Clinician Overview: Ethylene Oxide Transcript

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Clinician Overview of Ethylene Oxide

The findings and conclusions in this presentation have not been formally disseminated by the Agency for Toxic Substances and Disease Registry and should not be construed to represent any agency determination or policy.

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This presentation is designed by the Agency for Toxic Substances and Disease Registry, ATSDR, to familiarize health care providers with ethylene oxide health effects, provide information on identifying and treating patients exposed to ethylene oxide, and share strategies on addressing potential patient concerns.

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At the end of this presentation, participants will be able to, explain the properties of ethylene oxide and its sources in the environment, describe routes of exposure to ethylene oxide, describe populations at risk for ethylene oxide exposure, explain the biological fate and potential health effects from exposure to ethylene oxide, describe clinical evaluation and management of patients exposed to ethylene oxide, describe appropriate follow up of ethylene oxide exposed patients and explain patient counseling and risk reduction strategies.

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To begin, we will discuss the properties of ethylene oxide.

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Ethylene Oxide, or EtO, is produced by catalytically reacting ethylene and oxygen. It is a colorless, flammable, and explosive gas with a sweet, fruity odor at room temperature. It dissolves in water, alcohol, and most 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.

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Ethylene oxide is mostly used to produce other chemicals such as ethylene glycol (for antifreeze). A small percentage of ethylene oxide produced is used in the sterilization or fumigation of certain equipment (particularly medical equipment), cosmetics, and food. EtO 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.

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Next, we will discuss sources of ethylene oxide in the environment.

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Ethylene oxide is ubiquitous at very low levels in the air. The primary source of this background ethylene oxide is not known.

EtO is naturally occurring in the body, as it is formed from ethylene conversion during metabolic processes.

Tobacco smoke contains 7 milligrams of EtO per cigarette.

Ethylene oxide can be released into air, water, and soil at places where it is produced or used. The vast majority of EtO released, over 99%, is through air emissions. Release of EtO to the environment has decreased markedly since 1988.

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Ethylene oxide is formed during the combustion of fossil fuel, but the amount is expected to be negligible.

Occupational sources include factories where EtO is produced or used to make other chemicals, and facilities performing medical device sterilization or fumigation of foods, clothing, and cosmetics.

Some foods and consumer products retain ethylene oxide after fumigation. Fumigated foods and sterilized hospital equipment may have initially high levels of EtO, which dissipate and/or degrade into other products within a few days. Ethylene oxide is naturally occurring in the body, as it is formed from ethylene conversion during metabolic processes.

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Next, we will examine routes of exposure to ethylene oxide.

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Exposure can happen via inhalation or dermal absorption. Individuals who work where ethylene oxide is made or used (such as in hospitals or farms), could be exposed to it by breathing it in or getting it on skin. These workers generally have a higher exposure to EtO than the public. Workers may be exposed to EtO during sterilization of a variety of items such as medical equipment and products, including surgical instruments, single-use medical devices, disposable health-care products, pharmaceutical and veterinary products, food spices and animal feed. Examples of situations in which workers may be exposed include the following: during changing of pressurized ethylene oxide gas cylinders; from leaking valves, fittings, piping, and sterilizer door gaskets; when opening the sterilizer door at the end of a cycle; from improper ventilation at the sterilizer door; from an improperly ventilated or unventilated air gap between the discharge line and the sewer drain; during removal of items from the sterilizer and transfer of the sterilized load to an aerator; from improper ventilation of aerators and aeration areas; from incomplete aeration of items; from inadequate general room

ventilation; and when passing near sterilizers and aerators during operation. Health-care technicians can be exposed to short, concentrated bursts of the gas when the door of a sterilizing machine is opened.

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Inhalation is the primary route of exposure to ethylene oxide in both occupational and environmental settings. The general population may be exposed to EtO through first and second-hand smoking. Inhalation exposure can also occur during production or use of ethylene oxide. Because EtO 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.

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Workers who make or use ethylene oxide, such as in hospitals or farms, could be exposed to EtO by getting it on skin.

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Now, let’s highlight the populations at risk for ethylene oxide exposure.

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General populations at greater risk are those living or working near facilities releasing ethylene oxide, especially for long durations and those 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 chance of exposure, such as playing outside.

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The National Health and Nutrition Examination Survey, or 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. CDC analyzed ethylene oxide hemoglobin adducts, a biomarker of ethylene oxide exposure from all sources, from a random subsample of more than 2500 participants from the 2013-2014 and 2015-2016 NHANES cycles, a statistical summary of the results can be found online. 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.

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Now, we'll learn about biological fate.

