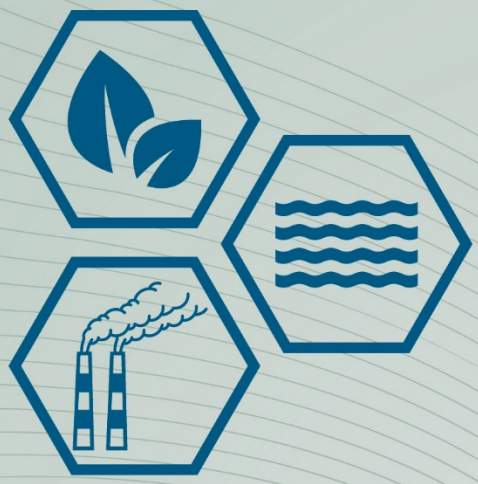

Toxicological Profile for Ethylene Oxide

August 2022

ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
August 2022	Final toxicological profile released
September 2020	Draft for public comment toxicological profile released
December 1990	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Ethylene oxide is a flammable gas with a sweet odor. It dissolves easily in water, alcohol, and most organic solvents. Ethylene oxide is produced in large volumes and is primarily used to make other chemicals, particularly ethylene glycol, a chemical that is used to make antifreeze and polyester. Most ethylene oxide is used in the factories where it is produced. A small amount is used to control insects on stored agricultural products, to sterilize food and cosmetics, and in hospitals and factories to sterilize medical equipment and supplies. The U.S. Environmental Protection Agency (EPA 2008) Registration Eligibility Decision document (RED) indicates that approximately 1,900 hospitals in the United States have ethylene oxide sterilization chambers.

When ethylene oxide is produced or used, some of the gas is released to air and water. In the environment, ethylene oxide is broken down by several types of reactions, including oxidation, hydrolysis, and biodegradation (breakdown by bacteria). In air, the most likely degradation pathway is oxidation via free-radical formation. Estimated half-lives of degradation of ethylene oxide in air vary widely, from approximately 1 month to >1 year. Ethylene oxide in water is broken down more quickly than in air, with hydrolysis and biodegradation as the main pathways. For most degradation pathways in water, estimated half-lives range from a few hours to <15 days, depending on environmental conditions. Ethylene oxide can also evaporate from water into air.

You are not likely to be exposed to high levels of ethylene oxide in the general environment; low levels of ethylene oxide have been measured in the air in many areas of the United States. There is no evidence that ethylene oxide is commonly found in water. The most likely way to be exposed to ethylene oxide is by working where it is used or produced. Heath care workers, such as nurses, doctors, and technicians in hospitals and offices may contact ethylene oxide, as it is used to sterilize medical equipment. Factory workers where ethylene oxide is produced or used to make other chemicals, and those working in sterilization facilities, may have contact with ethylene oxide. Residents living near facilities producing or using ethylene oxide may also be exposed to higher levels of ethylene oxide than people who do not live near these facilities.

The U.S. Environmental Protection Agency (EPA) has determined that there is reasonable certainty that dietary and drinking water risks from supported registered uses of ethylene oxide will not harm any

population subgroup (EPA 2006). Levels of ethylene oxide decrease with time as ethylene oxide evaporates or breaks down into other substances, and thus, little or none may remain when the food is eaten.

Ethylene oxide is produced in the body from oxidation of ethylene, and biological processes producing endogenous ethylene have been identified, such as lipid peroxidation, methionine and heme oxidation, and metabolic activity of intestinal bacteria. The contribution of these processes to internal levels of ethylene or ethylene oxide has not been directly quantified.

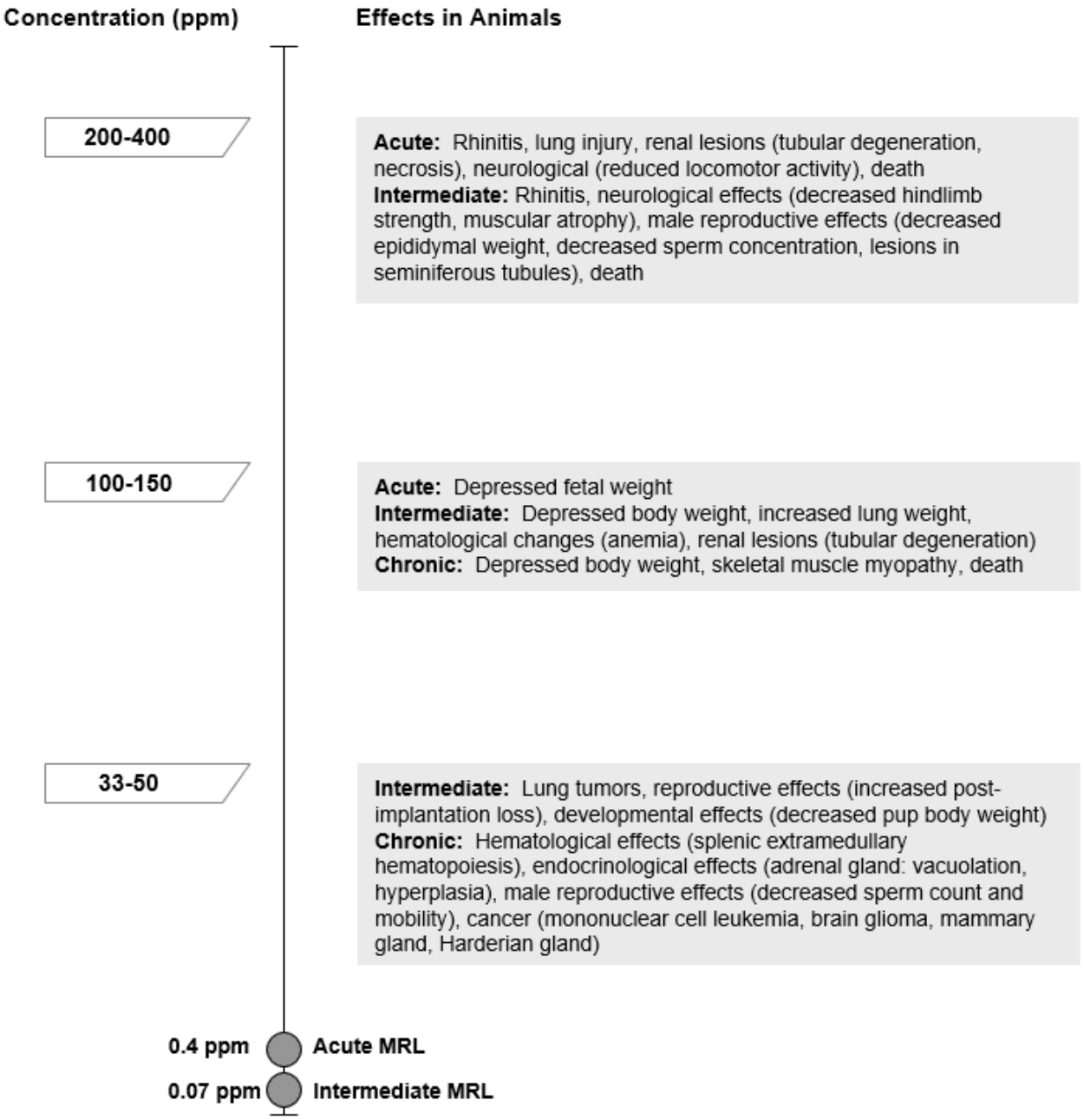
1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity and carcinogenicity of ethylene oxide comes from epidemiological studies and studies conducted in experimental animals. Most human studies evaluated only cancer endpoints in workers; inhalation is likely to have been the predominant route of exposure to ethylene oxide in these populations. These studies evaluated the carcinogenicity of inhaled ethylene oxide in cohorts involved in ethylene oxide production and/or workers in areas where ethylene oxide was used as a sterilizer. Information on noncancer health effects primarily comes from experimental animal studies. Nearly 90% of the animal studies employed the inhalation exposure route. The limited information available regarding ethylene oxide toxicity following dermal exposure suggests that it is a contact dermal and ocular irritant in humans and animals. As illustrated in Figures 1-1 and 1-2, the most sensitive noncancer targets of ethylene oxide toxicity appear to be hematological, endocrine, neurological, reproductive, and developmental endpoints; cancer effects also occur at lower exposure levels.

A systematic review of noncancer endpoints (see Appendix C for details) resulted in the following hazard identification conclusions:

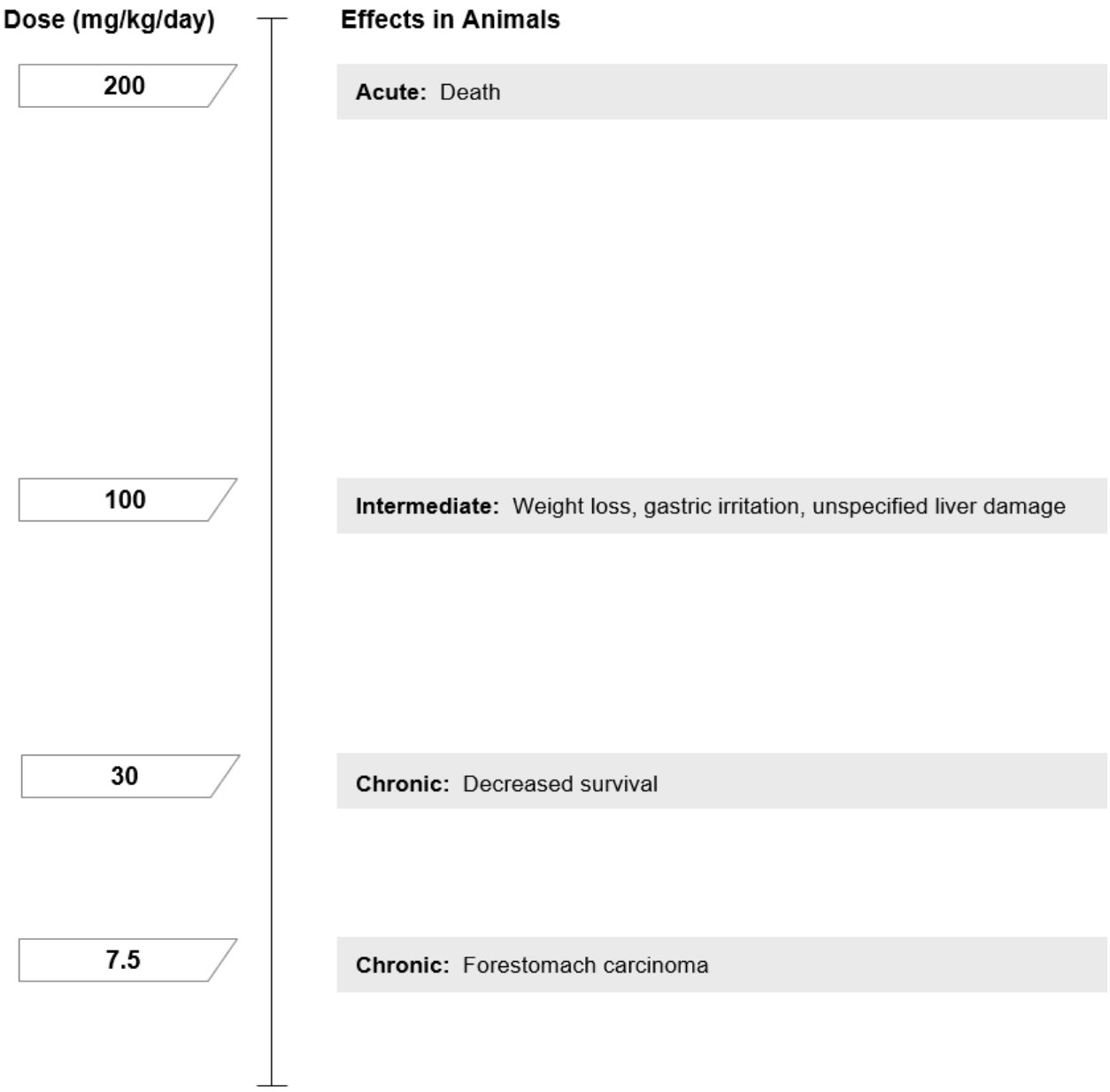
- Respiratory effects represent a presumed health effect endpoint for humans
- Hematological effects represent a suspected health effect endpoint for humans
- The endocrine system is a suspected health effect endpoint for humans
- Neurotoxicity is a presumed health effect for humans
- Reproductive toxicity is a presumed health effect for humans
- Developmental toxicity is a presumed health effect for humans

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Ethylene Oxide



*No chronic-duration inhalation MRL was derived for ethylene oxide.

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Ethylene Oxide*



*No oral MRLs were developed for ethylene oxide.

Respiratory Effects. Bronchitis, pulmonary edema, and emphysema have been reported in workers after acute-duration high-level exposure (Thiess 1963), but respiratory problems have not been reported to occur with relatively low-level chronic-duration exposure (estimated long-term average of 5–10 ppm) (Joyner 1964). Adverse respiratory effects such as labored breathing, nasal discharge, dyspnea, histopathologic pulmonary lesions, rhinitis, and/or pulmonary edema were observed in multiple animal species exposed to 113–841 ppm ethylene oxide vapor once or intermittently for up to 2 years (Hollingsworth et al. 1956; Jacobson et al. 1956; NTP 1987).

Hematological Effects. Decreases in hemoglobin, hematocrit, erythrocyte count, packed cell volume, and/or increased reticulocytes were reported in experimental animals (rats, mice, dogs) repeatedly exposed to ethylene oxide vapor at 250–500 ppm for 6–13 weeks (Fujishiro et al. 1990; Jacobson et al. 1956; Snellings et al. 1984a). One study reported splenic extramedullary hematopoiesis in rats repeatedly exposed at 50 or 100 ppm for 104 weeks and noted splenic focal fibrosis at 100 ppm; however, findings are confounded by a concurrent infection in the rat colony (Lynch et al. 1984a, 1984b).

Endocrine Effects. Pale coloration and enlargement of adrenals, and numerous fat vacuoles in the adrenal cortex were reported in rats and guinea pigs exposed two or three times to ethylene oxide vapor at 841 ppm for 7 hours per exposure (Hollingsworth et al. 1956). One study reported multifocal cortical vacuolation and hyperplasia in adrenal glands in rats intermittently exposed to ethylene oxide vapor at 50 ppm for up to 104 weeks; however, findings are confounded by a concurrent infection in the rat colony (Lynch et al. 1984a, 1984b).

Neurological Effects. Central nervous system effects are frequently associated with human exposure to ethylene oxide in occupational settings. Headache, nausea, and vomiting have been reported for >50 years (Blackwood and Erskine 1938; Sexton and Henson 1949; von Oettingen 1939). Reliable exposure levels are generally not available in these cases. Peripheral neuropathy, impaired hand-eye coordination, and memory loss have been reported in case studies of chronically-exposed workers (Crystal et al. 1988; Estrin et al. 1987; Kuzuhara et al. 1983; Zampollo et al. 1984) at estimated average exposure levels as low as 3 ppm (with possible short-term peaks as high as 700 ppm).

In studies using several animal species (monkeys, rats, mice, rabbits) at moderately high levels of ethylene oxide (200–375 ppm) for 6–7 months, hind leg paralysis and atrophy, abnormal knee and extensor reflexes, and diminished pain perception were reported (Hollingsworth et al. 1956). An 8-month exposure to 250 ppm resulted in distal axonal degeneration of myelinated fibers in both sural nerves and

gracile fascicles in rats (Ohnishi et al. 1986). Chronic exposures to ethylene oxide at 100 ppm resulted in demyelination in the brain of monkeys (Lynch et al. 1984a). This result raises concerns that similar morphological effects may occur in humans.

Reproductive Effects. Limited human data are available. Possible associations between exposure to ethylene oxide and spontaneous abortion have been explored in epidemiological studies of sterilizer workers (Gresie-Brusin et al. 2007; Hemminki et al. 1982; Rowland et al. 1996). Limitations in these studies preclude drawing conclusions regarding the associations between ethylene oxide exposure and pregnancy outcomes. In laboratory animals, inhalation exposure to ethylene oxide was associated with adverse male reproductive effects such as decreases in male reproductive organ weights, germ cell survival, and sperm count, as well as histopathologic lesions (Hollingsworth et al. 1956; Kaido et al. 1992; Lynch et al. 1984a; Mori et al. 1991a, 1991b). Decreased numbers of implantation sites and increased resorptions have been reported in studies of ethylene oxide-exposed rats (NIOSH 1982; Snellings et al. 1982b).

Developmental Effects. No data on potential human developmental effects of ethylene oxide exposure have been located. However, embryo and fetal toxicity were reported in the offspring of rats exposed to 100–150 ppm during gestation; the neonates were smaller in both length and weight and had reduced ossification of the skull and sternebrae (Neeper-Bradley and Kubena 1993; NIOSH 1982; Snellings et al. 1982a). Decreases in pup body weight and increases in post-implantation losses were observed in rats at 33 ppm (EPA 1994). Therefore, the offspring of humans exposed to ethylene oxide may be at risk for fetal and embryo toxicity.

Cancer. The carcinogenicity of ethylene oxide has been evaluated in a number of cohorts (ethylene oxide production and/or uses in sterilization) (Bisanti et al. 1993; Coggon et al. 2004; Hogstedt 1988; Hogstedt et al. 1986; Kiesselbach et al. 1990; Mikoczy et al. 2011; Morgan et al. 1981; Norman et al. 1995; Olsen et al. 1997; Steenland et al. 2003, 2004; Swaen et al. 2009; Wong and Trent 1993). Results of several studies show associations between exposure to ethylene oxide and increased risk of selected cancer types (e.g., lymphohematopoietic cancer, leukemia, breast cancer).

In laboratory animals exposed by inhalation, ethylene oxide was associated with a variety of cancer types (leukemia, mesotheliomas, lymphomas, tumors of lungs, brain, Harderian gland, and female mammary gland and reproductive organs) (Lynch et al. 1984a, 1984b; NTP 1987; Snellings et al. 1984b).

Forestomach cancer (at the application site) was reported in rats administered ethylene oxide by gavage (Dunkelberg 1982).

The Department of Health and Human Services (HHS) has classified ethylene oxide as *known to be a human carcinogen* (NTP 2016). The EPA characterized ethylene oxide as "carcinogenic to humans" by the inhalation exposure route (EPA 2016). The International Agency for Research on Cancer (IARC) has designated ethylene oxide as *carcinogenic to humans (Group 1)* (IARC 1987, 2012).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of acute- and intermediate--duration inhalation MRLs for ethylene oxide. The database was not considered adequate for derivation of a chronic-duration inhalation MRL. As presented in Figure 1-3, the available inhalation data for ethylene oxide suggest that hematological, endocrine, reproductive, and developmental endpoints are sensitive targets of toxicity following inhalation exposure.

The oral database was not considered adequate for derivation of acute-, intermediate-, or chronic-duration oral MRLs.

The MRL values for ethylene oxide are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Ethylene Oxide – Inhalation

Hematological, endocrine, reproductive, and developmental endpoints are the most sensitive noncancer targets of ethylene oxide inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no exposure-response human data were identified.

