

## CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene oxide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of ethylene oxide.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 6.1 INFORMATION ON HEALTH EFFECTS

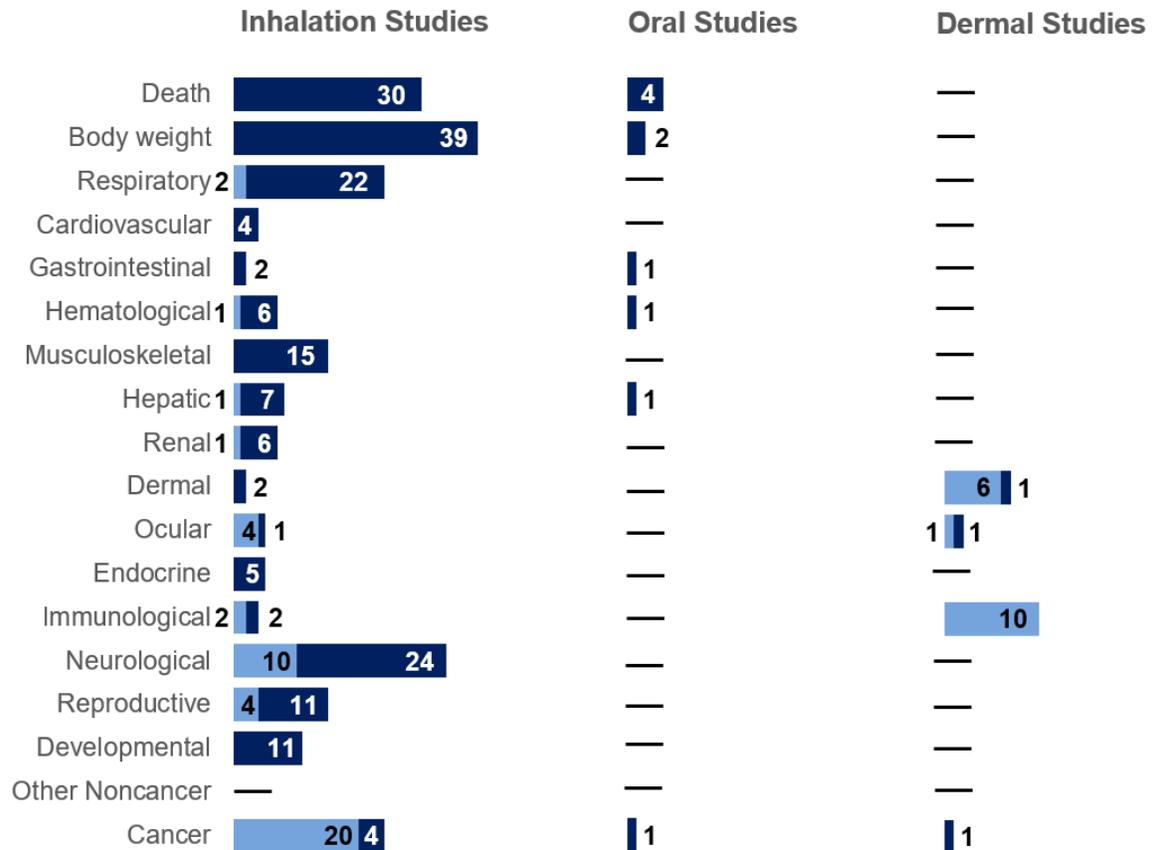
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to ethylene oxide that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of ethylene oxide. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

Most of the information concerning health effects in humans is reported in occupational studies. Cancer was the endpoint most often evaluated in human studies. No human oral studies were located. Human dermal studies evaluated dermal or ocular irritation endpoints and dermal sensitization potential. Most animal studies evaluated the effects of inhalation exposure to ethylene oxide. Body weight, respiratory, neurological, reproductive, and developmental endpoints were the most studied. Limited animal oral data indicated local irritative effects rather than systemic effects. Limited dermal studies in animals confirmed that ethylene oxide as a dermal and ocular irritant.