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Ethylene oxide is readily taken up by the lungs and is absorbed relatively efficiently into the blood. A study of workers exposed to EtO revealed 20 to 25% of inhaled ethylene oxide that reached the alveolar space was exhaled as the unchanged compound and 75 to 80% was taken up by the body and metabolized. Ethylene oxide is eliminated from the body quickly, with levels dropping by about fifty percent approximately every 42 minutes. At that rate, almost 90% of EtO would be eliminated from the body in 2 hours. 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 to 75 minutes, an average of 78% of the absorbed radioactivity was eliminated in the urine within 48 hours.

There are two major pathways for the elimination of DNA-reactive ethylene oxide: EtO is converted by enzymatic and non-enzymatic hydrolysis to ethylene glycol, which is partly excreted as such and partly metabolized further via glycolaldehyde, glycolic acid and glyoxalic acid to oxalic acid, formic acid and carbon dioxide. It is also converted by

conjugation with glutathione followed by further metabolism to cysteine and N-acetylated derivatives.

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Next, we'll discuss the potential health effects of ethylene oxide exposure. There are several factors that affect whether EtO 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.

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Occupational studies and case reports have reported numerous signs and symptoms from short-term exposure to ethylene oxide. Many of these reports document an EtO odor so exposures were assumed to exceed the lowest threshold of 260 parts per million or 470 milligrams per cubic meter. Some of the more common harmful effects identified include neurological effects, such as headache, dizziness, nausea, lethargy, fatigue, muscle weakness, numbness, memory loss, incoordination. Respiratory effects described include irritation of the nasal cavity and sinuses, coughing, shortness of breath, wheezing, bronchial constriction and hyperreactivity. Excessive thirst and dry mouth have been reported, as have gastrointestinal effects, such as vomiting, diarrhea, and stomach spasms, although the GI effects may be secondary related to neurotoxicity. Ocular effects, such as eye irritation and skin rashes have also been reported with short-term exposures.

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.

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All studies with documented health effects summarized on the previous slide had high levels of ethylene oxide exposure. Thus, it is unlikely that the non-cancer health effects noted would occur in the general or nearby worker populations.

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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, such as headache, nausea, memory loss, and numbness. Workers exposed to levels of EtO at 4.7 parts per million or 8.5 milligrams per cubic meter and higher over an average of 5 to 6.5 years demonstrated cognitive and motor impairment compared to unexposed controls.

At lower levels of ethylene oxide exposure, such as 0.08 to 0.17 parts per million or 0.145 to 0.3 milligrams per cubic meter, studies have shown detection of hemoglobin adducts of ethylene oxide in blood (a biomarker for ethylene oxide exposure), evidence of DNA damage, for example, sister chromatid exchanges, and hematological effects, for example, increases in leukocytes and decreases in neutrophil counts; and decreases in hematocrit and hemoglobin. Exposure at these levels is possible in occupational settings but has not been observed in outdoor air samples near medical sterilization facilities.

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Occupational studies in humans indicates that long-term, meaning years to decades, cumulative exposure to ethylene oxide increases the risk of lymphohematopoietic cancers, including non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia.

Studies also show that long-term cumulative exposure to EtO increases the risk of breast cancer in females. Similar cancers were also found in animal studies.

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The most informative epidemiological investigation of ethylene oxide and cancer risk was a study by the National Institute for Occupational Safety and Health, or NIOSH, of more than 18,000 at 14 commercial sterilization plants where EtO was used to sterilize medical supplies or food spices.

The Environmental Protection Agency's, or EPA's, inhalation unit risk, or IUR, estimates were developed for evaluating the potential cancer risks posed by inhalation exposure to ethylene oxide. The IUR for ethylene oxide is based on human data from the NIOSH study. EPA has calculated an inhalation unit cancer risk estimate of 3×10^{-3} per micrograms per cubic meter or 6×10^{-3}per parts per billion for ethylene oxide for both cancer types combined, lymphoid cancer and, in females, breast cancer.

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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 U.S. EPA's 2005 Guidelines for Carcinogen Risk Assessment. In addition, the National Toxicology Program within the U.S. Department of Health and Human Services classifies EtO as a known human carcinogen.

The International Agency for Research on Cancer Working Group concluded that ethylene oxide is a Group 1 carcinogen to humans. They noted limited evidence in humans for a causal association of ethylene oxide with lymphatic and hematopoietic cancers, specifically lymphoid tumors, such as non-Hodgkin lymphoma, multiple myeloma, and chronic lymphocytic leukemia, and breast cancer, but noted sufficient evidence in experimental animals for the carcinogenicity of ethylene oxide.