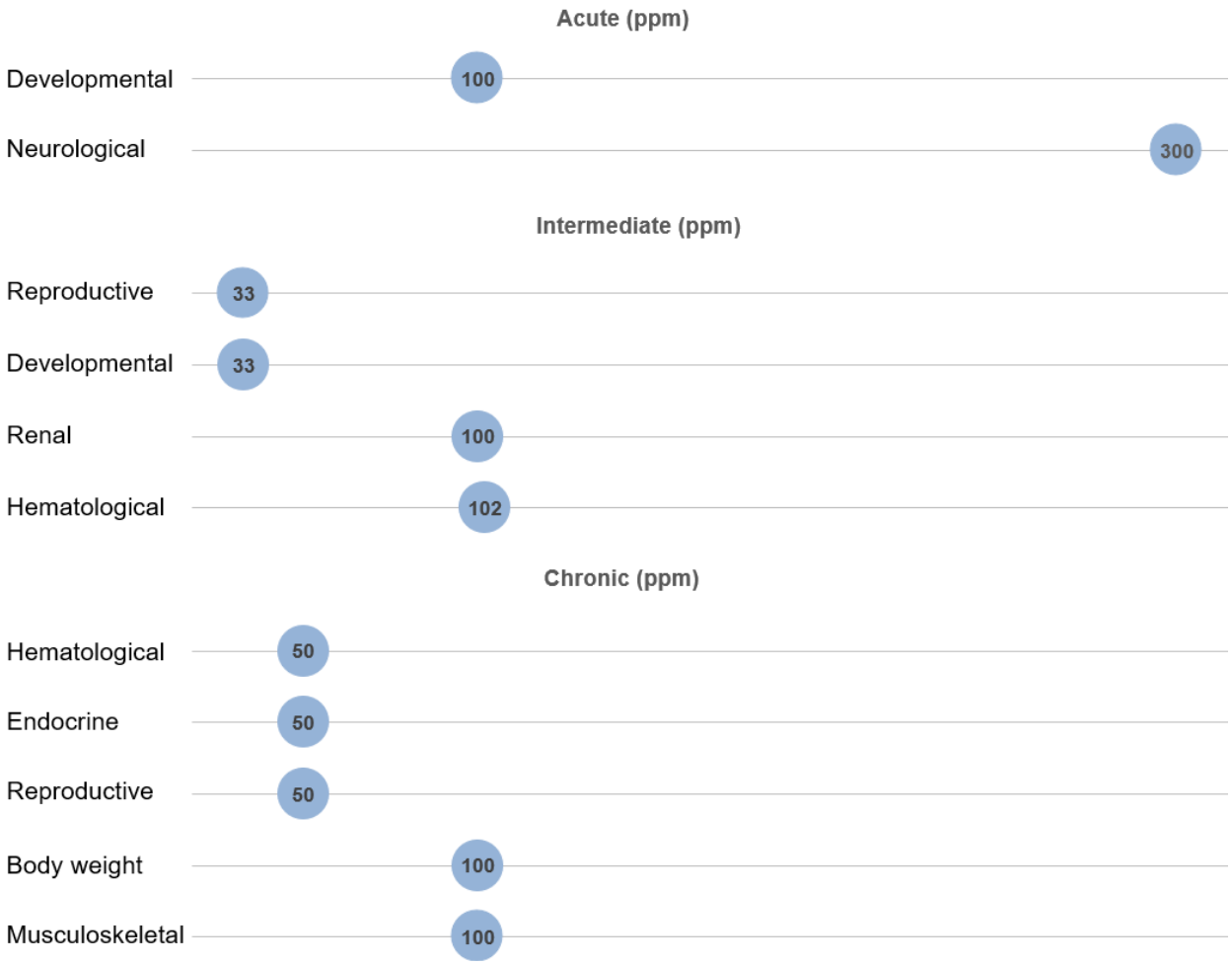


Table 1-1. Minimal Risk Levels (MRLs) for Ethylene Oxide[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factors	Reference
Inhalation exposure (ppm)					
Acute	0.4	Depressed fetal weight	$BMCL_{RD05}$: 45.50 ($BMCL_{HEC}$: 11.38)	UF: 30	Snellings et al. 1982a
Intermediate	0.07	Decreased male pup weight	NOAEL: 10 ($NOAEL_{HEC}$: 2.1)	UF: 30	EPA 1994
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

BMCL = 95% lower limit of benchmark concentration; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; RD05 = dose associated with a 5% relative deviation from control; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of ethylene oxide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to ethylene oxide, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to ethylene oxide was also conducted; the results of this review are presented in Appendix C.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; limited dermal data were identified for ethylene oxide.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant

dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of ethylene oxide are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of ethylene oxide have been evaluated in a number of occupational cohorts and a variety of animal studies. As illustrated in Figure 2-1, the inhalation exposure route was employed in the majority of animal studies; inhalation was assumed to be the predominant exposure route in the occupational cohort studies. The most examined endpoints in animal studies were body weight and neurotoxicity. Cancer was the most examined endpoint in epidemiological studies.

Human and/or animal studies suggest that relatively sensitive noncancer targets of ethylene oxide include respiratory, hematological, endocrine, neurological, reproductive, and developmental endpoints (see Appendix C for more information on the systematic review and for definitions of evidence levels). Human and animal studies have also reported carcinogenic effects.

- **Respiratory Endpoints:** Respiratory effects are a presumed health effect for humans based on a moderate level of evidence in workers and a high level of evidence in experimental animal studies. Compromised respiratory function has been reported in workers exposed to high levels of ethylene oxide. Inhalation studies in experimental animals have reported several respiratory effects including labored breathing, nasal discharge, pulmonary lesions, rhinitis, and pulmonary edema.

- **Hematological Endpoints:** Hematological effects are a suspected health effect for humans based on a moderate level of evidence in animal studies. Repeated exposure of experimental animals to ethylene oxide vapor has resulted in hematological effects such as decreases in hemoglobin, hematocrit, erythrocyte count, packed cell volume, and/or increased reticulocytes.

- **Endocrine Endpoints:** Adrenal gland effects are a suspected health effect in humans based on a moderate level of evidence in animal studies. Adverse effects (gross and/or histopathologic changes in the adrenal gland) have been observed in guinea pigs following acute- and/or chronic-duration exposure to ethylene oxide vapor.

- **Neurological Endpoints:** Neurological effects are a presumed health effect in humans based on a low level of evidence in occupational exposure studies and a high level of evidence in animal studies. Clinical signs of neurotoxicity (e.g., neuropathy, weakness in extremities, impaired hand-eye coordination, cognitive dysfunction, memory loss, headache, lethargy) were reported among workers exposed to ethylene oxide for various durations. Sural nerve biopsies revealed axonal degeneration and regeneration in two studies. Neurological effects such as ataxia, impaired sensory reflexes, hindlimb paralysis, and/or degenerative histopathologic lesions have been observed among laboratory animals exposed to ethylene oxide by inhalation.

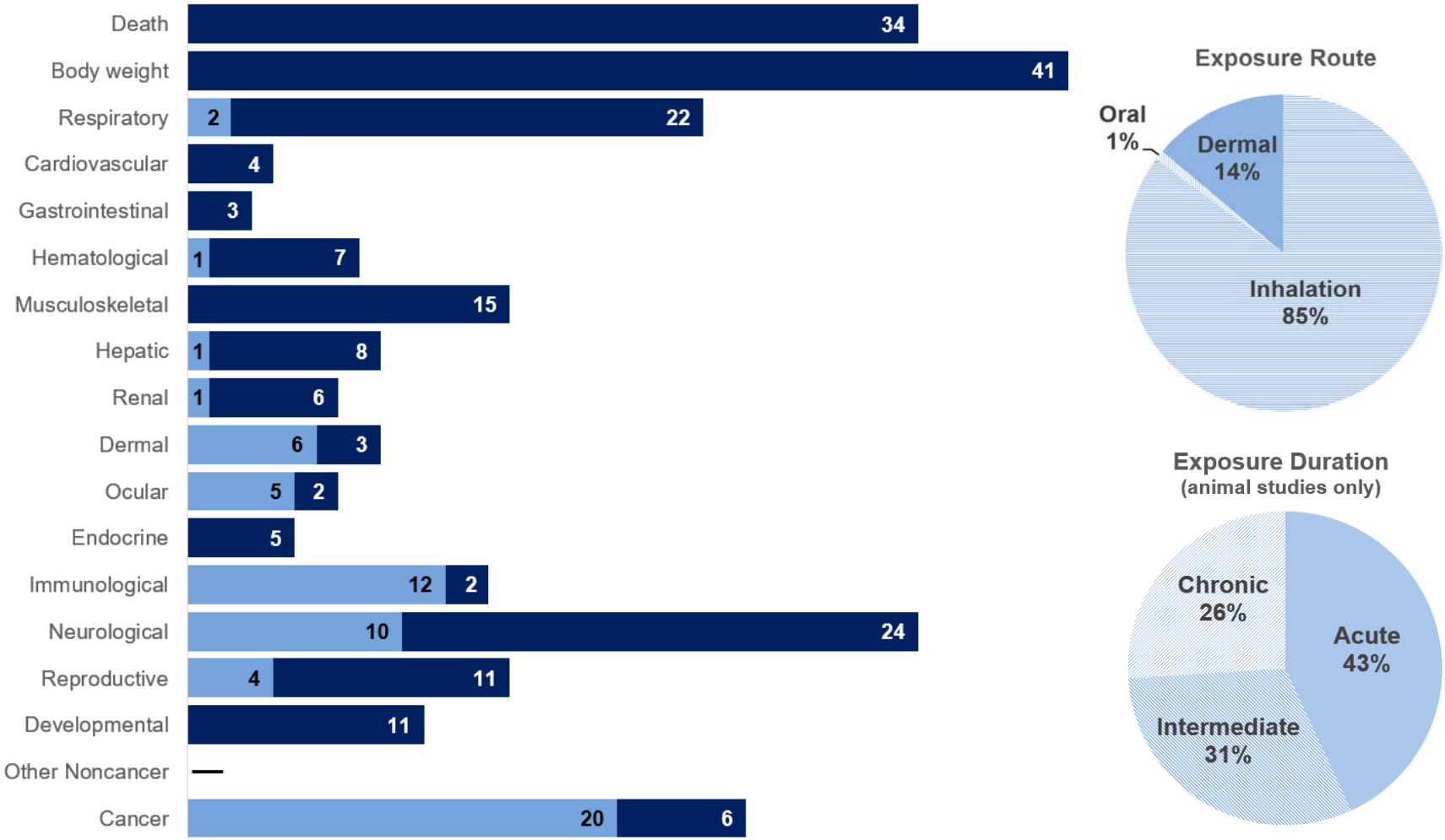
- **Reproductive Endpoints:** Male reproductive effects are a presumed health effect in humans based on a high level of evidence in animal studies. Animal studies provide convincing evidence of ethylene oxide-induced effects on the male reproductive system (e.g., decreases in male reproductive organ weights, germ cell survival, and sperm count; histopathologic lesions).

- **Developmental Endpoints:** Ethylene oxide is a presumed developmental toxicant in humans based on animal studies that demonstrated ethylene oxide-induced developmental effects such as depressed fetal weight, delayed ossification, fetal fluid retention, and ocular defects.

- **Cancer:** The carcinogenicity of ethylene oxide has been evaluated in a number of cohorts involved in ethylene oxide production and/or uses in sterilization. Results from some cohort studies suggest that exposure to ethylene oxide may increase the risk of selected cancer types (e.g., lymphohematopoietic cancer, leukemia, breast cancer). In laboratory animals exposed by inhalation, ethylene oxide was associated with a variety of cancer types (leukemia, mesotheliomas, lymphomas, tumors of lungs, Harderian gland, and female mammary gland and reproductive organs). Forestomach cancer (at the application site) was reported in rats treated by the oral exposure route.

Figure 2-1. Overview of the Number of Studies Examining Ethylene Oxide Health Effects*

Most studies examined the potential body weight, neurological, and cancer effects of ethylene oxide
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 124 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints. Chronic exposure was considered the most prevalent exposure duration for human occupational studies.

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 10 M, 10 F	Once for 6 hours	1, 100, 300, 500	BW, CS, FI, HP, LE, NX	Bd wt	300	500		Weight gain decreased by 16% (M) and 12% (F) compared to controls, with no change in food consumption
					Neuro	100 M 300 F	300 M 500 F		Decreased alertness and motor activity
EPA 2005a									
2	Rat, mouse, guinea pig, rabbit, monkey (NS) 1–10 (NS)	Up to 10 days Up to 8 exposures 7 hours/exposure	0, 841	GN, HP, LE	Death			841	100% mortality for each species
Hollingsworth et al. 1956									
3	Rat, guinea pig (NS) 5/sex/species	2 or 3 exposures 7 hours/exposure	0, 841	HP, LE	Resp		841		Slight to moderate edema; slight hemorrhage and congestion in lungs
					Hepatic		841		Light coloration and slight fatty degeneration
					Renal		841		Enlarged kidney; slight congestion and cloudy swelling of convoluted tubules
					Endocr		841		Pale coloration and enlargement in adrenals; numerous fat vacuoles in adrenal cortex
Hollingsworth et al. 1956									
4	Rat (NS) 10/sex Mouse (NS) 10 F	9 days 7 exposures 7 hours/exposure	0, 357	BW, GN, LE	Death			357	Death of 2/20 rats and 4/20 mice
					Bd wt		357		Moderate body weight loss (not otherwise described)
					Resp			357	Severe lung injury (not otherwise described)
Hollingsworth et al. 1956									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
5	Rat (White) 10 M	Once for 4 hours	882, 1,343, 1,648, 1,843, 1,992, 2,298	CS, LE	Death			1,460	4-hour LC_{50}
Jacobson et al. 1956									
6	Rat (CD) 25 F	GDs 6–15 6 hours/day	0, 50, 125, 225	BW, CS, DX, FI, FX, LE, MX, OF, OW	Bd wt	225			
					Develop	50	125		5% depressed mean fetal weight/litter
Neeper-Bradley and Kubena 1993									
7	Rat (Sprague-Dawley) 39 or 41 F	GDs 7–16 7 hours/day	0, 150	BW, DX, HP, OW	Bd wt	150			
					Develop		150		5–6% depressed fetal body weight; decreased crown-rump length; delayed ossification (skull, sternebrae)
NIOSH 1982									
8	Rat (Sprague-Dawley) 20–21 F	GDs 6–15 1 time/day 30 minutes	0, 400, 800, 1,200	BW, DX, FX, LE, MX	Bd wt	1,200			
					Develop	800	1,200		Increased incidence of dilation in renal pelvis and ureter
Saillenfait et al. 1996									
9	Rat (Sprague-Dawley) 18 F	GDs 5–16 3 times/day 30 minutes each	0, 200, 400	BW, DX, FX, LE, MX	Bd wt	400			NOAEL is for three 30-minute exposures at 400 ppm per day
					Develop	400			NOAEL is for three 30-minute exposures at 400 ppm per day
Saillenfait et al. 1996									
10	Rat (Sprague-Dawley) 21 F	GDs 6–15 3 times/day 30 minutes each	0, 800, 1,200	BW, DX, FX, LE, MX	Bd wt	800		1,200	70% depressed mean maternal body weight gain for GDs 6–16
					Develop		800		4–7% depressed mean fetal weight
Saillenfait et al. 1996									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
11	Rat (Fischer- 344) 22 F	GDs 6–15 6 hours/day	0, 0, 10, 33, 100	CS, DX	Develop	33[b]	100		3–9% depressed fetal body weight; $BMCL_{05}$ of 45.50 ppm
Snellings et al. 1982a									
12	Rat (Sprague-Dawley) 5 M or 5 F	Once for 1 hour	M: 4,827, 5,546, 6,161; F: 3,966, 4202, 4,827	CS, LE	Death			5,748 M 4,439 F	1-hour LC_{50}
Snellings et al. 2011									
13	Rat (Sprague-Dawley) 5 M or 5 F	Once for 4 hours	M: 1,850, 2,026, 2,182; F: 1,443, 1,637, 1,850	CS, LE	Death			1,972 M 1,537 F	4-hour LC_{50}
Snellings et al. 2011									
14	Mouse (White) 10 F	Once for 4 hours	533, 860, 882, 960, 1,343, 1,365	CS, LE	Death			835	4-hour LC_{50}
Jacobson et al. 1956									
15	Mouse (B6C3F1) 5 M, 5 F	Once for 4 hours	100, 200, 400, 800, 1,600	CS, LE	Death			800	5/5 males and 4/5 females died at 800 ppm and 5/5 males and 5/5 females died at 1,600 ppm
					Resp		800	1,600	LOAEL: Dyspnea observed after 4 hours of exposure to 800 ppm Serious LOAEL: Dyspnea observed after 3 hours of exposure to 1,600 ppm; dyspnea graded as severe in the 1,600 ppm after 3.5 hours of exposure

