ATSDR Clinician Brief: Ethylene Oxide

Properties

Ethylene oxide (EtO) is a colorless and flammable gas with a sweet, fruity odor at room temperature. It dissolves in water, alcohol, and most water-miscible organic solvents. It has an estimated half-life in air ranging from 69-149 days, while its half-life in water ranges from 12 to 14 days in sterile, deionized, and natural river water. Increased salinity decreases the half-life of ethylene oxide (ATSDR 2020, EPA 2018).

Ethylene oxide is mostly used to produce other chemicals such as ethylene glycol (antifreeze). A small percentage of ethylene oxide is used in the sterilization or fumigation of certain equipment (about 50% of all sterile medical devices), cosmetics, and food (ATSDR 2020, EPA 2018, NTP 2021). Ethylene oxide is highly effective as a sterilant gas where it can penetrate packaging (such as cardboard, shrink wrap, paper, and other wrappings) and destroy bacteria and viruses (ATSDR 2020).

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry

Sources of Ethylene Oxide

- Ethylene oxide is ubiquitous at very low levels in the air. The primary source of this background ethylene oxide is not known.
- Ethylene oxide is naturally occurring in the body, as it is formed from ethylene conversion during metabolic processes.
- Tobacco smoke contains 7 mg of ethylene oxide per cigarette (EPA 2018).
- Ethylene oxide is released into air, water, and soil at places where it is produced or used. The vast majority of ethylene oxide released (>99%) is through air emissions. Release of ethylene oxide to the environment has decreased markedly since 1988 (NTP 2021).
- Occupational sources include factories where ethylene oxide is produced or used to make other chemicals, and facilities performing medical device sterilization or fumigation of foods, clothing, and cosmetics.
- Fumigated foods and sterilized hospital equipment may have initially high levels of ethylene oxide, which dissipate and/or degrade into other products within a few days (ATSDR 2020).

Routes of Exposure

Inhalation is the primary route of exposure to ethylene oxide in both occupational and environmental settings (ATSDR 2020). Inhalation exposure can occur during production or use of ethylene oxide. Because ethylene oxide can be highly reactive and sometimes explosive, the equipment used for its processing generally consists of tightly closed and highly automated systems, which decreases the risk of occupational exposure (NTP 2021).

Workers who make or use ethylene oxide (such as in ethylene glycol production facilities; medical device sterilization facilities, food, and consumer products fumigation plants; hospitals; and farms) could be exposed to ethylene oxide by breathing it in or getting it on skin. Workers generally have higher inhalation and dermal exposures to ethylene oxide than the general public. Workers may be exposed to ethylene oxide during sterilization of a variety of items such as medical equipment and products (e.g., surgical instruments, single-use medical devices), disposable health-care products, pharmaceutical and veterinary products, food, spices, and animal feed. Health-care technicians can be exposed to short, concentrated bursts of the gas when the door of a sterilizing chamber is opened, unless the most modern ethylene oxide sterilizer is utilized to allow a continuous process from sterilization to aeration in the same chamber (ATSDR 2020, IARC 2018, NTP 2021).

The general population's exposure to ethylene oxide occurs primarily via inhalation. However, background ethylene oxide in the air is generally at very low levels; levels may be higher near places where ethylene oxide is produced or used. The general population also may be exposed to ethylene oxide through first and second-hand smoking (ATSDR 2020).

Populations at Risk

Populations at greater risk are those living or working near facilities releasing ethylene oxide, especially for long durations. Additionally, there are populations who may be at greater risk of health effects in general. For example, if a potential exposure in a community setting exists, children may be at a higher risk of health effects due to incomplete development of detoxification pathways, higher respiratory rate, and more opportunities for exposure such as playing outside (ATSDR 2020).

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of a nationally representative sample of the noninstitutionalized U.S. population. Data from NHANES provide a baseline measure of health for the U.S. population and can be used to evaluate chemical exposure. The Centers for Disease Control and Prevention (CDC) analyzed ethylene oxide hemoglobin adducts (a biomarker of ethylene oxide exposure from all sources) in more than 2,500 participants from the 2013-14 and 2015-16 NHANES cycles. The NHANES data indicate that more than 95% of the U.S. population have detectable levels of ethylene oxide hemoglobin adducts in their blood and that adducts levels in cigarette smokers are about 7 times higher than in non-smokers (CDC 2020).

Biological Fate

Ethylene oxide is readily taken up by the lungs and is absorbed relatively efficiently into the blood (Brugnone et al., 1985, 1986). Ethylene oxide is eliminated from the body quickly, with levels dropping by about 50% approximately every 42 minutes. At that rate, almost 90% of ethylene oxide would be eliminated from the body in two hours (EPA 2021). Animal studies showed that ethylene oxide and its metabolites were rapidly excreted in urine. In a study of mice exposed to radiolabeled ethylene oxide for 60–75 minutes, an average of 78% of the absorbed radioactivity was eliminated in the urine within 48 hours (ATSDR 2020).