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Now let's explore ethylene oxide's mechanism of carcinogenesis. EtO is a highly reactive alkylating agent that reacts with many constituents of tissue resulting in cellular and tissue dysfunction and destruction. Ethylene oxide caused genetic damage in all species studied, including prokaryotic, lower eukaryotic, and in vitro and in vivo mammalian systems. EtO caused gene mutations and heritable translocations in germ cells of rodents exposed in vivo. In occupationally exposed workers, EtO caused dose-related increases in the frequencies of chromosomal aberrations, sister chromatid exchange, hypoxanthine phosphoribosyltransferase gene mutations in peripheral lymphocytes, micronucleus formation in erythrocytes, and DNA single-strand breaks in peripheral mononuclear blood cells. The numerous studies on ethylene oxide that focused on toxicokinetics, DNA-adduct formation, biomarkers, genotoxicity, and molecular biology provide strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, involves a genotoxic mechanism of action. E-P-A concludes that the weight of evidence supports a mutagenic mode of action for EtO toxicity. The direct reaction of ethylene oxide with DNA is thought to initiate the cascade of genetic and related events that lead to cancer.

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Now that we have discussed properties, sources and routes of exposure, populations at risk, and health effects, we will turn to clinical evaluation.

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An exposure history should be taken as part of the patient's history. Taking an exposure history may enable physicians to make more accurate diagnoses, influence the course of disease by stopping current exposure, prevent disease in others by avoiding future exposure, and prompt workplace evaluations and the protection of workers.

An exposure history should include an environmental exposure history and an occupational exposure history. If a temporal association between symptoms and exposure to certain products is suspected, an attempt should be made to identify the specific chemical ingredients involved.

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The medical history should also include assessment of current and past diagnoses or symptoms of respiratory, neurologic, gastrointestinal, and skin disease.

The patient's complaints should be identified in terms of onset, duration, frequency and intensity.

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When performing the physical examination, focus should be on the major organ systems that ethylene oxide exposure is likely to affect, particularly respiratory, central nervous system or CNS, gastrointestinal, and skin.

Because neurologic and respiratory signs and symptoms may not be evident for as long as 72 hours after exposure, patients suspected to have serious exposure should be observed and reexamined periodically. Patients who have bronchospasm or pulmonary edema should be admitted and watched for signs of impending respiratory failure and treated accordingly.

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Routine laboratory studies for all acutely exposed patients (or those with higher occupational exposures) include a complete blood count, or CBC, glucose, and electrolyte determinations. Depending on the initial evaluation, additional studies for these patients might include renal function tests and liver function tests. Chest radiography, pulse oximetry, and arterial blood gas measurements can be considered for severe inhalation exposure

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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, they are not available by most commercial laboratories and not done in a physician's office. They also cannot tell whether the EtO in the body is from low levels of environmental exposure or was naturally produced.

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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 a 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 EtO.

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The hydroxylated N-terminal valine adduct is not available by commercial laboratories or done in a physician's office. It reflects exposure from all sources of ethylene oxide and ethylene, including exogenous and endogenous 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.

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Next, we will describe treatment and follow up of patients exposed to ethylene oxide.

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

Additional recommendations include the following:

Restrict use of alcohol or other CNS depressant medication.

Remove contaminated clothing.

Wash affected areas with mild soap and copious amounts of water.

Move from the contaminated area.

Maintain good ventilation.

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Symptoms related to chronic 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 symptoms and exposure, other causes for symptoms should be considered.

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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. Periodic clinical evaluation 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.

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

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Next, we will discuss aspects of patient counseling and risk reduction.

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Patient counseling on the importance of exposure mitigation and ways to reduce exposure risk would be 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 or conditions. 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 EtO 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 and medical counseling about this possible risk is recommended.

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Additional advice might include the following:

When at home,

Use safer alternatives to products with EtO.

When using products containing EtO, make sure there is plenty of airflow/ventilation by opening all windows and using fans.

Avoid cigarette smoking and exposure to second-hand tobacco smoke.

Use appropriate personal protective equipment, for example, wear a proper respirator or protective gloves, or both, when using products that contain EtO.

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When at work,

Be sure to use the employer supplied personal protective equipment such as gloves, goggles, mask, and respirator as recommended.

Read employer provided safety data sheet or SDS on products that are used. Employers are required by law to provide labeling, an SDS, and safety training on use of chemicals in the workplace as part of the Occupational Safety and Health Administration's, or OSHA's, Hazard Communication Standard.

Be sure that all chemical containers are clearly labeled.

Attend employer provided training on how to use chemicals at work safely.

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To conclude, we will highlight some important takeaways about ethylene oxide.

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Workers who make or use ethylene oxide, could be exposed to EtO by breathing it in or getting it on skin. Workers generally have higher inhalation and dermal exposures to ethylene oxide than the general public.

Evidence in humans indicates that long-term cumulative exposure to ethylene oxide increases the risk of lymphohematopoietic cancers, including non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia, as well as breast cancer in females.

Patient counseling on the importance of exposure mitigation and ways to reduce exposure risk would be prudent along with instructions to consult their physician for concerns about exposure.

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For more information or questions, please contact the Environmental Medicine and Health Systems Intervention Section at ceatsdr@cdc.gov or CDC at 1-800-CDC-INFO (Teletypewriter: 1-888-232-6348) or www.cdc.gov.