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Neuro			1,600	Incoordination after 3 hours and semi-consciousness after 3.5 hours of exposure to 1,600 ppm
NTP 1987									
16	Mouse (B6C3F1) 10 M, 10 F	Up to 2 weeks during a 14-week study 5 days/week 6 hours/day	0, 50, 100, 200, 400, 600	BW, CS, GN, HP, LE	Death			400	100% mortality at 400 and 600 ppm, deaths occurred during first 2 weeks of exposure
					Resp		400		Rhinitis
					Renal			400	Renal tubular degeneration and necrosis
					Immuno			600	Lymphocyte necrosis in thymus
NTP 1987									
17	Mouse (B6C3F1) 5 M, 5 F	2 weeks 5 days/week 6 hours/day	0, 50, 100, 200, 400, 800	BW, CS, GN, HP, LE	Death			800	100% mortality
					Bd wt	400			
NTP 1987									
18	Mouse (Hybrid) 22–55 F	Once for 1.5 hours 1, 6, 9, or 25 hours postmating	0, 1,200	DX, FX	Develop			1,200	Fetal defects (predominantly hydrops and eye defects)
Rutledge and Generoso 1989									
19	Dog (Beagle) 3 M	Once for 4 hours	327, 710, 1,393, 2,830	CS, LE	Death			960	4-hour LC_{50}
Jacobson et al. 1956									
20	Rabbit (New Zealand) 20 or 21 F	GDs 7–19 7 hours/day	0, 150	BW, DX, HP, OW	Bd wt	150			
					Develop	150			
NIOSH 1982									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
INTERMEDIATE EXPOSURE									
21	Monkey (NS) 3 M, 1 F	60 or 140 days 38–41 or 94 exposures 7 hours/exposure	0, 357	BW, CS, HP, LE	Musc/skel			357	Muscular atrophy in hindlimbs
					Neuro			357	Impaired sensory reflexes, paralysis of hindlimbs
Hollingsworth et al. 1956									
22	Rat (CD) 28 M, 28 F	6 hours/day, 5 days/week for 10 weeks pre-mating; 6 hours/day, 5 days/week during mating, GDs 0–20, and LDs 5–28	0, 10, 33, 100	CS, BW, OW, HP, DX, RX	Bd wt	100			
					Resp	100			
					Hepatic	100			
					Neuro	100			
					Repro	10		33	14% post implantation loss in F0 rats; decreased number of live pups per litter (36–45%) in F1 and F2 generations at 100 ppm
					Develop	10 M[c] 33 F	33 M	100	Decreased PND 21 body weight in F1 males (7%) at 33 ppm; decreased PND 21 body weight in F1 and F2 pups (11–13%) at 100 ppm
EPA 1994									
23	Rat (Sprague-Dawley) 15M, 15 F	14 weeks 5 days/week 6 hours/day	0, 25, 50, 100, 200	BW, CS, FI, HP, LE, NX	Death				No treatment-related mortality
					Bd wt	100	200		Body weight gain decreased by 16% (M) and 17% (F) relative to control, with no decrease in food consumption
					Neuro	200 M 100 F	200 F		Decreased hindlimb grip strength
EPA 2005b									
24	Rat (Wistar) 8 M	13 weeks 3 days/week 6 hours/day	0, 500	BW, EA, HE, OF, OW, UR	Bd wt	500			
					Hemato		500		Decreases in hemoglobin, hematocrit, erythrocyte count; increased reticulocytes
Fujishiro et al. 1990									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
25	Rat (White) 20 M	6 weeks 5 days/week 6 hours/day	0, 406	BW, CS, GN, LE	Death			406	13/20 rats died during the 6-week exposure period
					Resp			406	Labored breathing, nasal discharge
					Neuro			406	Loss of hindquarter usefulness
Jacobson et al. 1956									
26	Rat (White) 20 M	6 months 5 days/week 6 hours/day	0, 102	BW, CS, GN, LE	Resp	102			
					Neuro	102			
Jacobson et al. 1956									
27	Rat (Wistar) 6 or 8 M (28 M controls)	Up to 13 weeks 3 days/week 6 hours/day	0, 500	BW, CS, OF, OW	Neuro		500		Awkward gait
					Repro			500	Decreased testicular weight, decreased germ cell survival, degenerative effects on germ cells
Kaido et al. 1992									
28	Rat (Wistar) Up to 9 M	12 weeks 3 days/week 6 hours/day	0, 500	BW, CS, EA	Bd wt	500			
					Neuro		500		Ataxic gait
Matsuoka et al. 1990									
29	Rat (Wistar) 6 or 12 M	13 weeks 5 days/week 6 hours/day	0, 50, 100, 250	BW, EA, OF, OW	Bd wt	250			
					Repro	100		250	20% decreased epididymal weight, 73% decreased epididymal sperm count, histopathologic lesions in seminiferous tubules
Mori et al. 1991a									
30	Rat (Wistar) 8 M	6 weeks 3 days/week 6 hours/day	0, 500	BW, EA, OF, OW	Bd wt	500			
					Repro			500	26% decreased testicular weight, 32% decreased epididymal weight, 87% decrease in sperm counts, increased sperm head abnormalities
Mori et al. 1991b									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
31	Rat (Sprague-Dawley) 39 or 41 F	GDs 1–16 7 hours/day	0, 150	BW, DX, FX, HP, OW	Bd wt	150			
					Resp	150			
					Hepatic	150			
					Renal	150			
					Repro		150		Increased incidence of resorptions
					Develop		150		7–9% decreased fetal body weight; delayed ossification (skull, sternebrae)
NIOSH 1982									
32	Rat (Sprague-Dawley) 32–45 F	3 weeks premating and GDs 1–16 7 hours/day	0, 150	BW, DX, FX, OW	Bd wt	150			
					Resp	150			
					Hepatic	150			
					Renal	150			
					Repro		150		Increased incidence of resorptions
					Develop		150		10–12% decreased fetal weight, decreased crown-rump length, delayed ossification (skull, sternebrae)
NIOSH 1982									
33	Rat (Wistar) 5 M	13 weeks 3 days/week 6 hours/day	0, 500	CS, HP, OF	Bd wt	500			
					Neuro			500	Peripheral neuropathy
Ohnishi et al. 1985									
34	Rat (Wistar) 7 M	9 months 5 days/week 6 hours/day	0, 250	CS, HP, OF	Neuro		250		Retarded growth and maturation of myelinated fibers in hindleg nerves and mild axonal degeneration in absence of clinical signs of neuropathy
Ohnishi et al. 1986									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
35	Rat (Fischer- 344) 30 M, 20 F	12 weeks premating, 2 weeks mating, and throughout gestation and lactation 5 or 7 days/week 6 hours/day	0, 0, 10, 33, 100	BW, DX, FX	Bd wt	100			
					Repro	33	100		Decreases in the number of pups/litter and the ratio of fetuses born to implantation sites
					Develop	100			
Snellings et al. 1982b									
36	Rat, mouse, rabbit, monkey (NS) 1–10 (NS)	48–85 days 33–59 exposures 7 hours/exposure	0, 357	CS, LE	Death			357	Death of 18/20 rats, 10/10 mice,1/2 rabbits
					Bd wt			357	Markedly subnormal growth of each species (not otherwise described)
					Musc/skel			357	Muscular atrophy in hindlimbs of rats, rabbits, and monkey
					Neuro			357	Impaired sensory and motor function; paralysis in hindlimbs of rats, rabbits, monkey
Hollingsworth et al. 1956									
37	Rat, mouse, monkey, guinea pig (NS) 2–20 (NS)	176–226 days 122–157 exposures 7 hours/exposure	0, 113	BW, CS, HP, LE, OF, OW	Bd wt	113 F	113 M		13% depressed final body weight in male rats
					Resp		113		20–22% increased relative lung weight in male and female rats
Hollingsworth et al. 1956									
38	Rat, mouse, rabbit, monkey, guinea pig (NS) 2–20 (NS)	176–226 days 122–157 exposures 7 hours/exposure	0, 204	BW, CS, HP, LE, OF, OW	Death			204	Death of 14/20 male and 8/20 female rats
					Bd wt		204		10–<20% depressed final body weight among male and female rats and female guinea pigs
					Resp		204		18–31% increased relative lung weight among male and female rats and female guinea pigs

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Musc/skel			204	Muscular atrophy in hindlimbs of monkeys
					Neuro			204	Impaired sensory reflexes and partial paralysis in hind quarters and back of monkeys; slight to marked paralysis in hindlegs of rabbits
Hollingsworth et al. 1956									
39	Mouse (A/J) 30 F	6 months 5 days/week 6 hours/day	0, 70, 200	HP, LE	Cancer			70	CEL: Lung tumors
Adkins et al. 1986									
40	Mouse (White) 30 F	6 weeks 5 days/week 6 hours/day	0, 406	BW, CS, GN, LE	Death			406	24/30 mice died
Jacobson et al. 1956									
41	Mouse (White) 30 F	6 months 5 days/week 6 hours/day	0, 102	BW, CS, GN, LE	Bd wt	102			
Jacobson et al. 1956									
42	Mouse (B6C3F1) 10 M, 10 F	Up to 14 weeks 5 days/week 6 hours/day	0, 50, 100, 200, 400, 600	BW, CS, GN, HP, LE	Bd wt	200			
					Resp	100	200		Rhinitis in males and females
					Renal	100 F	100 M 200 F		Renal tubular degeneration (5/10 M; 8/10 F)
NTP 1987									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
43	Mouse (B6C3F1) 30 M, 30 F	10–11 weeks 5 days/week 6 hours/day	0, 10, 50, 100, 250	BC, BW, HE, HP, MX	Bd wt	250			
					Hemato	100	250		Males: decreases in hemoglobin Females: decreases in RBC count, hemoglobin, packed cell volume, mean corpuscular hemoglobin concentration
					Musc/skel	250			
					Hepatic	250			
					Repro	250 M			
Snellings et al. 1984a									
44	Dog (Beagle) 3 M	6 months 5 days/week 6 hours/day	0, 102	BC, BW, CS, HE, LE	Bd wt	102			
					Hemato		102		Signs indicative of normochromic anemia in 2/3 dogs
Jacobson et al. 1956									
45	Dog (Beagle) 3 M	6 weeks 5 days/week 6 hours/day	0, 292	BC, BW, CS, GN, HE	Bd wt	292			
					Resp		292		Pulmonary congestion, moderate alveolar collapse; consistent with mild irritation of lung parenchyma
					Hemato		292		Decreases in erythrocyte count, hemoglobin, hematocrit
					Musc/skel			292	Fatty changes consistent with muscular atrophy
					Neuro			292	Slight tremors, hindleg weakness
Jacobson et al. 1956									
46	Rabbit (New Zealand) 21 or 23 F	GDs 1–19 7 hours/day	0, 150	BW, DX, HP, OW	Bd wt	150			
					Resp	150			
					Hepatic	150			
					Renal	150			
					Develop	150			
NIOSH 1982									

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
47	Monkey (Cynomolgus) 12 M	Up to 2 years 5 days/week 7 hours/day	0, 50, 100	BC, BW, GN, HE, HP, LE, OF, OP, UR	Cardio	100			
					Hemato	100			
					Repro		50		Decreased sperm count and motility
Lynch et al. 1984a									
48	Rat (Fischer-344) 120 M, 120 F	Up to 2 years 5 days/week 6 hours/day	0, 0, 10, 33, 100	BW, HP, LE	Death			100	Increase in mortality in months 22–23
					Bd wt	33	100		M: Up to 12% depressed body weight gain F: 12–18% depressed body weight gain
					Cancer			33	CEL: Mononuclear leukemia in females at ≥33 ppm; peritoneal mesothelioma in males at 100 ppm; subcutis fibroma in males at 100 ppm; brain tumors in males and females at ≥33 ppm
Garman et al. 1986; Snellings et al. 1984b									
49	Rat (Fischer- 344) 80 M	Up to 2 years 5 days/week 7 hours/day	0, 50, 100	BC, BW, GN, HE, HP, UR	Death			100	Decreased survival
					Bd wt	50	100		16% decrease in body weight gain
					Cardio	100			
					Gastro	100			
					Hemato		50		Splenic extramedullary hematopoiesis at ≥50 ppm and splenic focal fibrosis at 100 ppm; no alterations in hematological parameters
					Musc/skel	50	100		Multifocal myopathy in skeletal muscle
					Hepatic	100			
					Renal	100			
					Ocular	100			

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Endocr		50		Multifocal cortical vacuolation and hyperplasia in the adrenal gland
					Neuro	100			
					Repro	100			
					Cancer			50	CEL: Mononuclear cell leukemia at ≥50 ppm; peritoneal mesotheliomas and brain gliomas at 100 ppm
Lynch et al. 1984a, 1984b									
50	Mouse (B6C3F1) 50 M, 50 F	102 weeks 5 days/week 6 hours/day	0, 50, 100	BW, CS, GN, HP, LE	Bd wt	100			
					Resp	100			
					Cardio	100			
					Gastro	100			
					Musc/skel	100			
					Hepatic	100			
					Renal	100			
					Dermal	100			
					Endocr	100			
					Neuro	100			
					Repro	100			

Table 2-1. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Cancer			50 M	CEL: Harderian gland papillary cystadenoma in males at ≥50 ppm and females at 100 ppm; mammary gland tumors in females at 50 ppm; lung alveolar/bronchiolar adenoma or carcinoma, malignant lymphomas (females only), and uterine adenocarcinomas at 100 ppm

NTP 1987

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.4 ppm for ethylene oxide; based on a rat $BMCL_{HEC}$ of 11.38 ppm ($BMCL_{RD05}$ of 45.50 ppm adjusted for intermittent exposure and converted to a human equivalent concentration) and an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration inhalation MRL of 0.07 ppm for ethylene oxide; based on a $NOAEL_{HEC}$ of 2.1 ppm (NOAEL of 10 ppm adjusted for intermittent exposure and converted to a human equivalent concentration) and an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

Principal studies for the MRLs.

Bd wt or BW = body weight; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk; $_{RD05}$ = dose associated with a 5% relative deviation from control); Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day(s); GN = gross necropsy; HE = hematology; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = lethal concentration, 50% kill; LD = lactation day; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive effects; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Acute (≤14 days)

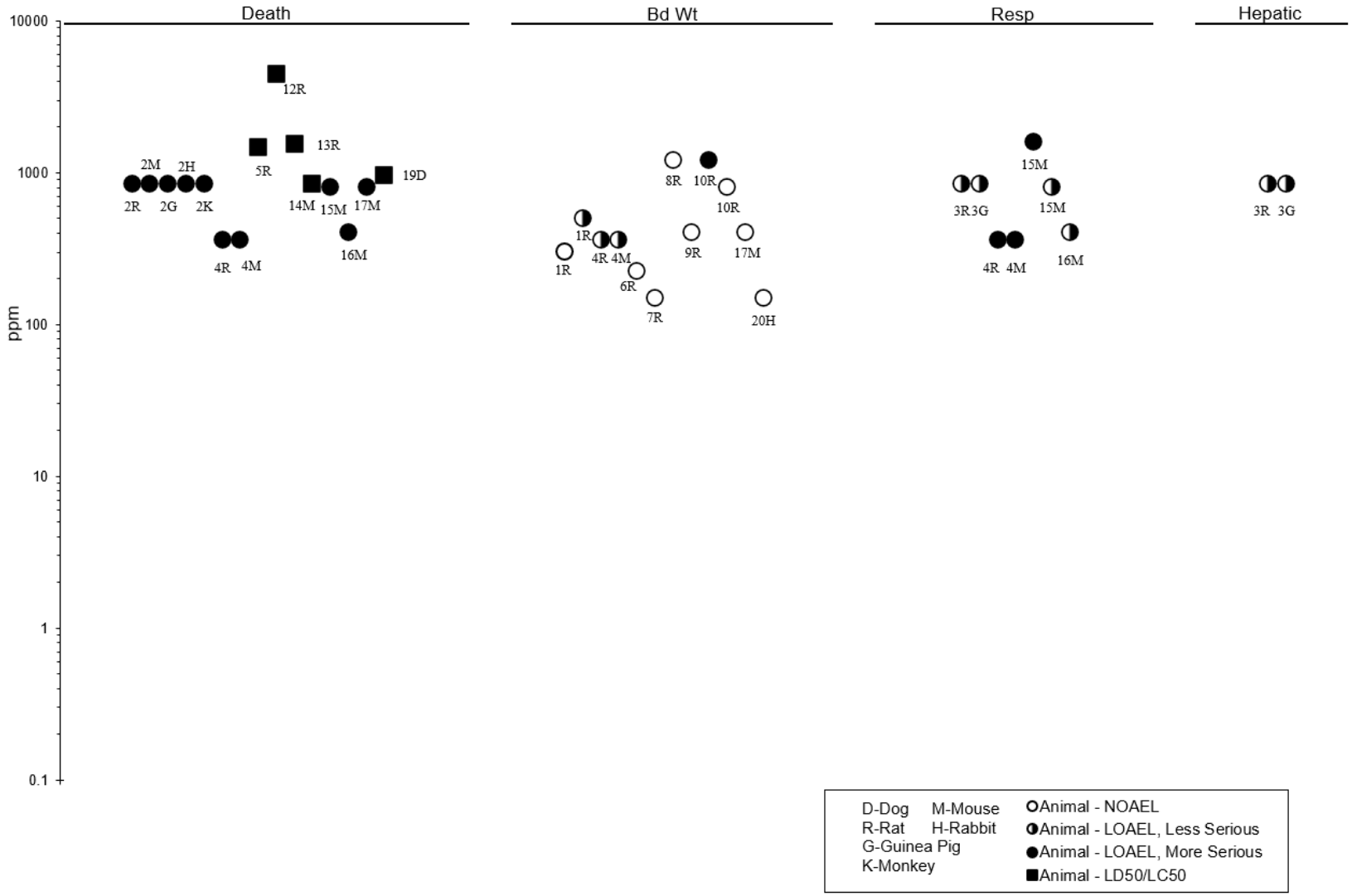


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Acute (≤14 days)

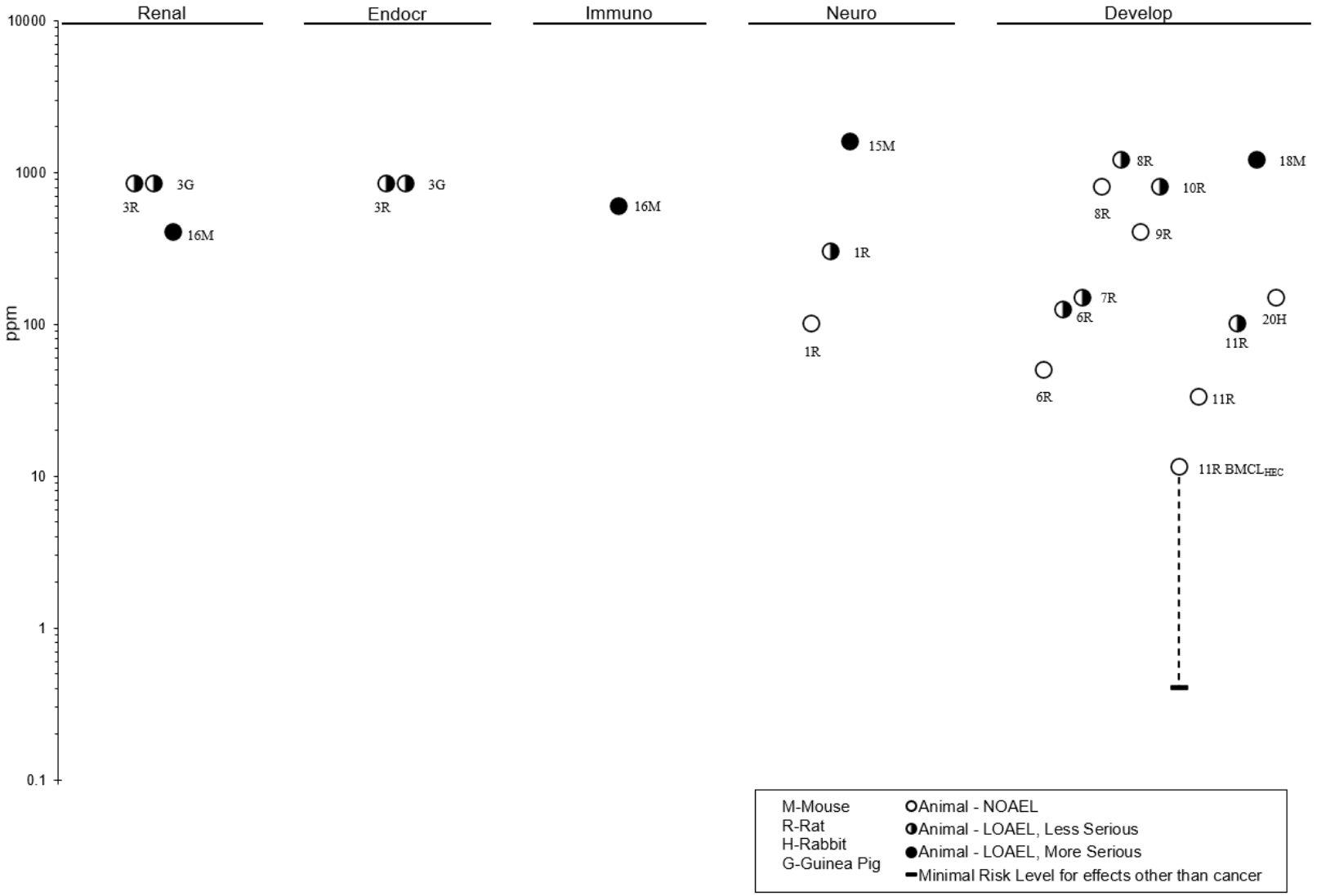


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Intermediate (15-364 days)