Health Effects

There are several factors that affect whether ethylene oxide may harm an individual's health. In addition to the route of exposure to ethylene oxide and how much, how long, and how often a person is exposed, general health condition, genetics, age, family history, lifestyle choices, and other environmental exposures may play a role.

SHORT-TERM EXPOSURE

Occupational studies and case reports have reported numerous signs and symptoms from short-term exposure to ethylene oxide. Many of these reports document an ethylene oxide odor so exposures were assumed to exceed the lowest odor threshold of 260 parts per million (ppm) (470 milligram per cubic meter, or mg/m3). Some of the more common harmful effects identified (ATSDR 2018, 2020, NRC 2010) include

- neurological effects (headache, dizziness, nausea, lethargy, fatigue, muscle weakness, numbness, memory loss, incoordination),
- respiratory irritation (irritation of the nasal cavity and sinuses, coughing, shortness of breath, wheezing, and bronchial constriction and hyperreactivity),
- excessive thirst and dry mouth, and gastrointestinal effects (vomiting, diarrhea, stomach spasms - secondary effects due to neurotoxicity rather than a primary effect of inhaled ethylene oxide on the gastrointestinal tract),
- ocular effects (eye irritation) and
- skin rashes.

Animal studies have shown the developing fetus to be sensitive to ethylene oxide exposure. At concentrations similar to those in occupational settings, animal studies have shown low fetal birth weight and increased incidence of dilated renal pelvis and dilated ureter (ATSDR 2020).

All the occupational studies with documented health effects summarized above had high levels of ethylene oxide exposures. Thus, it is unlikely that the non-cancer health effects noted above would occur in the general or nearby worker populations because ethylene oxide exposure is much lower. Even in areas near facilities that release ethylene oxide, ambient outdoor levels are very low compared to occupational levels (ATSDR 2018, 2020).

CHRONIC EXPOSURE

Non-cancer effects

Major effects observed in workers exposed to ethylene oxide at low levels for several years are irritation of the eyes, skin, and respiratory passages and effects to the nervous system (e.g., headache, nausea, memory loss, and numbness [EPA 2018]). Workers exposed to levels of ethylene oxide at 4.7 ppm (8.5 mg/m3) and higher over an average of 5-6.5 years demonstrated cognitive and motor impairment compared to unexposed controls. At lower levels of ethylene oxide exposure (0.08-0.17 ppm) (0.145-0.3mg/m3), studies have shown detection of hemoglobin adducts of ethylene oxide in blood (a biomarker for ethylene oxide exposure), evidence of DNA damage (e.g., sister chromatid exchanges), and hematological effects (e.g., increases in leukocytes and decreases in neutrophil counts; and decreases in hematocrit and hemoglobin) (California EPA, 2008). Exposure at these levels is possible in occupational settings but has not been observed in outdoor air samples in areas near medical sterilization facilities (ATSDR 2018, 2020).

Cancer effects

Occupational studies indicate that humans with long-term (years or decades) cumulative exposure to elevated ethylene oxide concentrations are at increased risk of lymphohematopoietic cancers, including non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia. Studies also show that long-term exposure to elevated ethylene oxide concentrations increases the risk of breast cancer in females. Similar cancers were also found in animal studies.

The most informative epidemiological investigation of ethylene oxide and cancer risk was a study by the National Institute for Occupational Safety and Health (NIOSH) of more than 18,000 employees at 14 commercial sterilization plants where ethylene oxide was used to sterilize medical supplies or food spices (Steenland, et al., 2004). U.S. Environmental Protection Agency's (EPA's) inhalation unit risk (IUR) value for ethylene oxide is used to calculate the potential cancer risks posed by inhalation exposure to ethylene oxide. The EPA inhalation unit risk value for ethylene oxide is based on human data from the NIOSH study on occupational exposure. EPA has calculated an inhalation unit cancer risk estimate of 3×10^{-3}per µg/m^3 (6×10^{-3}per ppb) for ethylene oxide for both cancer types combined (lymphoid cancer and, in females, breast cancer) (EPA 2016).

Although the evidence of carcinogenicity from human studies was deemed short of conclusive on its own, ethylene oxide is characterized as "carcinogenic to humans" by the inhalation route of exposure based on the total weight of evidence, in accordance with the EPA's 2005 Guidelines for Carcinogen Risk Assessment (EPA 2016). In addition, the National Toxicology Program within the U.S. Department of Health and Human Services classifies ethylene oxide as a known human carcinogen (NTP 2016). The International Agency for Research on Cancer (IARC) Working Group concluded that ethylene oxide is carcinogenic to humans (Group 1). They noted limited evidence in humans for a causal association of ethylene oxide with lymphatic and hematopoietic cancers (specifically lymphoid tumors, i.e., non-Hodgkin lymphoma, multiple myeloma, and chronic lymphocytic leukemia), and breast cancer, but sufficient evidence in experimental animals for the carcinogenicity of ethylene oxide (IARC 2018).

