

TOP TAKEAWAYS

A new systematic review finds a lack of evidence of a clear and consistent relationship between ethylene oxide and stomach, breast, and lymphohematopoietic (LHM) cancers at occupational levels.



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Ethylene oxide is a highly reactive gas primarily used as an intermediate in chemical production and as a sterilant of medical equipment and food products.

This new review sought to answer the key question: what human exposure levels, if any, might increase the risk of cancer from ethylene oxide exposure?

Recent epidemiological studies, and the findings of this new review, have determined a lack of evidence of an association between ethylene oxide and cancer at occupational exposure levels orders of magnitude above expected environmental or general population exposures, even near sterilization facilities.

WHY IT MATTERS

- Ethylene oxide is a gas that has been used in many industries for over a century. It is currently used in the sterilization of personal protective equipment, protective clothing for medical staff, and other medical equipment. This includes stents, catheters, sutures, and wound care devices, adding up to more than 20 billion medical devices sold in the U.S. each year.
- Approximately 50 percent of medical supplies in the United States that require sterilization are done so using ethylene oxide, making it necessary for the protection of first responders and frontline health care workers. Its use in health care can be regarded as essential to life for many patients and health care workers.
- The findings of this new review challenge the findings of previously well-cited reviews. It focused on inhaled ethylene oxide in humans and three types of cancer that were previously noted by the World Health Organization's International Agency for Research on Cancer as being associated with the gas: breast, stomach, and lymphohematopoietic (LHM).
- The findings should help address concerns particularly of those who live nearby or work at the sterilization facilities that use EtO, as well as medical and health care professionals and hospital workers who use products sterilized by the gas. The review does not link EtO at the levels these individuals are exposed to with increased risk for the three cancers.
- This systematic review followed PRISMA guidelines (considered the gold standard for systematic reviews and meta-analyses) and used a hybrid framework drawn from the strongest elements in EPA risk assessment guidelines, combined with frameworks from the Institute of Medicine (IOM) of the National Academy of Medicine. These robust frameworks included:
 - The National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) framework (NTP, 2019)
 - Integrated Risk Information System (IRIS)
 - Toxic Substances Control Act (TSCA)
 - The Office of Pollution Prevention and Toxics (OPPTS) Application of Systematic Review in TSCA Risk Evaluations (EPA, 2018)
 - Guidance from the National Academies of Sciences, Engineering, and Medicine (NASEM)

To view the full systematic review, visit: H. Lynch, J.S. Kozal, A.J. Russell, W.J. Thompson, H.R. Divis, R.D. Freid, E.J. Calabrese, K.A. Mundt, Systematic review of the scientific evidence on ethylene oxide as a human carcinogen, *Chemico-Biological Interactions* (2022), doi: <https://doi.org/10.1016/j.cbi.2022.110031>.

This new systematic review of the literature was recently released in *Chemico-Biological Interactions*, a well-regarded journal of molecular, cellular, and biochemical toxicology. The review was conducted by scientists at Cardno ChemRisk in Boston, MA.

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.

METHODS

- This review adhered to PRISMA guidelines and incorporated the strongest aspects of frameworks developed by the Institute of Medicine (IOM) of the National Academy of Medicine and the U.S. Environmental Protection Agency (EPA) for systematic reviews.
- Study quality was determined based upon the Toxic Substance Control Act (TSCA) framework.
- Three types of studies were explored: human epidemiological studies, experimental animal studies, and mechanistic studies.
- A total of 24 human and animal studies and more than 50 mechanistic studies were identified from the literature search and selection process.

KEY FINDINGS

The review concluded that, according to the IOM classification framework, there was *suggestive evidence*¹ of no association between ethylene oxide and stomach cancer at human relevant exposure levels.

In addition, *limited evidence*¹ was found for no association between ethylene oxide and LHM cancer, due to the very small amount of evidence for specific types of tumors.

In addition, *suggestive evidence*¹ was found for no association between ethylene oxide and breast cancer at human relevant exposures, but conclusions are limited to the conditions, levels of exposure, and length of observation covered by the available studies.

¹ Evidence is suggestive of no association between exposure of a specific agent and a health outcome in humans, but is limited because chance, bias, and confounding could not be ruled out (Institute of Medicine, 2009).

The findings of this systematic review are in alignment with other published reviews (Vincent et al, 2019; Marsh et al, 2019 and Valdez-Flores et al, 2010).

This review identified gaps in the data for the mechanisms of action (i.e., DNA adduct and mutation frequency below levels causing tumors in animals) that can guide future research.

A key question is what human exposure levels might increase the risk of cancer from ethylene oxide exposure that would be able to be seen in epidemiological studies? Recent epidemiological studies have determined a lack of evidence of ethylene oxide's association with cancer at relatively high occupational exposures orders of magnitude above current expected levels of exposure in humans, and should not be a concern. This is a change from earlier studies that is due most likely to better precision in studies after 2000.

Of note, the authors describe in detail in the paper and supplemental materials supplied to the journal, their methods, assumptions, and interpretations so that this work can be verified, replicated, and discussed constructively.