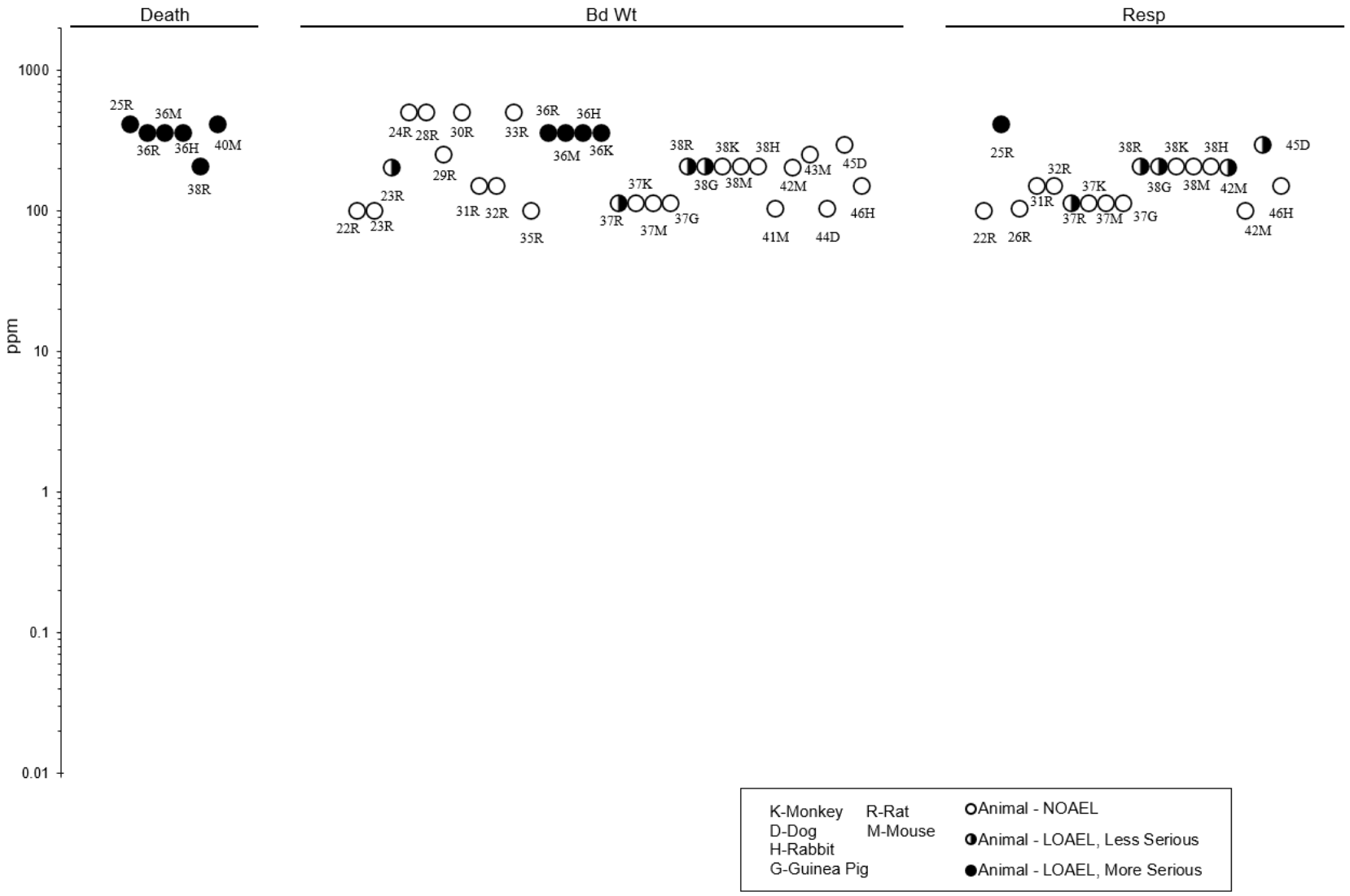


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Intermediate (15-364 days)

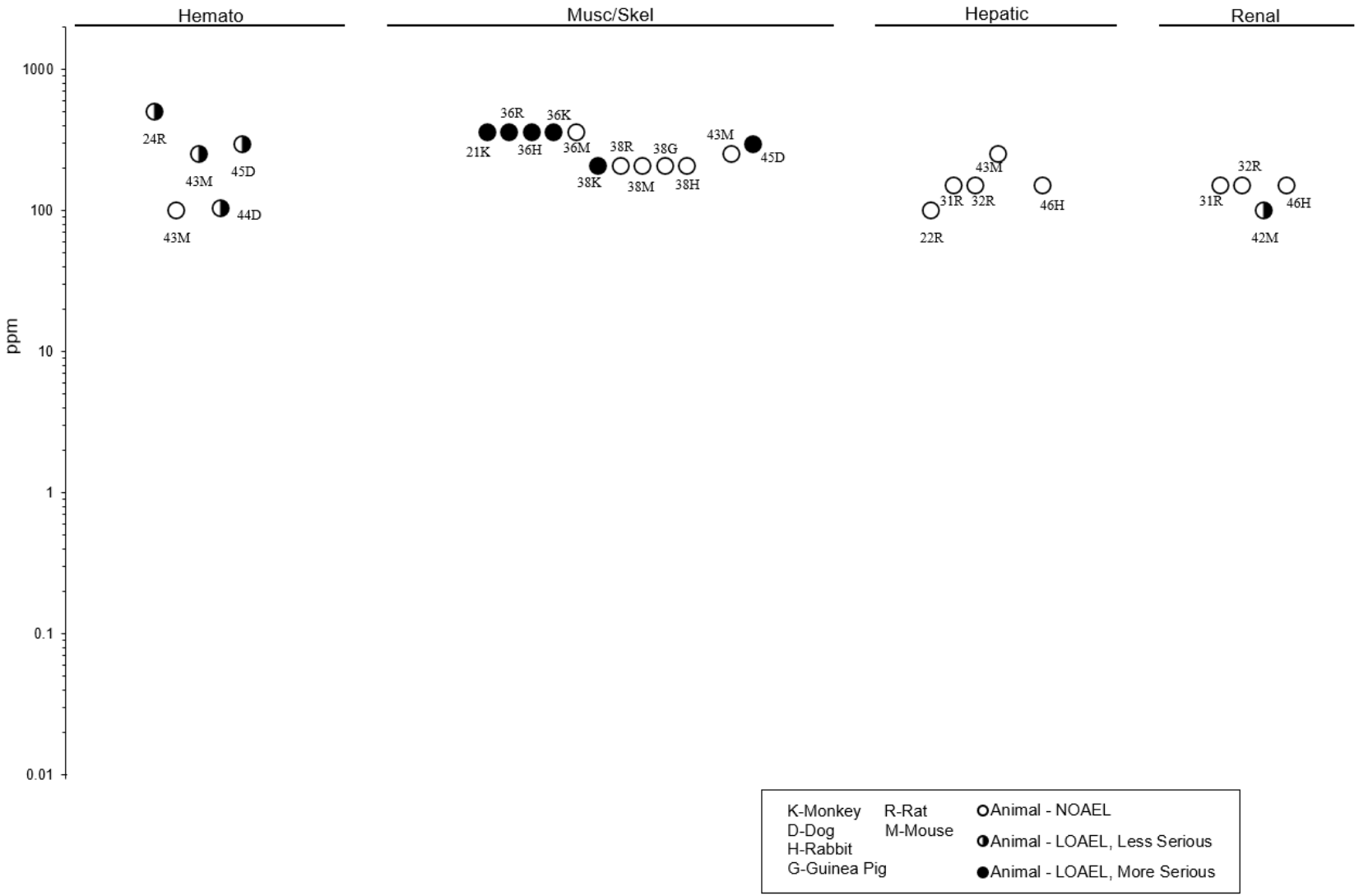
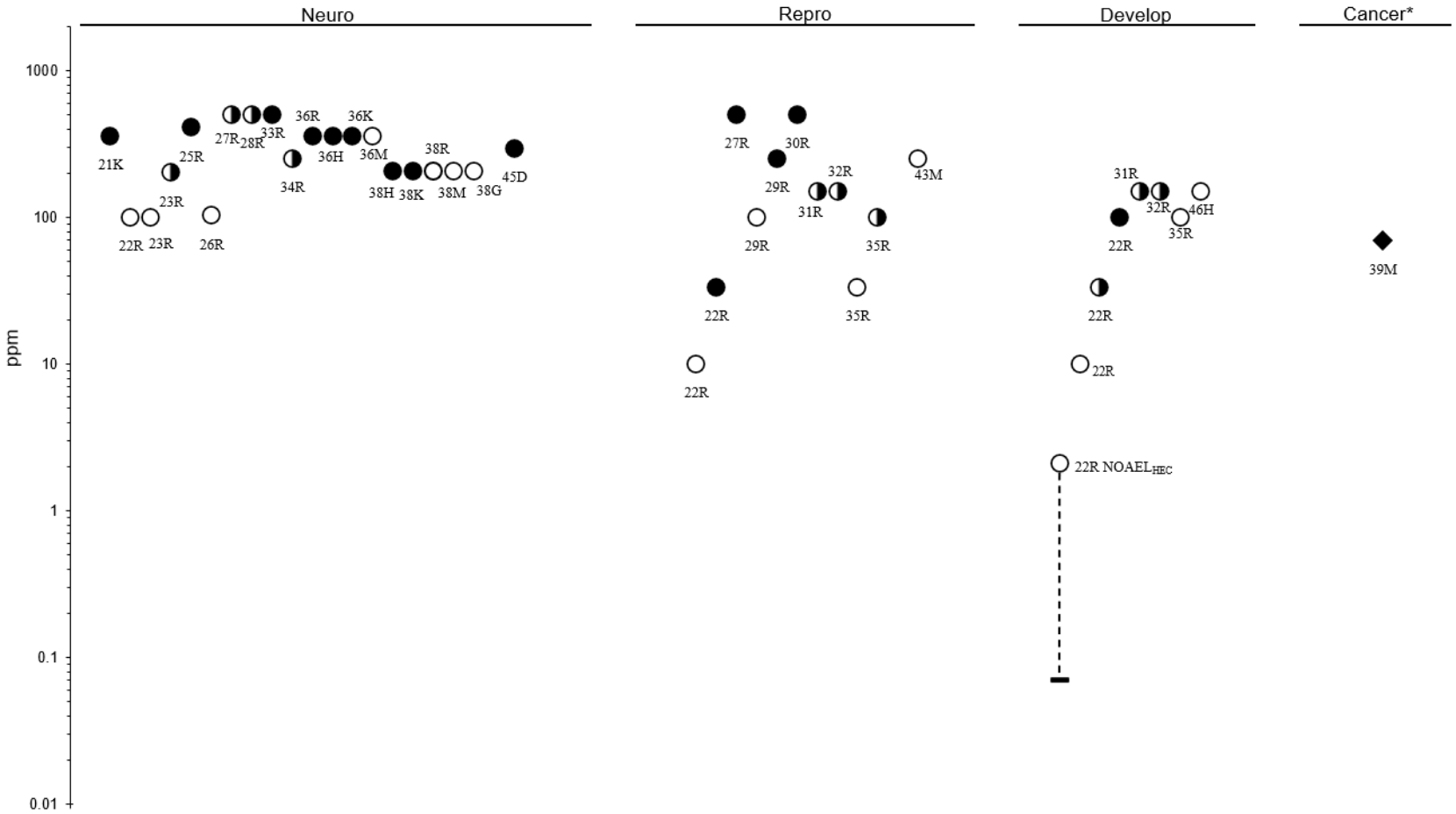


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Intermediate (15-364 days)



*Exposure concentrations represent the lowest concentrations tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Chronic (≥365 days)

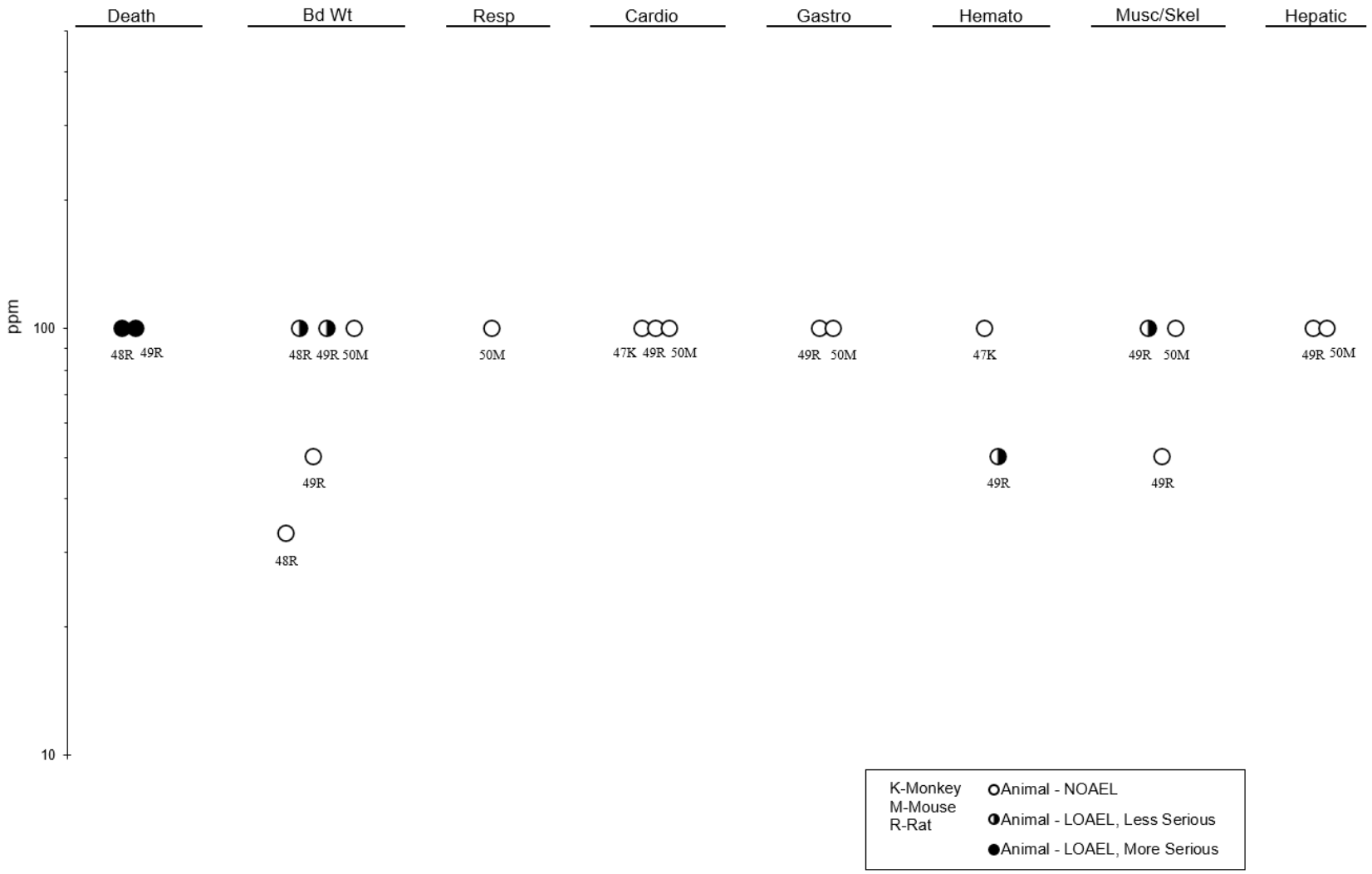
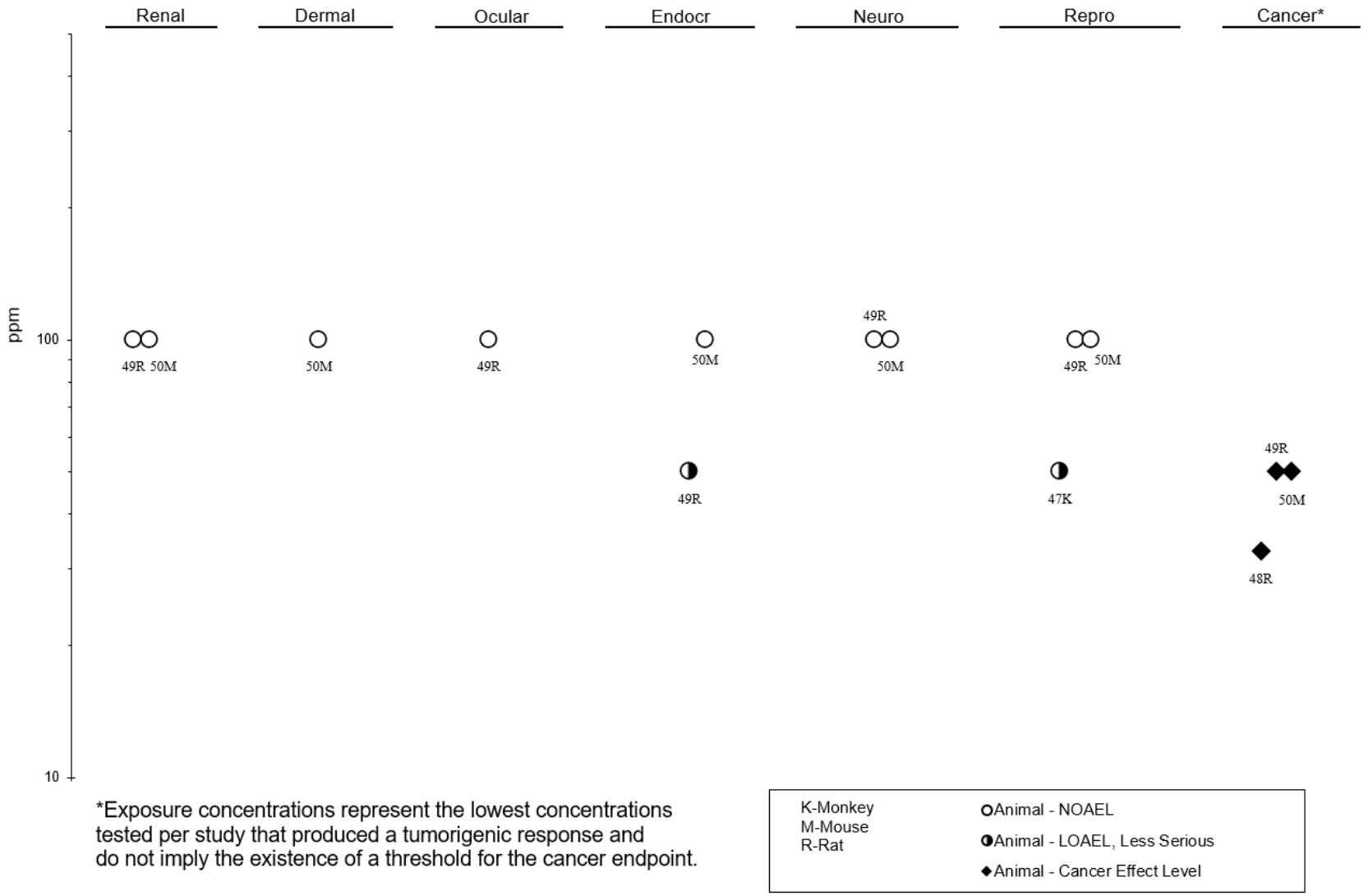


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Chronic (≥365 days)



*Exposure concentrations represent the lowest concentrations tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

Table 2-2. Levels of Significant Exposure to Ethylene Oxide – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (NS) 5 M, 5 F	Once (GO)	100, 200	BW, LE	Death			200	100% mortality
					Bd wt	100			
Hollingsworth et al. 1956									
2	Rat (Wistar) 10 M	Once (GW)	NS	LE	Death			330	LD_{50}
Smyth et al. 1941									
3	Guinea pig (NS) NS M, NS F	Once (GW)	NS	LE	Death			270	LD_{50}
Smyth et al. 1941									
INTERMEDIATE EXPOSURE									
4	Rat (NS) 5 F	15 times in 21 days (100 mg/kg/day) 22 times in 30 days (3, 10, 30 mg/kg/day) (GO)	0, 3, 10, 30, 100	BW, GN, HE, HP, OW	Bd wt	30		100	Weight loss, magnitude not reported
					Gastro	30	100		Gastric irritation; no additional information
					Hemato	30			
					Hepatic	30	100		Slight liver damage; no additional information
Hollingsworth et al. 1956									
CHRONIC EXPOSURE									
5	Rat (Sprague-Dawley) 50 F	150 weeks 2 times/week (GO)	0, 7.5, 30	HP, LE	Death			30	Decreased survival
					Cancer			7.5	CEL: Forestomach squamous cell carcinoma
Dunkelberg 1982									

[a]The number corresponds to entries in Figure 2-3.

