommended improvements in the science supporting EPA's formaldehyde assessment and improvements in the EPA program responsible for producing chemical risk evaluations. There also has been a continual call in the scientific community regarding greater data access to enable other researchers to evaluate and reproduce an original researcher's findings.¹ The newly published results of Mundt *et al.* and Checkoway *et al.* provide further evidence of the importance of data access; until the recent release of the raw data from these studies, it was impossible to adequately evaluate the validity of the original conclusions.

The Mundt *et al.* and Checkoway *et al.* publications and dozens of other studies published since the draft formaldehyde EPA assessment was released in 2010 address many of the criticisms and fill some of the data gaps highlighted by the 2011 NAS peer-review report. Taken as a whole, the current body of scientific evidence shows that exposure to formaldehyde vapors, even in the workplace, does not cause leukemia.

To learn more, visit americanchemistry.com/formaldehyde.

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¹ See for examples:

- <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0020124>
- <http://www.nature.com/news/reproducibility-1.17552>