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**Figure 6-1. Summary of Existing Health Effects Studies on Ethylene Oxide By Route and Endpoint\***

**Potential body weight, neurological, and cancer effects were the most studied endpoints**  
 The majority of the studies examined inhalation exposure in **animals** (versus **humans**)



\*Includes studies discussed in Chapter 2; the number of studies include those finding no effect; many studies examined multiple endpoints

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**6.2 IDENTIFICATION OF DATA NEEDS**

Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

**Acute-Duration MRLs.** The inhalation database was considered adequate for derivation of an acute-duration inhalation MRL for ethylene oxide. An acute-duration inhalation MRL was based on developmental effects (decreased fetal weight) in a study by Snellings et al. (1982a), with supportive data from other studies (Neeper-Bradley and Kubena 1993; NIOSH 1982; Saillenfait et al. 1996). The oral database was not considered adequate for derivation of an acute-duration oral MRL for ethylene oxide. No dose-response data are available for humans. Available oral animal data are restricted to a single study in which 100% mortality occurred in rats treated with ethylene oxide by single gavage dose at 200 mg/kg; treatment at 100 mg/kg did not affect body weight (Hollingsworth et al. 1956). An acute-duration oral study could be designed to examine exposure-response relationships for a comprehensive set of endpoints. However, human oral exposure scenarios resulting in adverse health effects are not likely.

**Intermediate-Duration MRLs.** The inhalation database was considered adequate for derivation of an intermediate-duration inhalation MRL for ethylene oxide. The oral database was not considered adequate for derivation of an intermediate-duration oral MRL for ethylene oxide. No dose-response data are available for humans. Available oral animal data are restricted to a single study in which gavage dosing of rats at 100 mg/kg/day for 15 or 22 treatments in 15 or 30 days resulted in weight loss, gastric irritation, and slight liver damage (not otherwise described); the noncancer NOAEL was 30 mg/kg/day (Hollingsworth et al. 1956). An intermediate-duration oral study could be designed to examine exposure-response relationships for a comprehensive set of endpoints. However, human oral exposure scenarios resulting in adverse health effects are not likely.

**Chronic-Duration MRLs.** The inhalation database was considered inadequate for derivation of a chronic-duration inhalation MRL for ethylene oxide. No adequate exposure-response data were available for humans. The animal inhalation database was limited to studies that were considered inadequate for MRL derivation due to various reasons, not limited to lack of information on nonneoplastic effects and/or inability to assess exposure-related effects due to a concurrent colony infection. Well-controlled, chronic

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inhalation studies in healthy animals evaluating a comprehensive set of nonneoplastic endpoints at concentrations below those associated with cancer could be useful. The oral database was not considered adequate for derivation of a chronic-duration oral MRL for ethylene oxide. No dose-response data are available for humans. Available oral animal data are restricted to a single study in which gavage dosing at 30 mg/kg/day, 2 times/week for up to 150 weeks resulted in decreased survival; forestomach squamous cell carcinoma (at the oral gavage application site) was reported at 7.5 mg/kg/day (Dunkelberg 1982). A chronic-duration oral animal study could be designed to evaluate a comprehensive set of endpoints. However, human oral exposure scenarios resulting in adverse health effects are not likely.

**Health Effects.**

***Hematological effects.*** Ethylene oxide has been shown to affect the hematological system in animals exposed via inhalation. The effects on the hematological system appear to have been adequately addressed. Additional animal studies are not necessary at this time. However, ethylene oxide-exposed human populations should be monitored for possible exposure-related hematological effects.

***Endocrine effects.*** One acute-duration inhalation study reported adrenal gland effects at an exposure level of 841 ppm. Adrenal gland effects were reported in a 2-year rat study, but the animals were compromised by a pulmonary infection at times. Additional evaluation of ethylene oxide exposure-related adrenal gland effects is needed. Ethylene oxide-exposed human populations should be monitored for possible exposure-related effects on the endocrine system.