Bd wt or BW = body weight; CEL = cancer effect level; F = female(s); (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

Figure 2-3. Levels of Significant Exposure to Ethylene Oxide – Oral

Acute (≤14 days)

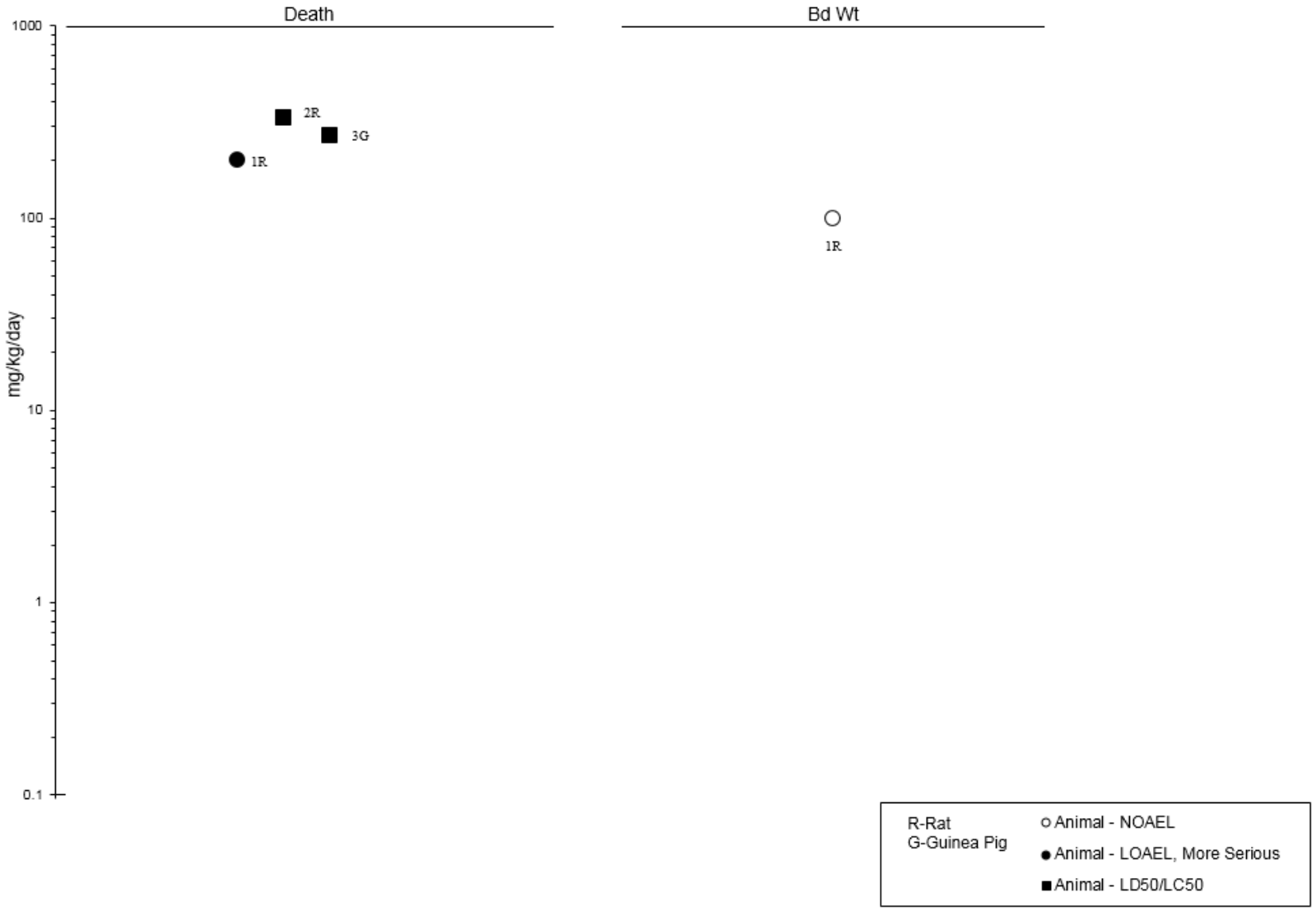


Figure 2-3. Levels of Significant Exposure to Ethylene Oxide – Oral

Intermediate (15-364 days)

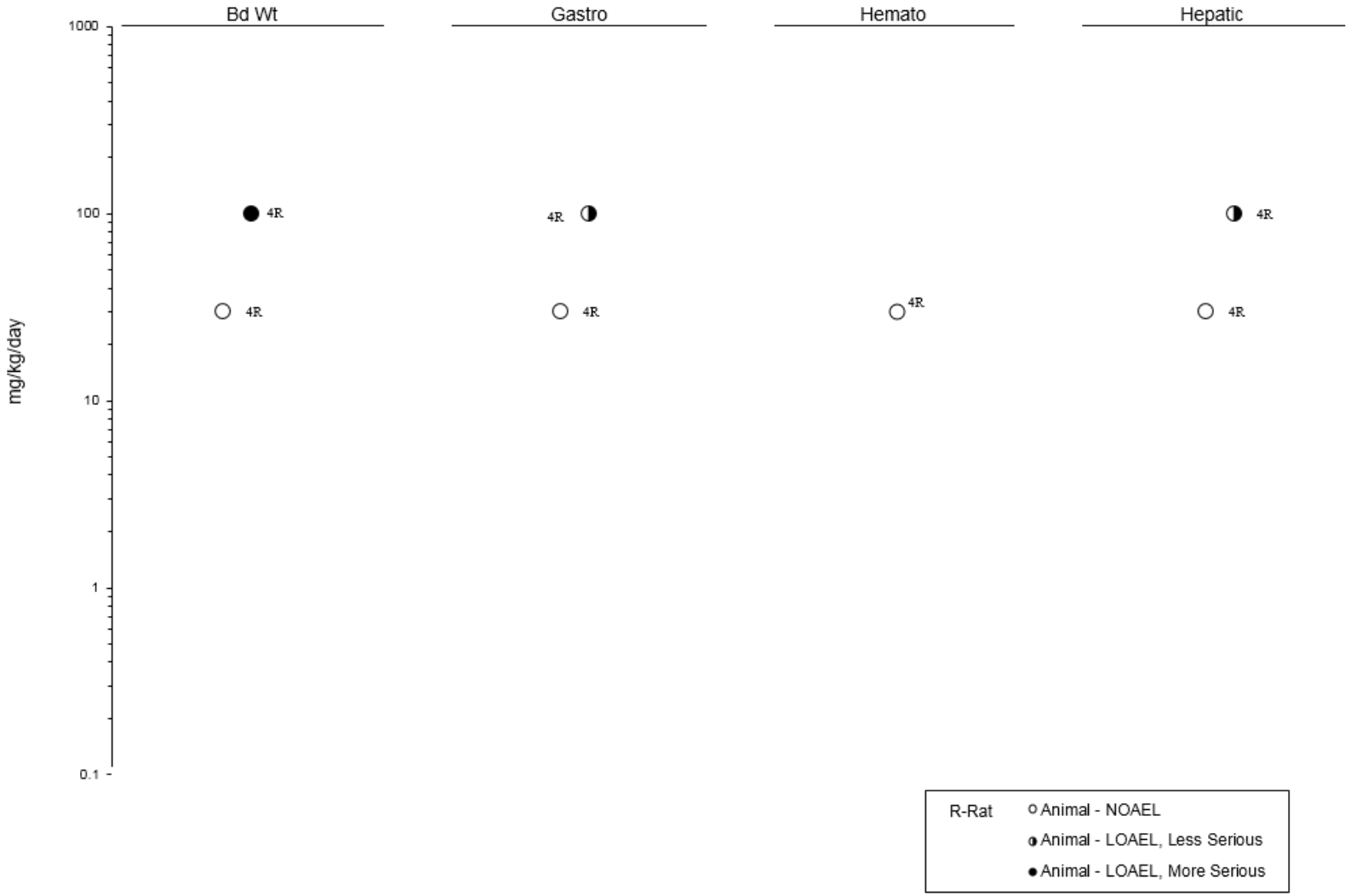
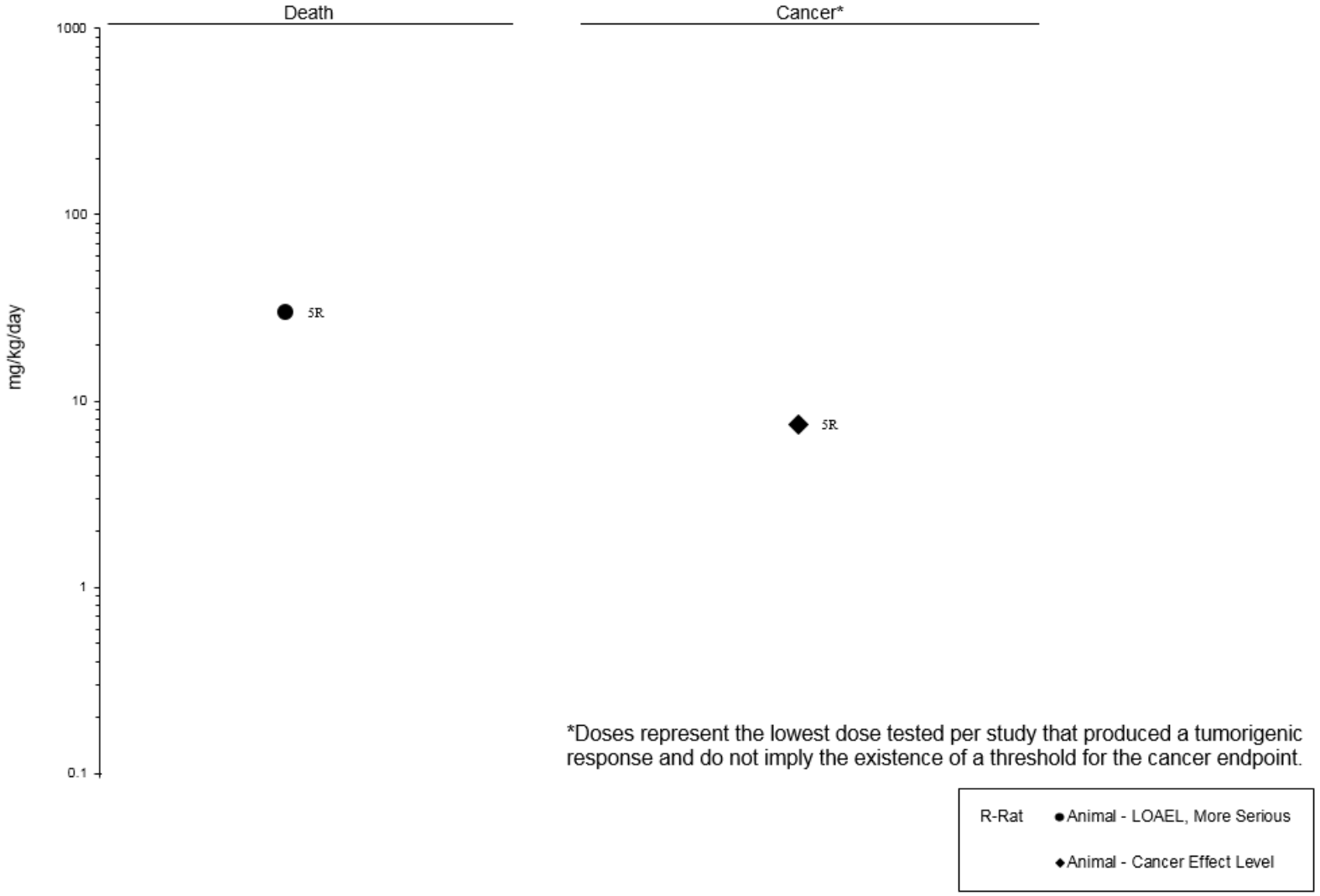


Figure 2-3. Levels of Significant Exposure to Ethylene Oxide – Oral

Chronic (≥365 days)



2.2 DEATH

Results from a number of epidemiological studies involving occupational exposure to ethylene oxide and risk of death from various cancer types (particularly all cancers, lymphohematopoietic cancer, leukemia, stomach cancer, pancreatic cancer, and brain and nervous system cancer) are summarized in Section 2.19.

Information regarding death in experimental animals following inhalation exposure to ethylene oxide is available. Limited information is available for the oral exposure route. No information was located for the dermal exposure route.

For rats exposed once to ethylene oxide vapor, 1-hour LC_{50} values were 5,748 and 4,439 ppm for males and females, respectively; 4-hour LC_{50} values were 1,972 and 1,537, respectively (Snellings et al. 2011). A 4-hour LC_{50} of 1,460 ppm was reported for male rats (Jacobson et al. 1956). Mice and dogs were more sensitive to acute lethality than rats; reported 4-hour LC_{50} values were 835 and 960 ppm, respectively (Jacobson et al. 1956). Lethality occurred in rats, mice, rabbits, guinea pigs, and monkeys following single or repeated inhalation exposure at 204–841 ppm for periods up to 6 weeks (Hollingsworth et al. 1956; Jacobson et al. 1956; NTP 1987). Studies that employed repeated exposure of rats for up to 2 years reported increased mortality at exposures as low as 100 ppm (Garman et al. 1986; Lynch et al. 1984a, 1984b; Snellings et al. 1984b).

Hollingsworth et al. (1956) reported 100% mortality among rats (5/sex) gavaged once at 200 mg/kg. Dunkelberg (1982) reported decreased length of survival among 50 female rats gavaged at 30 mg/kg/day, 2 times/week, for up to 150 weeks.

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following inhalation, oral, or dermal exposure to ethylene oxide.

Information for the inhalation exposure route is available for body weight effects in experimental animals. Limited information is available for the oral exposure route. No information was located for the dermal exposure route.

Decreased weight gain was observed in rats 14 days after a single exposure to 500 ppm ethylene oxide; weight gain was decreased by 16 and 12% in males and females, respectively, compared to controls (EPA 2005a). Depressed body weight was reported in a few acute-duration studies of rats or mice repeatedly exposed to ethylene oxide vapor at levels in the range of 357–1,200 ppm (Hollingsworth et al. 1956; Saillenfait et al. 1996). Following a 14-week repeated exposure to 200 ppm ethylene oxide, weight gain was decreased by 16 and 12% in male and female rats, respectively (EPA 2005b). Decreases in final body weights (10–20%) were observed in rats and guinea pigs exposed to 113–204 ppm ethylene oxide for up to 226 days (Hollingsworth et al. 1956). Hollingsworth et al. (1956) also reported "markedly subnormal growth" (magnitude not reported) among rats, mice, rabbits, guinea pigs, and/or monkeys intermittently exposed to ethylene oxide vapor at 357 ppm for up to 85 days. Other acute- and intermediate-duration inhalation studies of rats, mice, and/or rabbits found no body weight effects at exposure levels in the range of 100–500 ppm (EPA 1994; Jacobson et al. 1956; Matsuoka et al. 1990; Mori et al. 1991a, 1991b; Neeper-Bradley and Kubena 1993; NTP 1987; Ohnishi et al. 1985; Saillenfait et al. 1996; Snellings et al. 1982a, 1982b). In 2-year rat studies that employed repeated exposure to ethylene oxide vapor, 12–18% depressed body weight gain was reported at an exposure level of 100 ppm (Lynch et al. 1984a, 1984b; Snellings et al. 1984b). No body weight effects were observed for mice repeatedly exposed at up to 100 ppm for 102 weeks (NTP 1987).

Hollingsworth et al. (1956) found no body weight effects among rats gavaged once at 100 mg/kg/day. Repeated dosing of female rats at 100 mg/kg/day resulted in an unspecified magnitude of weight loss; the NOAEL was 30 mg/kg/day.

2.4 RESPIRATORY

Limited data are available regarding ethylene oxide-related respiratory effects in humans. Inhalation of ethylene oxide is irritating to mucous membranes including those associated with the respiratory system. Inhalation exposure of workers to high concentrations of ethylene oxide for brief periods has resulted in bronchitis, pulmonary edema, and emphysema (Thiess 1963). Deschamps et al. (1992) reported a case of persistent asthma in a 35-year-old male who was highly exposed to ethylene oxide from a leaky railroad tank. Pulmonary function remained compromised when tested 1 and 3 years after the accidental exposure. There was no evidence of increased risk of death from non-malignant respiratory disease within various cohorts of workers involved in production or use of ethylene oxide (Bisanti et al. 1993; Coggon et al. 2004; Hogstedt 1988; Morgan et al. 1981; Steenland et al. 1991; Swaen et al. 2009; Wong and Trent 1993).

Information is available regarding respiratory effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Dyspnea was observed after 4 hours of exposure of mice to ethylene oxide vapor at a lethal exposure level of 800 ppm (NTP 1987). Adverse respiratory effects (e.g., dyspnea, pulmonary edema, pulmonary hemorrhage and congestion, "severe lung injury") were reported for experimental animals (rats, mice, and/or guinea pigs) exposed to 357–841 ppm ethylene oxide vapor for acute durations (Hollingsworth et al. 1956; NTP 1987). Rhinitis was also observed in mice exposed to 400 ppm ethylene oxide for up to 2 weeks (NTP 1987). Intermediate-duration studies reported labored breathing and nasal discharge in rats exposed to 406 ppm for 6 weeks (Jacobson et al. 1956), an increase in relative lung weight in rats and guinea pigs exposed to 113–204 ppm for up to 226 days (Hollingsworth et al. 1956), rhinitis in mice exposed to 200 ppm for up to 14 weeks (NTP 1987), and pulmonary congestion and alveolar collapse in dogs exposed to 292 ppm for 6 weeks (Jacobson et al. 1956). Acute bronchopneumonia, chronic pneumonia, pulmonary edema, and suppurative rhinitis were observed in rats exposed at 50 ppm for 104 weeks (Lynch et al. 1984a, 1984b). However, all groups of rats in this study (including controls) experienced a pulmonary bacterial infection as early as 8 months into the treatment period and were treated at months 8, 16, and 20. The infection likely played a significant role in the reported respiratory effects. There were no indications of exposure-related respiratory effects in rats exposed to 100 ppm as part of a 2-generation reproduction study (EPA 1994) or in mice repeatedly exposed at up to 100 ppm for 102 weeks (NTP 1987).

2.5 CARDIOVASCULAR

Limited data are available regarding ethylene oxide-related cardiovascular effects in humans. There was no evidence of increased risk of death from cardiovascular or cerebrovascular diseases within various cohorts of workers involved in production or use of ethylene oxide (Bisanti et al. 1993; Coggon et al. 2004; Hagmar et al. 1991; Hogstedt 1988; Kiesselbach et al. 1990; Morgan et al. 1981; Olsen et al. 1997; Steenland et al. 2004; Swaen et al. 2009; Wong and Trent 1993).

Limited information is available regarding cardiovascular endpoints in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Lynch et al. (1984b) found no effects on electrocardiograms of male monkeys during repeated exposure to ethylene oxide vapor at 50 or 100 ppm for up to 2 years. There was no histopathological evidence of ethylene oxide-induced cardiovascular effects in mice repeatedly exposed at 100 ppm for 102–104 weeks (Lynch et al. 1984a, 1984b; NTP 1987).

2.6 GASTROINTESTINAL

Limited information is available regarding the potential for ethylene oxide-induced gastrointestinal effects in humans. Nausea and vomiting have been reported, but these are considered to be secondary effects due to neurotoxicity rather than a primary effect of inhaled ethylene oxide on the gastrointestinal tract. There was no evidence of increased risk of death from gastrointestinal effects within cohorts of workers with potential for ethylene oxide exposure (Bisanti et al. 1993; Morgan et al. 1981; Steenland et al. 1991; Wong and Trent 1993).

Limited information is available regarding gastrointestinal effects in experimental animals following inhalation or oral exposure to ethylene oxide. No information was located for the dermal exposure route.