Clinical Evaluation

The diagnosis of acute ethylene oxide toxicity is primarily clinical, based on exposure history, symptoms of central nervous system (CNS) depression or irritation, and related physical findings.

TESTS AND IMAGING

Routine laboratory studies for all exposed patients include complete blood count (CBC), glucose, and electrolyte determinations. Depending on the initial evaluation, additional studies for patients exposed to ethylene oxide might include renal function tests and liver function tests. Chest radiography and pulse oximetry (or arterial blood gas [ABG] measurements) should be considered for severe inhalation exposure (Born 2018).

Specific tests for the presence of ethylene oxide in blood or urine generally are not useful for clinical decision making. These tests

- cannot be used to predict if an adverse health effect will occur, or the type or severity of health effects that may result from exposure.
- are not available by most commercial laboratories and not done in a physician's office.
- cannot tell whether the ethylene oxide in the body is from environmental exposure or was naturally produced.

Biomarkers of Exposure

Several biomarkers of exposure have been identified for ethylene oxide. These include the hemoglobin adduct of ethylene oxide hydroxylated N-terminal valine, a DNA adduct, and urinary metabolite, HEMA (S-[2-hydroxyethyl]mercapturic acid).

The hydroxylated N-terminal valine adduct has been widely used as a biomarker of occupational exposure to ethylene oxide. It is not available by commercial laboratories or done in a physician's office. It reflects exposure from all sources (exogenous and endogenous [Kirman 2017]) of ethylene oxide and ethylene and cannot be used to determine a specific source of exposure or length of time an exposure may have lasted. In addition, there is no blood level at which an adverse health effect is expected, and it cannot be used to determine whether an existing or future medical condition, including cancer, could be associated with exposure (ATSDR 2020).

Treatment and Patient Management

There is no antidote to treat ethylene oxide toxicity. Treatment is supportive. Removal from exposure is recommended in all suspected cases. Patients exposed only to ethylene oxide gas who have no skin or eye irritation may be transferred immediately to the hospital for supportive care. Other patients will require decontamination (ATSDR 2001). Standard support for respiratory and cardiovascular functions should be provided as needed (Born 2018).

Non-cancer symptoms related to chronic (inhalation) exposure tend to worsen during exposure and improve when exposure stops, such as during vacation or after a job transfer. If there is no clear association between onset of symptoms and timing of exposure, other causes for symptoms should be considered.

Patient Follow-Up

Because long-term exposure to ethylene oxide may increase the risk of developing lymphoid and breast cancers, patients who are at high risk should have regular preventive cancer screenings recommended by U.S. Preventive Services Task Force (USPSTF 2016). Regular health maintenance visits may help detect abnormalities at an early stage.

Consultation with a specialist in occupational and environmental medicine or others with expertise and experience treating patients exposed to ethylene oxide may help the primary care physician with development of a periodic monitoring plan, as appropriate.

Patient Counseling and Risk Reduction

Patient counseling on the importance of exposure mitigation and ways to reduce exposure risk are prudent along with instructions to consult their physician if concerns about exposure arise.

Patients should be advised to avoid exposures and conditions that might further increase their risk for disease or worsen their existing condition(s). For persons with ethylene oxide toxicity, the level of exposure either must be reduced, or the source eliminated. Depending on the setting, this might be accomplished by using an agent less hazardous than ethylene oxide or increasing air ventilation. Workers using or making ethylene oxide should wear protective eye wear, clothing, gloves, and when needed, respiratory protection.

Based on limited data, there is some evidence that exposure to ethylene oxide can cause a pregnant woman to lose a pregnancy (ATSDR 2020) and medical counseling about this possible risk is recommended.

Patients should be advised to consult their physician if they develop respiratory symptoms, CNS symptoms, or other health changes.

Other Sources of Information on Ethylene Oxide

Please refer to the following online resources for more information on the adverse effects of ethylene oxide, the treatment of ethylene oxide poisoning, and management of persons exposed to ethylene oxide:

ADDITIONAL RESOURCES

- ATSDR Toxicological Profile for Ethylene Oxide
  https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=734&tid=133
- ATSDR ToxFAQs™ for Ethylene Oxide
  https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsDetails.aspx?faqid=733&toxid=133
- ATSDR Community Stress Resource Center
  https://www.atsdr.cdc.gov/stress
- The National Institute for Occupational Safety and Health (NIOSH)
  https://www.cdc.gov/niosh/topics/ethyleneoxide/

CLINICAL RESOURCES

- Pediatric Environmental Health Specialty Units -PEHSUs
  https://www.pehsu.net/
- Association of Occupational and Environmental Clinics
  http://www.aoec.org
- The American College of Occupational and Environmental Medicine
  http://www.acoem.org
- American College of Medical Toxicologists
  http://www.acmt.net
- The American Association of Poison Control Centers
  http://www.aapcc.org

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