***Neurotoxicity.*** Ethylene oxide exposure has resulted in clinical signs of neurotoxicity in both occupational cohort studies and animal studies. The human data are based on very limited case studies. In animals, acute- and intermediate-duration inhalation studies have adequately assessed neurotoxicity. Additional studies should be designed to evaluate mechanisms of ethylene oxide neurotoxicity.

***Reproductive toxicity.*** Limited human data indicate that occupational exposure to ethylene oxide may result in effects such as increased spontaneous abortions. Available animal studies indicate that inhaled ethylene oxide may cause effects such as decreases in numbers of implantations, testicular weight, and sperm production, and testicular degeneration. An additional animal study employing the inhalation exposure route should be designed to

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comprehensively evaluate the potential of ethylene oxide to affect reproductive function. Additional studies of human populations and animals could improve confidence in exposure-response relationships for reproductive effects.

**Epidemiology and Human Dosimetry Studies.** Most of the available information on the adverse effects of ethylene oxide in humans comes from occupational studies of workers exposed during ethylene oxide production and/or related to its uses in sterilization. Limitations include unquantifiable exposure levels and durations, exposures to other potentially hazardous substances, small sample sizes, and/or small numbers of workers exhibiting selected adverse effects (particularly cancer endpoints). Additional occupational cohorts should be evaluated for ethylene oxide exposure-related health effects; reliable historical exposure levels should be determined for these cohorts. Also, epidemiological studies should be conducted in communities located near facilities releasing ethylene oxide to the atmosphere. The ethylene oxide NIOSH cohort is continuing to be followed.

**Biomarkers of Exposure and Effect.** Several biomarkers have been identified for ethylene oxide. Ethylene oxide levels in blood and alveolar air are used as biomarkers of exposure. Ethylene oxide forms adducts with macromolecules, such as DNA and hemoglobin; detection of these adducts can be used as a biomarker of effect, even in the absence of adverse effects. The primary DNA adduct formed is 7-HEG. The ethylene oxide hemoglobin adduct, HOEtVal, has been widely used as a biomarker for ethylene oxide. Additional data on the biomarkers of effect, particularly HOEtVal, would be valuable for animal to human dose extrapolation.

**Absorption, Distribution, Metabolism, and Excretion.** Toxicokinetic properties of inhaled ethylene oxide have been widely evaluated in animal models and, to a lesser extent, in humans. However, additional studies on the half-life of ethylene oxide in blood would be helpful for interpreting biological monitoring and for designing future exposure and epidemiological studies. Additional studies could be designed to evaluate the toxicokinetics of ethylene oxide following oral and dermal exposure. However, the oral exposure route for ethylene oxide is not of particular human concern.

**Comparative Toxicokinetics.** Similarities and differences in toxicokinetic properties of ethylene oxide have been studied across species, particularly among rats, mice, and humans. PBPK models have been developed to predict the internal dose metrics of inhaled ethylene oxide (Csanady et al. 2000; Fennell and Brown 2001; Filser and Klein 2018a, 2018b; Krishnan et al. 1992; NIOSH 1987). The

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proximal toxicant(s) responsible for ethylene oxide-induced noncancer effects (e.g., neurological effects) should be identified in order to apply PBPK modeling to derivation of MRLs for ethylene oxide.

**Children's Susceptibility.** No data were located regarding age-related differences in susceptibility to ethylene oxide toxicity or carcinogenicity. However, very young children with incomplete development of detoxification pathways that are known to metabolize ethylene oxide might be at increased susceptibility to ethylene oxide exposure-related effects. Additional studies are needed to assess possible age-related toxicokinetic differences.

**Physical and Chemical Properties.** Ethylene oxide is commonly used in the synthesis of many other products, and its basic physical and chemical properties are well known and documented (see Chapter 4). However, limited data exist on the properties related to its fate in the environment. For example, there are no recent studies that verify the degradation rates of ethylene oxide in environmental media, and many current studies simply reiterate data from past studies.