There was no histopathological evidence of gastrointestinal effects in rats or mice repeatedly exposed to ethylene oxide vapor at 100 ppm for 102–104 weeks (Lynch et al. 1984a, 1984b; NTP 1987). Hollingsworth et al. (1956) reported gastric irritation in female rats following repeated gavage exposure at 100 mg/kg/day; the NOAEL was 30 mg/kg/day.

2.7 HEMATOLOGICAL

Limited human data are available. Joyner (1964) reported no effects on hemoglobin levels or red blood cell (RBC) or white blood cell (WBC) counts in workers exposed to ethylene oxide at about 5–10 ppm for approximately 10 years.

Information is available regarding hematological effects in experimental animals following inhalation or oral exposure to ethylene oxide. No information was located for the dermal exposure route.

Decreases in hemoglobin, hematocrit, erythrocyte count, packed cell volume, and/or increased reticulocytes were reported in experimental animals (rats, mice, dogs) repeatedly exposed to ethylene oxide vapor at 250–500 ppm for 6–13 weeks (Fujishiro et al. 1990; Jacobson et al. 1956; Snellings et al.

1984a). Hematological alterations indicative of normochromatic anemia were also observed in dogs exposed to 102 ppm for 6 months (Jacobson et al. 1956). One study reported splenic extramedullary hematopoiesis in rats repeatedly exposed at 50 or 100 ppm for 104 weeks and noted splenic focal fibrosis at 100 ppm; however, findings are confounded by a concurrent infection in the rat colony (Lynch et al. 1984a, 1984b). There was no histopathological evidence of ethylene oxide-induced hematological effects in mice intermittently exposed at 100 ppm for up to 102 weeks (NTP 1987).

Hollingsworth et al. (1956) found no evidence of exposure-related hematological effects in female rats repeatedly gavaged with ethylene oxide at up to 30 mg/kg/day.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans exposed to ethylene oxide.

Information is available regarding musculoskeletal effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Histopathologic indicators of muscular atrophy were reported for experimental animals (rats, rabbits, monkeys, dogs) repeatedly exposed to ethylene oxide vapor for 6 weeks to 226 days at exposure levels in the range of 204–357 ppm (Hollingsworth et al. 1956; Jacobson et al. 1956). There was no indication of musculoskeletal effects in mice repeatedly exposed to ethylene oxide vapor for up to 14 weeks at 250 ppm (Snellings et al. 1984a). However, multifocal myopathy in skeletal muscle was reported in rats following inhalation exposure at 100 ppm for 104 weeks; the NOAEL was 50 ppm (Lynch et al. 1984a, 1984b). See Section 2.15 for a discussion of neuromuscular alterations.

2.9 HEPATIC

Information regarding hepatic effects in humans after inhalation exposure to ethylene oxide is limited to a report by Joyner (1964). The results suggested that workers exposed to about 5–10 ppm for 10.7 years did not have major signs of hepatic toxicity such as jaundice or palpable liver.

Limited information is available regarding hepatic effects in experimental animals following inhalation or oral exposure to ethylene oxide. No information was located for the dermal exposure route.

Hollingsworth et al. (1956) reported slight discoloration and fatty degeneration in livers from rats and guinea pigs exposed to ethylene oxide vapor at 841 ppm for two or three 7-hour exposures. Snellings et al. (1984a) reported an elevation in the liver to body weight ratio in female mice exposed to ethylene oxide at 250 ppm for 11 weeks; however, histological examination showed that the livers were normal at this and all other lower exposure levels for both sexes in this study. No evidence for hepatic effects were seen among rats or mice repeatedly exposed at 100 ppm during a 10-week premating period (EPA 1994) or for 50 or 100 ppm for up to 102–104 weeks (Lynch et al. 1984a, 1984b; NTP 1987).

Slight liver damage (no further details) was reported in rats following repeated gavage exposure to ethylene oxide at 100 mg/kg/day, but not in animals dosed at ≤30 mg/kg/day (Hollingsworth et al. 1956).

2.10 RENAL

Information regarding renal effects in humans after inhalation exposure to ethylene oxide is limited to a report by Joyner (1964) which indicates that there was no evidence of nephritis or other parenchymal disease among workers exposed to ethylene oxide at 5–10 ppm for a mean exposure time of 10.7 years.

Information is available regarding renal effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Hollingsworth et al. (1956) reported enlargement, slight congestion, and cloudy swelling of convoluted tubules in kidneys from rats and guinea pigs exposed to ethylene oxide vapor at 841 ppm for two or three 7-hour exposures. In a 14-week study of mice repeatedly exposed to ethylene oxide vapor, renal tubular degeneration was observed in 5/10 and 6/10 males exposed at 100 and 200 ppm, respectively, and in 8/10 females exposed at 200 ppm (NTP 1987). Renal tubular necrosis was observed in 1/10 males of the 100 and 200 ppm exposure groups. Lethal exposure levels (400 and 600 ppm) resulted in increased incidences of necrosis in both sexes exposed for up to 2 weeks. There were no indications of renal effects in rats or mice exposed at 50 or 100 ppm for up to 102–104 weeks (Lynch et al. 1984a, 1984b; NTP 1987).

2.11 DERMAL

Data related to human dermal exposure to ethylene oxide are generally associated with case reports of industrial accidents, some of which occurred in the 1930s and 1940s. Concentrated ethylene oxide

evaporates rapidly from the skin and produces a freezing effect, often compared to frostbite, leaving burns ranging from first- to third-degree severity (Taylor 1977). Workers drenched with a 1% solution developed large vesiculated blisters (Sexton and Henson 1949).

A study using volunteers by Sexton and Henson (1950) showed that the magnitude of skin injury was related to the concentration of ethylene oxide in solution but peaked at about 50%. This was attributed to the rapid evaporation of the more concentrated solutions, which prevented more prolonged skin contact.

Case reports of patients whose intact skin or wounds had contact with gauze or other hospital supplies that had been sterilized with ethylene oxide indicated that the observed skin reactions included erythema, blister formation, scaling, crusted ulcerations, and second-degree burns (Alomar et al. 1981; Hanifin 1971; Karacalar and Karacalar 2000).

Shupack et al. (1981) demonstrated that human skin reactions to ethylene oxide in patch materials were directly related to the total dose.

Limited information is available regarding dermal effects in experimental animals following inhalation or dermal exposure to ethylene oxide. No information was located for the oral exposure route.

NTP (1987) found no evidence of dermal effects in mice repeatedly exposed to ethylene oxide vapor for up to 102 weeks at up to 100 ppm. Dermal application of ethylene oxide (10 and 50% aqueous solutions) to rabbits for ≥6 minutes resulted in hyperemia and edema (Hollingsworth et al. 1956). Dermal application of undiluted ethylene oxide to the back of rabbits (0.5 mL for 4 hours under occluded conditions) resulted in severe erythema and edema, subdermal hemorrhages, and chemical burns during 72 hours post-application; the chemical was considered corrosive (Celanese Chem Co. 1972).

2.12 OCULAR

There is some evidence that occupational exposure to high levels of ethylene oxide can result in cataracts and corneal burns (McLaughlin 1946; Thiess 1963). For example, cataracts developed in four sterilizer operators who were exposed to ethylene oxide from a leaking sterilizer for up to 2 months (Gross et al. 1979; Jay et al. 1982). Because these persons could intermittently smell the fumes, a level of ≥700 ppm was estimated by the authors in retrospect. Although none of the patients were examined before this accidental exposure, the occurrence of cataracts was viewed as unlikely to be a chance occurrence in all

four persons in this age range (31–35 years old) who had no systemic or ocular disease that might be associated with cataract formation.

Ocular instillation of a 1% solution of ethylene oxide-to eyes of rabbits resulted in slight corneal cloudiness (severity score 0.8–1.9; maximum possible score of 4.0) during 48 hours post-instillation (McDonald et al. 1977). Lynch et al. (1984a, 1984b) reported cataracts in monkeys and rats intermittently exposed to ethylene oxide vapor for 2 years. Incidences in 50 and 100 ppm groups of monkeys were 2/11 and 3/12, respectively, compared to 0/11 among controls. Incidences in 50 and 100 ppm groups of rats were 3/79 and 9/78, respectively, compared to 2/77 among controls.

2.13 ENDOCRINE

No information was located regarding endocrine effects in humans associated with ethylene oxide exposure.

Information is available regarding endocrine effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Hollingsworth et al. (1956) reported pale coloration and enlargement of adrenals, and numerous fat vacuoles in the adrenal cortex from rats and guinea pigs exposed two or three times to ethylene oxide vapor at 841 ppm for 7 hours per exposure. Lynch et al. (1984a, 1984b) reported multifocal cortical vacuolation and hyperplasia in adrenal glands from rats intermittently exposed to ethylene oxide vapor at 50 ppm for up to 104 weeks; however, findings are confounded by a concurrent infection in the rat colony. There was no histopathological evidence of ethylene oxide-induced effects on the thyroid, parathyroid, adrenals, or pituitary gland of mice intermittently exposed at 100 ppm for up to 102 weeks (NTP 1987).

2.14 IMMUNOLOGICAL

The immunological effects of human inhalation exposure to ethylene oxide were studied in workers employed for up to 14 years in an ethylene oxide manufacturing plant. Workplace concentrations were generally <0.05 ppm (the detection limit of the analytical method) with occasional peaks of 8 ppm during the 4 years that the air was monitored. There was no effect on any of the blood parameters relating to

immune function that were investigated, including T and B lymphocyte counts, lymphocyte activation, and serum IgG, IgM, and IgA levels (Van Sittert et al. 1985).

Thiess (1963) did not observe skin sensitization in ethylene oxide plant workers (average exposure: 10.4 years) who were challenged with a single dermal application of 1% ethylene oxide. However, ethylene oxide was implicated as a skin sensitizer in studies of volunteers following dermal exposure (Sexton and Henson 1950; Shupack et al. 1981). Contact dermatitis and delayed-type hypersensitivity dermatitis have been observed in case reports of ethylene oxide-exposed health care workers and patients (Alomar et al. 1981; Belen and Polat 2015; Brashear et al. 1996; Caroli et al. 2005; Dagregorio and Guillet 2004; Kerre and Goossens 2009; Lerman et al. 1995; Romaguera and Vilaplana 1998).

Limited information is available regarding immunological effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Thymic lymphocytic hypoplasia was reported for male and female mice intermittently exposed to ethylene oxide vapor at 400 ppm for up to 2 weeks; at 600 ppm, necrosis was observed in the thymus (males and females) and spleen (males) (NTP 1987).

2.15 NEUROLOGICAL

Neurological effects have frequently been reported in association with human and animal exposure to ethylene oxide via inhalation at a wide range of concentrations and exposure durations.

In humans exposed to ethylene oxide in occupational settings, headache, nausea, and vomiting were reported (Blackwood and Erskine 1938; Sexton and Henson 1949; von Oettingen 1939). Reliable measured or estimated exposure levels were not available in these situations.

Case studies of neurological effects in workers exposed to ethylene oxide have been reported. These studies are insufficient to establish a causal relationship between exposure to ethylene oxide and neurological effects in humans. Neuropathy, impaired hand-eye coordination, cognitive dysfunction, memory loss, headache, and hand numbness were reported in case studies of workers exposed to ethylene oxide for various durations (Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Zampollo et al. 1984). These effects were seen at estimated average exposure levels as low as 3 ppm; however, short-

term exposures may have been as high as 700 ppm for some of these workers. Sural nerve biopsies revealed axonal degeneration and regeneration in two studies (Kuzuhara et al. 1983; Schröder et al. 1985).

Information on the neurological effects of inhalation exposure to ethylene oxide has also been derived from case studies of longer-term occupational exposure. Headaches, nausea, vomiting, clumsiness, blunting of the senses, lethargy, numbness, and weakness in the extremities were reported among four sterilizer operators exposed to ethylene oxide for up to 2 months on an intermittent basis at levels of approximately 700 ppm (estimated by the authors based on the fact that the exposed workers could smell the vapors emitted from a leaking apparatus) (Gross et al. 1979). One of the operators experienced recurrent major motor seizures at 20–30-minute intervals near the end of the work shift; nerve conduction testing indicated sensorimotor neuropathy.

Information is available regarding neurological effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Incoordination and semiconsciousness were reported during a 4-hour exposure of mice to ethylene oxide vapor at 1,600 ppm (NTP 1987). Decreased alertness and motor activity was decreased in male rats following a single exposure to 300 ppm and in female rats exposed to 500 ppm (EPA 2005a). Repeated inhalation exposures of experimental animals resulted in neurological effects at similar or lower exposure levels. Effects including impaired sensory and motor function (particularly in hindlimbs), decreased grip strength, altered gait, slight tremors, various degrees of hindlimb paralysis, and peripheral neuropathy have been reported in experimental animals intermittently exposed to ethylene oxide vapor at 100–500 ppm for periods in the range of 48–226 days (EPA 2005b; Hollingsworth et al. 1956; Jacobson et al. 1956; Kaido et al. 1992; Matsuoka et al. 1990; Ohnishi et al. 1985). Snellings et al. (1984a) also reported neurological effects (hunched posture and decreased motor activity) in mice at exposures ≥50 ppm; however, these findings could not be specifically attributed to ethylene oxide exposure due to inadequate descriptions of methods and the limited evaluations of small numbers of animals.

In a 9-month study of rats exposed to ethylene oxide at 250 ppm, retarded growth and maturation of myelinated fibers and mild axonal degeneration in hindleg nerves were observed in the absence of clinical signs of neuropathy (Ohnishi et al. 1986). There were no indications of ethylene oxide exposure-related neurological effects in a 2-generation study of rats exposed to concentrations as high as 100 ppm (EPA 1994) or in a 2-year study of mice intermittently exposed to airborne concentrations as high as 100 ppm (NTP 1987). Lynch et al. (1984a) reported axonal dystrophy in the brain of 1/2 control monkeys and

2/2 and 1/2 monkeys exposed at 50 and 100 ppm, respectively. Demyelination was reported in 1/2 monkeys at the 50 and 100 ppm exposure levels. However, the results could not be specifically attributed to ethylene oxide exposure due to the small number of animals evaluated and the reported histopathologic brain lesion in a control animal.

Nagata et al. (1992) designed a study to investigate potential mechanisms of ethylene oxide neurotoxicity in the rat. Groups of male Wistar rats (5/group) were exposed to ethylene oxide vapor at 0 or 500 ppm for 6 hours/exposure, 3 days/week, for 15 weeks. Following the final exposure period, ^{35}S-methionine was injected into the right dorsal root ganglion to evaluate rapid anterograde axonal transport. The velocity in the ethylene oxide-exposed rats was 33% slower than that of controls. Morphometric analysis of selected portions of sural and peroneal nerve preparations revealed significantly greater incidental degeneration of myelinated fibers from the ethylene oxide-exposed rats than from controls. The study authors suggested that the morphological changes and decreased axonal transport velocity might play a causative role in the development of peripheral neuropathy from chronic ethylene oxide exposure.

2.16 REPRODUCTIVE

Possible associations between exposure to ethylene oxide and spontaneous abortion have been explored in epidemiological studies of sterilizer workers (Gresie-Brusin et al. 2007; Hemminki et al. 1982; Rowland et al. 1996). Limitations in these studies preclude drawing conclusions regarding the associations between ethylene oxide exposure and pregnancy outcomes.

Hemminki et al. (1982) evaluated possible associations between exposure to ethylene oxide and spontaneous abortion in a retrospective study of 1,443 sterilizer workers in hospitals in Finland. Information on exposures was obtained from questionnaires sent to supervising nurses and information on pregnancy outcomes and other potential confounding factors was obtained from worker self-surveys. Rates of spontaneous abortion were adjusted for age, parity, decade of pregnancy, smoking, and consumption of coffee and alcohol. Rates of spontaneous abortion were 15.1% in workers who were reported to have ethylene oxide exposure during pregnancy (n=545), 11.3% in workers whose exposure to ethylene oxide during pregnancy was recorded as uncertain (n=293), and 4.6% in workers without reported exposure to ethylene oxide during pregnancy (n=605). Estimates of variance on these rates were not reported; however, rates in the exposed and uncertain exposure groups were reported as significantly different from the group not exposed ($p<0.001$). Rates were significantly higher ($p<0.01$) in workers who reported that they were exposed to ethylene oxide but not to glutaraldehyde or formaldehyde (16.1%,

n=1,068). Exposure levels were not measured in this study; however, surveys of Finnish hospital sterilizing units found 8-hour weighted mean concentrations that ranged from 0.1 to 0.5 ppm with a highest measured concentration of 250 ppm. Major limitations in this study include absence of measured exposure levels and reliance on self-administered questionnaires for data on exposure, outcomes, and potential confounders.

Rowland et al. (1996) evaluated possible associations between ethylene oxide exposure and the risk of spontaneous abortion, preterm birth, and post-term birth in a retrospective study of 1,320 female dental assistants. The study included 32 sterilizer operators and 1,288 referents with no reported exposure to ethylene oxide. Information on exposures, pregnancy outcomes, and other potential confounding factors was obtained from self-surveys. After adjusting for age, relative risks (RRs) were 2.5 (95% confidence interval [CI] 1.0–6.3) for spontaneous abortion, 2.7 (95% CI 0.8–8.8) for preterm birth, and 2.1 (95% CI 0.7–5.9) for post-term birth. The RR for any of these outcomes was 2.5 (95% CI 1.0–6.1) after adjustment for age and exposure to nitrous oxide and elemental mercury during preparation of mercury amalgam restorations. The major limitations of this study were absence of measurements of exposure levels and reliance on self-reporting for data on potential exposures to ethylene oxide, outcomes, and potential confounding factors.

Gresie-Brusin et al. (2007) evaluated risks of spontaneous abortion and pregnancy loss in a retrospective study of 98 singleton pregnancies among women with ethylene oxide exposure in sterilizing units of 22 hospitals in South Africa. The study subjects were grouped according to “high” exposure (sterilizer operators, n=19) and “low” exposure (not directly involved in ethylene oxide sterilization, n=79). The median level of ethylene oxide measured with personal monitors of sterilizer operators was below the limit of detection (0.01 ppm) and the mean was 1.03 ppm (standard deviation [SD] 4.2). Information on pregnancy outcomes and other potential confounding factors was obtained from surveys conducted by trained interviewers. Prevalence odds ratios (PORs) were 20.8 (95% CI 2.1–199.3; 4 of 19 in the high-exposure group) for risk of spontaneous abortion and 8.6 (95% CI 1.8–43.7; 6 of 19 in the high-exposure group) for pregnancy loss. The study explored various potential confounders, including age and height, pregnancy rank and gestation length, education, antenatal care, emotional stress, smoking (active and passive), exposure to carbon monoxide and anesthetic gases, alcohol consumption, high blood pressure, diabetes and other medical conditions, and physical activity. Of these, maternal height, antenatal care, and emotional stress were associated with exposure to ethylene oxide and none were associated with pregnancy outcomes. The main limitation of this study was its relatively small size (19 in the high-exposure group), which may have contributed to the relatively wide CIs on the PORs.

Information is available regarding reproductive effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Increased incidence of resorptions, decreased numbers of pups per litter, and decreased numbers of fetuses born relative to numbers of implantation sites were reported in a study of female rats intermittently exposed to ethylene oxide vapor at 150 ppm for 3 weeks premating and during gestation days 1–16 (NIOSH 1982). In a 2-generation study, increased post-implantation loss was observed in F0 rats exposed to 33 ppm (EPA 1994) and decreased numbers of live pups per litter were observed at 100 ppm in the F1 and F2 generations (EPA 1994). Exposure-related effects on male reproductive organs (decreases in testicular and epididymal weights, germ cell survival, sperm count; histopathologic lesions in seminiferous tubules) have been reported for rats following intermittent inhalation exposure to ethylene oxide vapor for 6–13 weeks at exposure levels in the range of 250–500 ppm (Kaido et al. 1992; Mori et al. 1991a, 1991b). Intermittent inhalation exposure of monkeys to ethylene oxide vapor at 50 ppm (the lowest exposure level tested) for 24 months resulted in decreases in sperm count (28% less than controls) and motility (32% less than controls); however, reproductive function was not tested (Lynch et al. 1984a). There was no evidence of histopathological lesions in reproductive organs of rats or mice intermittently exposed for 102–104 weeks at 100 ppm (highest exposure level tested) (Lynch et al. 1984a, 1984b; NTP 1987).

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans after inhalation exposure to ethylene oxide.

Information is available regarding developmental effects in experimental animals following inhalation exposure to ethylene oxide. No information was located for oral or dermal exposure routes.

Decreases in fetal body weight and crown-rump length and increased incidence of reduced ossification were reported following intermittent exposure of maternal rats to ethylene oxide vapor at 150 ppm (the only exposure level tested) for 3 weeks premating and during gestation days 1–16 (NIOSH 1982). Depressed fetal weight (3–9% less than controls) was noted in other studies of maternal rats intermittently exposed to ethylene oxide vapor in the range of 100–800 ppm during gestation (Neeper-Bradley and Kubena 1993; NIOSH 1982; Saillenfait et al. 1996; Snellings et al. 1982a). Decreases in the number of

pups/litter and the ratio of fetuses born to implantation sites were reported in a study of rats intermittently exposed to ethylene oxide vapor at 100 ppm for 12 weeks prior to mating and throughout gestation and lactation periods (Snellings et al. 1982b). In a 2-generation study, decreased pup body weight was observed in the F1 and F2 generations at 33 and 100 ppm (EPA 1994). Saillenfait et al. (1996) reported increased incidence of dilation in the renal pelvis and ureter of rat fetuses following intermittent maternal exposure at 1,200 ppm during gestation days 6–15. Fetal defects (predominantly hydrops and ocular defects) were reported following maternal exposure of mice to ethylene oxide vapor at 1,200 ppm for a single 1.5-hour exposure at timepoints between 1 and 25 hours postmating (Rutledge and Generoso 1989). There were no indications of ethylene oxide exposure-related developmental effects in rabbit fetuses following intermittent inhalation exposure of their mothers at 150 ppm during gestation days 7–19 or 1–19 (NIOSH 1982).

2.18 OTHER NONCANCER

No information was located regarding other noncancer effects in humans or animals following exposure to ethylene oxide.

2.19 CANCER

Carcinogenicity Assessments. The HHS has classified ethylene oxide as *known to be a human carcinogen* (NTP 2016) based on sufficient evidence of carcinogenicity from studies in humans (increased risk of cancer in workers exposed to ethylene oxide during its synthesis, production, and use), and evidence for a common mechanism of carcinogenesis in humans and experimental animals (similar genetic damage in cells of animals and workers exposed to ethylene oxide).

EPA (2016) characterized ethylene oxide as “carcinogenic to humans” by the inhalation exposure route, based on the total weight of evidence. The lines of evidence included “(1) strong, but less than conclusive on its own, including epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO- [ethylene oxide] exposed workers, (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the occurrence of key precursor events are anticipated to occur and progression to tumors in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EtO.” EPA derived unit risk estimates

were based on results from the National Institute for Occupational Safety and Health (NIOSH) study (Steenland et al. 2003, 2004) that evaluated cancer risk in a cohort of workers exposed to ethylene oxide. The authors found positive exposure responses for breast cancer mortality in females for log cumulative exposure and a 20-year lag. Odds ratios (ORs) increased with increasing cumulative exposure level, with elevated ORs in the highest quartile (>123,22 ppm-days), 3.13 (1.42, 6.92). There was also a positive exposure-response for lymphoid tumors (non-Hodgkin's lymphoma, myeloma, and lymphocytic leukemia) in both sexes for cumulative exposure, with elevated ORs in males in the highest quartile (>123,22 ppm-days), 3.76 (1.03, 13.64). The adult-based unit risk estimates were $2.6x10^{-3}$ per $\mu g/m^3$ $4.8x10^{-3}$ per ppb) for lymphoid cancer, $7.0x10^{-4}$ per $\mu g/m^3$ ($1.3x10^{-3}$ per ppb) for female breast cancer (15-year lag), and $3.0x10^{-3}$ per $\mu g/m^3$ ($5.5x10^{-3}$ per ppb) for both cancer types combined. Application of standard age-dependent adjustment factors yields a full lifetime total cancer unit risk estimate of $5.0x10^{-3}$ per $\mu g/m^3$ ($9.1x10^{-3}$ per ppb) (EPA 2016). The commensurate lifetime chronic (lower bound) exposure level of $2x10^{-4}$ $\mu g/m^3$ ($1x10^{-4}$ ppb) corresponds to an increased cancer risk of 10^{-6} (1 in 1,000,000). The unit risk estimate was developed for environmental ethylene oxide exposures up to about 40 $\mu g/m^3$ (20 ppb) and is not applicable to higher exposure levels that may occur in occupational exposure scenarios. Maximum likelihood estimates of extra risk of lymphoid cancer and breast cancer (combined) occupational exposure scenarios in the range of 0.1–1 ppm for an 8-hour time-weighted average (TWA) for 35 years range from 0.037 to 0.11 (upper bound estimates 0.081–0.22).

IARC has produced several reports on the carcinogenicity of ethylene oxide (IARC 1976, 1985, 1987, 1994, 2008, 2012). IARC has designated ethylene oxide as *carcinogenic to humans (Group 1)* (IARC 1987, 2012) based on limited evidence for a causal association between exposure to ethylene oxide and lymphatic and hematopoietic cancers and breast cancer in humans, sufficient evidence for carcinogenicity in animals, and strong evidence for a genotoxic mechanism of action for ethylene oxide carcinogenicity.

The Texas Commission on Environmental Quality (TCEQ 2020) evaluated the carcinogenicity of ethylene oxide and concluded that ethylene oxide is *likely to be carcinogenic to humans*. The TCEQ also determined that the epidemiological data support an association between ethylene oxide exposure and lymphohematopoietic tumors but do not support an association with breast cancer.

Occupational Studies. A number of epidemiological studies have examined possible associations between occupational exposure to ethylene oxide and risk of cancer. Ethylene oxide was first produced using a chlorohydrin process (reaction of ethylene gas with hypochlorous acid to produce ethylene chlorohydrin, which was reacted with calcium oxide to produce ethylene oxide). Workers involved with

this process were exposed to a variety of chemicals, including organochlorine byproducts. The chlorohydrin process was inefficient and was gradually replaced with a direct vapor phase oxidation process (oxidation of ethylene gas in the presence of oxygen and silver catalyst at 10–30 atmospheres of pressure). Workers involved in the oxidation process did not experience exposures to the various chemicals used or produced during the chlorohydrin process. Available epidemiological studies include evaluation of cancer risk among cohorts of production workers involved in the chlorohydrin process and/or the ethylene oxidation process. Sterilization processes using ethylene oxide do not include exposures to the variety of chemicals encountered in the chlorohydrin process of ethylene oxide production.

As noted above, IARC and EPA have evaluated ethylene oxide for carcinogenicity (EPA 2016; IARC 2008, 2012). Both agencies concluded that the most convincing evidence for increased risk among workers exposed to ethylene oxide is for lymphohematopoietic cancers and female breast cancer. The discussion of the epidemiological database in this toxicological profile focuses on evaluations of ethylene oxide and risk of lymphohematopoietic cancers, leukemia, myeloma/multiple myeloma, non-Hodgkin's lymphoma, lymphosarcoma/reticulosarcoma, and breast cancer. Results from a few epidemiological studies and animal studies suggested associations between ethylene oxide exposure and cancer at other sites (e.g., stomach, pancreas, nervous system).

Selected study details for cohorts evaluated for possible associations between exposure to ethylene oxide and selected cancer endpoints are presented in Table 2-3. Study results for leukemia, non-Hodgkin's lymphoma, breast cancer, lymphohematopoietic cancer, myeloma/multiple myeloma, and lymphosarcoma/reticulosarcoma are summarized in Figures 2-4, 2-5, 2-6, 2-7, 2-8, and 2-9, respectively. Note that lymphosarcomas and reticulosarcomas are old cancer classifications; these cancer types are now classified as non-Hodgkin's lymphoma. However, the cancer types discussed below are classified as reported by study authors.

Figures 2-4, 2-5, 2-6, 2-7, 2-8, and 2-9 include information on cohort size, exposure via production or use in sterilization processes, number of observed cancers/expected number, and the plotted risk estimates with 95% CIs. Standard mortality ratios and standard incidence ratios compare rates of cancer deaths or incidence rates in the study population with national rates of cancer death or incidence. Analyses comparing different groups within the same study population to national rates of cancer death or incidence may result in different findings. The footnote ([1]) is used to identify cohorts exposed during ethylene oxide production via the chlorohydrin process. The footnote ([2]) is used to identify cohorts

exposed during ethylene oxide production via the nonchlorohydrin process. Some studies included cohorts that may have been exposed during production of ethylene oxide by the chlorohydrin process in earlier years and by direct oxidation during later years; therefore, these cohorts were not assigned a footnote. The study of Kiesselbach et al. (1990) did not specify a method of ethylene oxide production. A bias in occupational studies is the "healthy worker effect" which can result in a worker population having a lower mortality or morbidity rate compared to the general population resulting in bias towards the null.

Meta-Analyses of Epidemiological Studies. Shore et al. (1993) conducted a review and meta-analysis on cohorts from previously-published studies. The meta-estimate of effect size was the sum of observed cancer deaths for all studies divided by the sum of expected cancer deaths for all studies (E/O ratio, synonymous with standardized mortality ratio [SMR]). This metric gives more weight to studies that have larger numbers of expected cancers. CIs on E/O were calculated using an approximate variance (V) estimate, 1/E; $e^{\ln(E/O)-1.96\cdot sqrt(V)}$. Variance was adjusted for χ^2 heterogeneity. The meta-analysis for leukemia was conducted using data from Bisanti et al. (1993), Gardner et al. (1989), Hagmar et al. (1991), Hogstedt (1988), Kiesselbach et al. (1990), Teta et al. (1993), Wong and Trent (1993), and an unpublished study (update to Greenberg et al. 1990). The reported meta-O/E ratio was 1.06 (95% CI 0.73–1.48) based on 31 incident cases or deaths versus 29.31 expected. No trend in O/E was evident when the meta-data were analyzed by exposure frequency, duration, or cumulative exposure. The meta-analysis for non-Hodgkin's lymphoma was conducted using data from Bisanti et al. (1993), Gardner et al. (1989), Hagmar et al. (1991), Hogstedt (1988), Teta et al. (1993), Thiess et al. (1981), Wong and Trent (1993), and an unpublished study (update to Greenberg et al. 1990). The reported meta-O/E ratio was 1.35 (95% CI 0.93–1.90) based on 31 incident cases or deaths versus 22.93 expected. No trend in O/E was evident when the meta-data were analyzed by exposure frequency, duration, or cumulative exposure.

Teta et al. (1999) updated the meta-analysis of Shore et al. (1993) by including results from Hagmar et al. (1995) and Olsen et al. (1997) and excluding results from Greenberg et al. (1990), Morgan et al. (1981), and Thiess et al. (1981). The meta-estimate of the effect size was the same as that used in Shore et al. (1993), reported as SMR, rather than E/O. The updated meta-analysis included nearly 33,000 workers and >800 cancers. For leukemia and non-Hodgkin's lymphoma risks, reported SMRs were 1.08 (95% CI 0.61–1.93) based on 35 deaths versus 32 expected, and 1.34 (95% CI 0.96–1.89) based on 33 deaths versus 25 expected, respectively; neither leukemia nor non-Hodgkin's lymphoma results exhibited positive trends with duration, intensity, or latency. No trend in SMR was evident when the meta-data

were analyzed by exposure frequency, duration, or cumulative exposure. The study authors considered the results inconclusive for leukemia and for non-Hodgkin's lymphoma.

Marsh et al. (2019) conducted a systematic literature review of occupational exposure to ethylene oxide and risk of lymphohematopoietic cancer and breast cancer and identified 13 studies that were included in a meta-analysis. Marsh et al. (2019) limited their quantitative analysis to comparisons of national or broad geographic rates of cancer death or incidence (e.g., SMR/SIR) rather than estimating exposure-risk relationships within each cohort. Overall meta-relative risks (meta-RRs) were 1.48 (95% CI 1.07–2.05) for lymphohematopoietic cancer and 0.97 (95% CI 0.80–1.18) for breast cancer. For lymphohematopoietic cancer, the study authors reported meta-RRs of 1.46 (95% CI 0.85–2.50) among ethylene oxide production workers and 1.07 (95% CI 0.87–1.30) among ethylene oxide sterilization workers. Higher risks of lymphohematopoietic cancer were noted for earlier published studies, compared to more recent studies. Marsh et al. (2019) considered studies published in the 2000s to have used more sound experimental methods and are, therefore, more informative than earlier studies.

Case Reports. Hogstedt et al. (1979a) reported 3 cases of leukemia within a group of 230 workers at a Swedish facility where hospital equipment was sterilized using ethylene oxide. The study authors estimated an 8-hour time-weighted average (TWA) ethylene oxide level of 20±10 ppm in a storage hallway, which was considered higher than levels in the sterilization area. According to national statistics, 0.2 leukemia cases would have been expected. In a 5-year update of the study, 4 cases of lymphohematopoietic cancer (0.3 expected) were observed among 203 of the workers employed ≥1 year (Hogstedt et al. 1986).

Tompa et al. (1999) reported 8 cases of breast cancer within a group of 98 nurses exposed to ethylene oxide for 5–15 years in a hospital in Hungary. Reported ethylene oxide concentrations in the working area ranged from 5 to 150 mg/m^3 (2.75–82.5 ppm). However, the study did not account for natural low dose radioactivity from radon in local drinking water, genetic predisposition, or effects of potential environmental, occupational, and/or lifestyle confounders.

Swaen et al. (1996) investigated a cluster of 10 cases of Hodgkin's lymphoma within a large chemical manufacturing complex in Belgium. Among 214 different chemical substances evaluated, 5 chemicals exhibited elevated ORs (ammonia, benzene, ethylene oxide, sodium hydroxide, and oleum). The cluster of cases could not be specifically associated with ethylene oxide exposure.

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Hogstedt et al. 1979b	
241 male workers at a Swedish ethylene oxide production facility using the chlorohydrin method of production	Workers employed ≥1 year; 10-year latency applied; study included years 1961–1977; expected deaths based on Swedish national rates:
66 unexposed workers (955 person-years)	O/E ratio 0/0 for leukemia; no reported SMR
89 full-time production workers (1,324 person-years)	O/E ratio 2/0.14 for leukemia; no reported SMR
86 maintenance workers (1,211 person-years)	O/E ratio 1/0.13 for leukemia; no reported SMR
Hogstedt et al. 1986 (5-year update of Hogstedt et al. 1979b subcohort)	
89 full-time production workers (chlorohydrin method) employed ≥1 year with 10-year latency	Results for leukemia and lymphohematopoietic cancers are summarized in Figures 2-4 and 2-7, respectively; update included the years 1961–1982; expected deaths based on Swedish national rates; the study authors noted that excess mortality was most pronounced among workers with ≥10 years of exposure
Hogstedt 1988 (8-year update of Hogstedt et al. 1979b cohort)	
233 male workers at a Swedish ethylene oxide production facility using the chlorohydrin method of production	Update included the years 1962–1985; restricted to male production workers at chlorohydrin unit and employed ≥1 year:
66 unexposed workers	O/E ratio 0/0.1 for leukemia; no reported SMR
89 exposed operators	O/E ratio 2/0.2 for leukemia; no reported SMR
78 exposed repairmen	O/E ratio 1/0.2 for leukemia; no reported SMR
167 exposed operators and repairmen	O/E ratio 3/0.4 for leukemia; reported SMR 7.03 (no reported 95% CI)
Hogstedt 1988 (follow-up of combined cohorts of Hogstedt et al. 1979a, 1979b, 1986)	
709 workers (539 men, 170 women) at production facility using the chlorohydrin process, a production facility using ethylene oxidation process, and an ethylene oxide sterilization unit	Update performed through 1985; most excess mortality attributed to the facility using chlorohydrin method to produce ethylene oxide O/E ratio for leukemia 7/0.8; SMR 9.21 (no 95% CI) O/E ratio for blood/lymphatic cancers 9/2; SMR 4.59 (no 95% CI)
539 male workers only	Results for leukemia and lymphohematopoietic cancers are summarized in Figures 2-4 and 2-7, respectively

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Hagmar et al. 1991	
2,170 ethylene oxide-exposed workers (58,220 person-years) at two Swedish plants producing disposable medical equipment; 1,151 workers (594 men, 557 women) at plant A employed ≥12 months during 1964–1985; 1,019 workers (267 men, 752 women) at plant B employed ≥12 months during 1964–1985	Results for leukemia, female breast cancer, and lymphohematopoietic cancers are summarized in Figures 2-4, 2-6, and 2-7, respectively Expected cancer incidences based on rates in the surrounding county; exposure estimates up to 10–40 ppm during 1970–1981 and ≤3 ppm during 1982–1986 in plant A and up to 10–75 ppm during 1964–1975 and ≤4 ppm during 1976–1986 in plant B
Hagmar et al. 1995 (4-year update of Hagmar et al. 1991 cohort)	
2,170 (1,309 women and 861 men) ethylene oxide-exposed workers (24,851 person-years) at plants A and B with no induction latency	Results for leukemia, female breast cancer, lymphohematopoietic cancers, and multiple myeloma are summarized in Figures 2-4, 2-6, 2-7, and 2-8, respectively
1,649 ethylene oxide-exposed workers (7,326 person-years) at plants A and B with ≥10-year induction latency	2 leukemia cases (0.28 expected) among 930 workers with at least 0.14 ppm-years of cumulative exposure to ethylene oxide and ≥10-year induction latency considered “minor evidence” of association (SIR 7.14; 95% CI 0.87–25.8)
Mikoczy et al. 2011 (20-year update of Hagmar et al. 1991 cohort)	
2,171 ethylene oxide-exposed workers (58,220 person-years); no induction latency period	Results for leukemia, non-Hodgkin’s lymphoma, female breast cancer, lymphohematopoietic cancers, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-6, 2-7, and 2-8, respectively
2,046 ethylene oxide-exposed workers (58,220 person-years; induction latency ≥15 years	Results for leukemia, non-Hodgkin’s lymphoma, female breast cancer, lymphohematopoietic cancers, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-6, 2-7, and 2-8, respectively Incidence rate ratios were elevated in upper quartile of cumulative exposure groups relative to lower quartiles for breast cancer.