**Production, Import/Export, Use, Release, and Disposal.** Available production, use, release, and disposal data indicate that most ethylene oxide manufactured in the United States is consumed in the synthesis of other chemicals. However, aside from noting that the primary mechanism of release of ethylene oxide to the atmosphere is through sterilization and fumigation practices, current quantitative data on the amounts of ethylene oxide released to the environment during ethylene oxide production and use are sparse. This information would be helpful in evaluating the effect of industrial practices on environmental levels of ethylene oxide.

**Environmental Fate.** Data on the fate of ethylene oxide in the atmosphere are limited. The half-life estimates of this chemical should be updated. Historical data on the fate of ethylene oxide in the water environment are available but are very limited, and current studies were not found. More information is needed on the rates of transport of ethylene oxide between water and air. Also, more data on the rates of biodegradation of ethylene oxide in natural environments such as lakes, rivers, groundwater, and soil are needed. Data on the fate of ethylene oxide in the soil environment would be useful. Because all of the ethylene oxide that does not degrade in the atmosphere eventually returns to the soil and water, data on transport and degradation of ethylene oxide would be helpful in determining its potential contamination of water supplies. Many studies rely on outdated estimates for fate and transport of ethylene oxide in environmental media. Current experimental data are needed to better understand the fate and transformation of ethylene oxide in water, soil, air, and biota.

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**Bioavailability from Environmental Media.** Ethylene oxide has been shown to be absorbed following inhalation of contaminated air. However, there are no data on absorption after oral or dermal administration of this compound. No information was located on the bioavailability of ethylene oxide from contaminated water, soil, or plant material. These data would be useful in determining potential exposure levels for organisms (humans, animals, and plants) that may have contact with ethylene oxide in these media.

**Food Chain Bioaccumulation.** WHO (1985) concluded that ethylene oxide will not bioaccumulate in animals since it is readily metabolized via hydrolysis and glutathione conjugation and excretion. This conclusion was based on the review of several studies in both humans and animals (terrestrial and marine species). No data are available in the literature that indicate that ethylene oxide bioaccumulates in plants, although estimates based on the low log  $K_{ow}$  indicate that bioaccumulation is not expected. Research on the possible mechanisms of plant uptake, absorption, and assimilation of ethylene oxide would be useful since it may be a common and natural constituent in the soil environment, as discussed in Section 5.5.3, and because it is also an atmospheric pollutant.

**Exposure Levels in Environmental Media.** Little recent environmental monitoring data were found for ethylene oxide in soil, air, or water. Ambient concentrations of ethylene oxide in high density urban and industrial areas that have potentially large sources of ethylene oxide would be helpful in determining the ambient concentrations of ethylene oxide so that exposure estimates can be made for the general population. Additionally, monitoring data from rural and/or remote locations would provide valuable information on background levels.

**Exposure Levels in Humans.** Available data indicate that some work environments provide exposure to ethylene oxide at levels that may exceed OSHA regulations. While the majority of the monitoring data found were for sterilization facilities, data on other industrial workers such as building and agricultural fumigators, construction workers, and the general population located near sources of ethylene oxide would be useful. Estimates of the exposure levels of the general population would also be helpful. Further development and refinement of models to extrapolate blood-adduct levels to external exposure levels would be helpful to advance the use and interpretation of biomarker data.

**Exposures of Children.** There are limited data available that specifically measured environmental exposures of ethylene oxide to children; the 2013–2014 and 2015–2016 NHANES measured ethylene

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oxide hemoglobin adducts in children aged 6–11 and 12–19 years (CDC 2022). Additional monitoring data would be useful, particularly in younger children and infants.

**6.3 ONGOING STUDIES**

Relevant ongoing studies on ethylene oxide are identified by search of the NIH RePorter database. This database lists ongoing studies that are sponsored by the National Institutes of Health. A search of this database in 2021 (RePORTER 2021) identified the following study.

Mark L. Rubenstein, M.D., of the University of California, San Francisco, is evaluating the levels of toxicants, including ethylene oxide, in adolescent users of electronic nicotine delivery systems.

In addition, the NIOSH cohort of sterilization workers continues to be evaluated. Earlier evaluations of this cohort are provided in Steenland et al. (1991, 2003, 2004).