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Gardner et al. 1989	
1,471 workers (1,470 men, 1 woman) in England and Wales employed at four companies that produced/used ethylene oxide	Result for leukemia is summarized in Figure 2-4
	O/E ratio 2/1.04 for non-Hodgkin's lymphoma; no reported 95% CIs O/E ratio 0/0.06 for breast cancer; no reported 95% CIs
1,405 workers (394 men, 1,011 women) at hospital sterilization units in England and Wales	No leukemia deaths; 0.76 expected
	O/E ratio 2/0.57 for non-Hodgkin's lymphoma; no reported 95% CIs O/E ratio 4/5.91 for breast cancer; no reported 95% CIs
	Study spanned the years 1956–1987; expected deaths based on local and national rates; industrial hygiene data not available before 1977, but subsequent TWA exposures considered <5 ppm in most jobs and <1 ppm in many of the jobs; previous exposures likely somewhat higher
Coggon et al. 2004 (13-year update of Gardner et al. 1989 cohort)	
1,471 workers (1,470 men, 1 woman at 4 four companies that produced/used ethylene oxide)	Results for leukemia, non-Hodgkin's lymphoma, and multiple myeloma are summarized in Figures 2-4, 2-5, and 2-8, respectively
1,405 workers (394 men, 1,011 women) at hospital sterilization units in England and Wales	Results for leukemia, non-Hodgkin's lymphoma, female breast cancer, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-6, and 2-8, respectively
Combined cohort of 2,876 workers (1,864 men, 1,012 women) at ethylene oxide production facilities and hospital sterilization units	Results for leukemia, non-Hodgkin's lymphoma, female breast cancer, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-6, and 2-8, respectively
Greenberg et al. 1990	
Cohort included 2,174 ethylene oxide-exposed workers at Union Carbide Corporation chemical production facilities in West Virginia (278 workers ever assigned to chlorohydrin units; 1,896 workers never assigned to chlorohydrin units)	Study spanned the years 1940–1978; expected deaths based on U.S. general population, regional population, and 26,965 unexposed men from the same facilities
Subcohort of male workers (number not specified) assigned ≥2 years to chlorohydrin units	Results for leukemia, non-Hodgkin's lymphoma, lymphohematopoietic cancers, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-7, and 2-8, respectively

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Subcohort of male workers (number not specified) assigned ≥2 years to ethylene oxide areas, but never to chlorohydrin units	Results for leukemia, non-Hodgkin's lymphoma, lymphohematopoietic cancers, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-7, and 2-8, respectively
Combined cohort of 2,174 male workers ever assigned to ethylene oxide using/producing departments	Results for leukemia, non-Hodgkin's lymphoma, lymphohematopoietic cancers, and multiple myeloma are summarized in Figures 2-4, 2-5, 2-7, and 2-8, respectively
Benson and Teta 1993 (10-year update of Greenberg et al. 1990 subcohort ever assigned to chlorohydrin units)	
278 male workers ever assigned to chlorohydrin units	Results for lymphohematopoietic cancers are summarized in Figure 2-7 SMRs not calculated for leukemia or lymphosarcoma/reticulosarcoma (observed and/or expected deaths <5).
Teta et al. 1993 (10-year update of a subcohort from the cohort of Greenberg et al. 1990)	
1,896 male workers (excludes 278 workers with "low" potential for exposure to ethylene oxide)	Results for leukemia and lymphohematopoietic cancers are summarized in Figures 2-4 and 2-7, respectively SMR not calculated for lymphosarcoma/reticulosarcoma (observed and expected deaths <5)
Swaen et al. 2009 (25-year update of subcohort of male workers within original cohort of Greenberg et al. 1990)	
Subcohort of 2,063 male workers from the original cohort of 2,174 workers	Results for leukemia, non-Hodgkin's lymphoma, and lymphohematopoietic cancers are summarized in Figures 2-4, 2-5, and 2-7, respectively Update included years 1940–2003; original cohort of 2,174 workers from Greenberg et al. 1990 redefined, proportional hazards modeling for leukemia, lymphoid malignancies revealed no trends or associations with cumulative exposure; estimated 8-hour TWA exposure levels 0.3–21 ppm during 1940–1988 and up to 70 ppm during 1925–1939

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Steenland et al. 1991 (NIOSH-based cohort)	
18,254 workers (8,214 men, 10,040 women) at 14 facilities producing sterilized medical supplies and spices; workers had at least 90 days of exposure to ethylene oxide	Results for leukemia, non-Hodgkin's lymphoma, breast cancer, hematopoietic cancers, myeloma/multiple myeloma, and lymphosarcoma/reticulosarcoma are summarized in Figures 2-4, 2-5, 2-6, 2-7, 2-8, and 2-9, respectively Mortality evaluated through 1987 and compared to that of U.S. general population; estimated 8-hour TWA exposure levels 4.3 ppm for sterilizer operators and 2.0 ppm for other workers after 1977, likely several times higher in earlier years
Stayner et al. 1993 (evaluation includes 13 of the 14 facilities from the NIOSH-based cohort of Steenland et al. 1991)	
Workers at 13 facilities producing sterilized medical supplies and spices	Results for leukemia, non-Hodgkin's lymphoma, and hematopoietic cancers are summarized in Figures 2-4, 2-5, and 2-7, respectively One of the original 14 facilities excluded due to inadequate data for historical exposure estimation
Wong and Trent 1993 (evaluation includes the 14 facilities from the NIOSH-based cohort of Steenland et al. 1991)	
18,728 workers (8,709 men, 10,019 women) at 14 facilities producing sterilized medical supplies and spices	Results for leukemia, female breast cancer, lymphopoietic cancers, and lymphosarcoma/reticulosarcoma are summarized in Figures 2-4, 2-6, 2-7, and 2-9, respectively. Mortality evaluated through 1988; 8-hour TWA exposure estimates for sterilizer workers (20% of cohort) were 4–5 ppm after 1978 and 16 ppm for earlier times; exposure estimates for the rest of the cohort were 2 ppm after 1978 and 5 ppm for earlier times; possibly higher short-term exposures.
Steenland et al. 2004 (11-year update of the cohort of Steenland et al. 1991)	
18,235 workers (8,214 men, 10,040 women) at 14 facilities using ethylene oxide for sterilization	Results for leukemia, non-Hodgkin's lymphoma, female breast cancer, hematopoietic cancers, and myeloma/multiple myeloma are summarized in Figures 2-4, 2-5, 2-6, 2-7, and 2-8, respectively Positive trend for hematopoietic cancers in males with a 15-year lag time (driven by lymphoid tumors); positive trend for breast cancer using log of cumulative exposure and 20-year lag time

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Steenland et al. 2003 (NIOSH-based cohort)	
7,576 female workers employed for at least 1 year at 14 facilities using ethylene oxide for sterilization	Results for breast cancer are summarized in Figure 2-6
	Positive trends for breast cancer in females with a 15-year time lag using log of cumulative exposure using all cases and cases with interviews
Bisanti et al. 1993	
1,971 male chemical workers licensed to handle ethylene oxide for ≥1 year in northern Italy	Results for leukemia, hematopoietic cancers, and lymphosarcoma/reticulosarcoma are summarized in Figures 2-4, 2-7, and 2-9, respectively
Subcohort of 637 workers licensed to handle ethylene oxide only	Results for leukemia, hematopoietic cancers, and lymphosarcoma/reticulosarcoma are summarized in Figures 2-4, 2-7, and 2-9, respectively
	Evaluation included the years 1938–1984; expected deaths based on rates within the regional general population
Kiesselbach et al. 1990	
2,658 employees exposed to ethylene oxide for ≥1 year at German chemical companies	Results for leukemia and lymphohematopoietic cancers are summarized in Figures 2-4 and 2-7, respectively
	Evaluation included the years 1928–1981; expected deaths based on rates within the German general population
Morgan et al. 1981	
767 male workers employed for ≥5 years at ethylene oxide production facility (production method not specified)	Evaluation included the years 1955–1977
	No leukemia deaths versus 0.70 expected deaths based on U.S. vital statistics
Norman et al. 1995	
928 female workers employed for any time from July 1, 1974 through September 30, 1980 at a plant with potential for ethylene oxide exposure	Results for breast cancer are summarized in Figure 2-6; evaluated through December, 1987; expected incidences based on SEER rates

Table 2-3. Study Design Details for Selected Cohorts of Workers Exposed to Ethylene Oxide

Reference/cohort description	Comments
Olsen et al. 1997	
1,361 male workers employed at Dow Chemical facilities for ≥1 year and potentially engaged for ≥1 month in ethylene chlorohydrin and/or propylene chlorohydrin production	Results for leukemia, lymphohematopoietic cancers, and lymphosarcoma/ reticulosarcoma are summarized in Figures 2-4, 2-7, and 2-9, respectively Evaluation included the years 1940–1992; expected death rates based on U.S. white males; analyses examining location, production process, duration of employment, and 25-year induction latency did not result in significant findings

95% CI = 95% confidence interval; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; O/E = observed deaths or incidences/expected deaths or incidences; RR = rate ratio; SEER = Surveillance Epidemiology and End Results; SIR = standardized incidence ratio; SMR = standardized mortality ratio; TWA = time-weighted average

Figure 2-4. Summary of Studies Evaluating Leukemia in Workers Exposed to Inhaled Ethylene Oxide

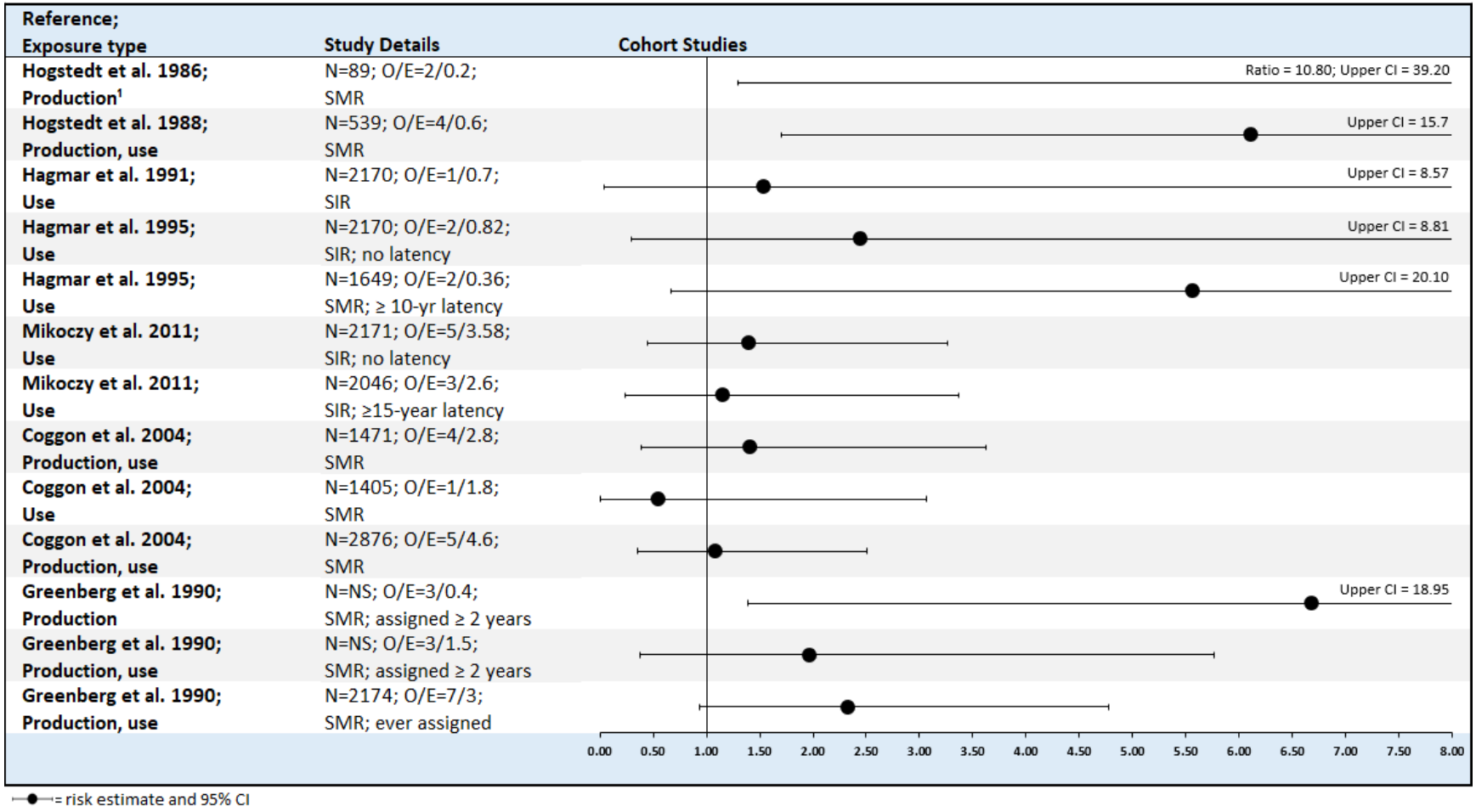
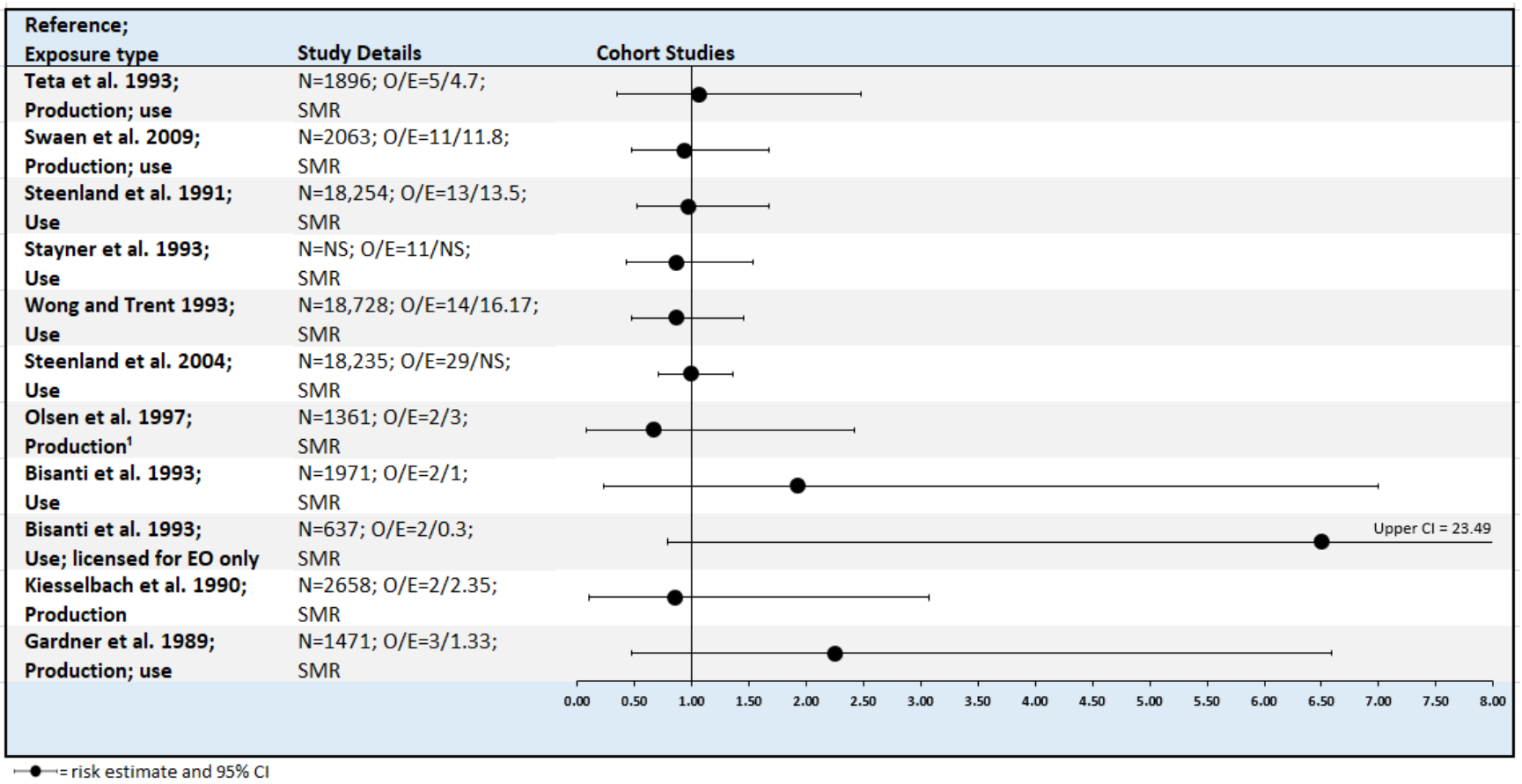
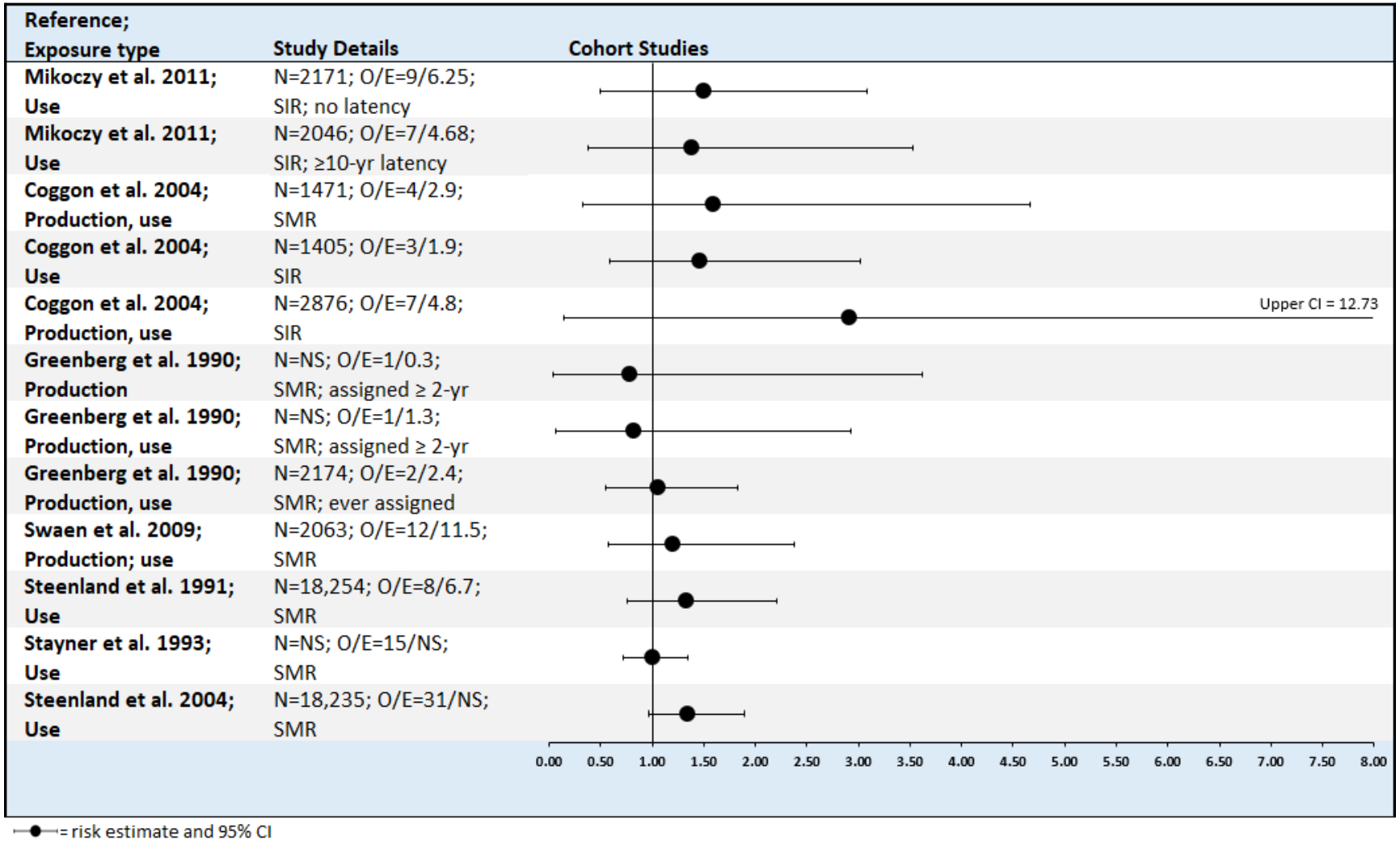


Figure 2-4. Summary of Studies Evaluating Leukemia in Workers Exposed to Inhaled Ethylene Oxide (continued)



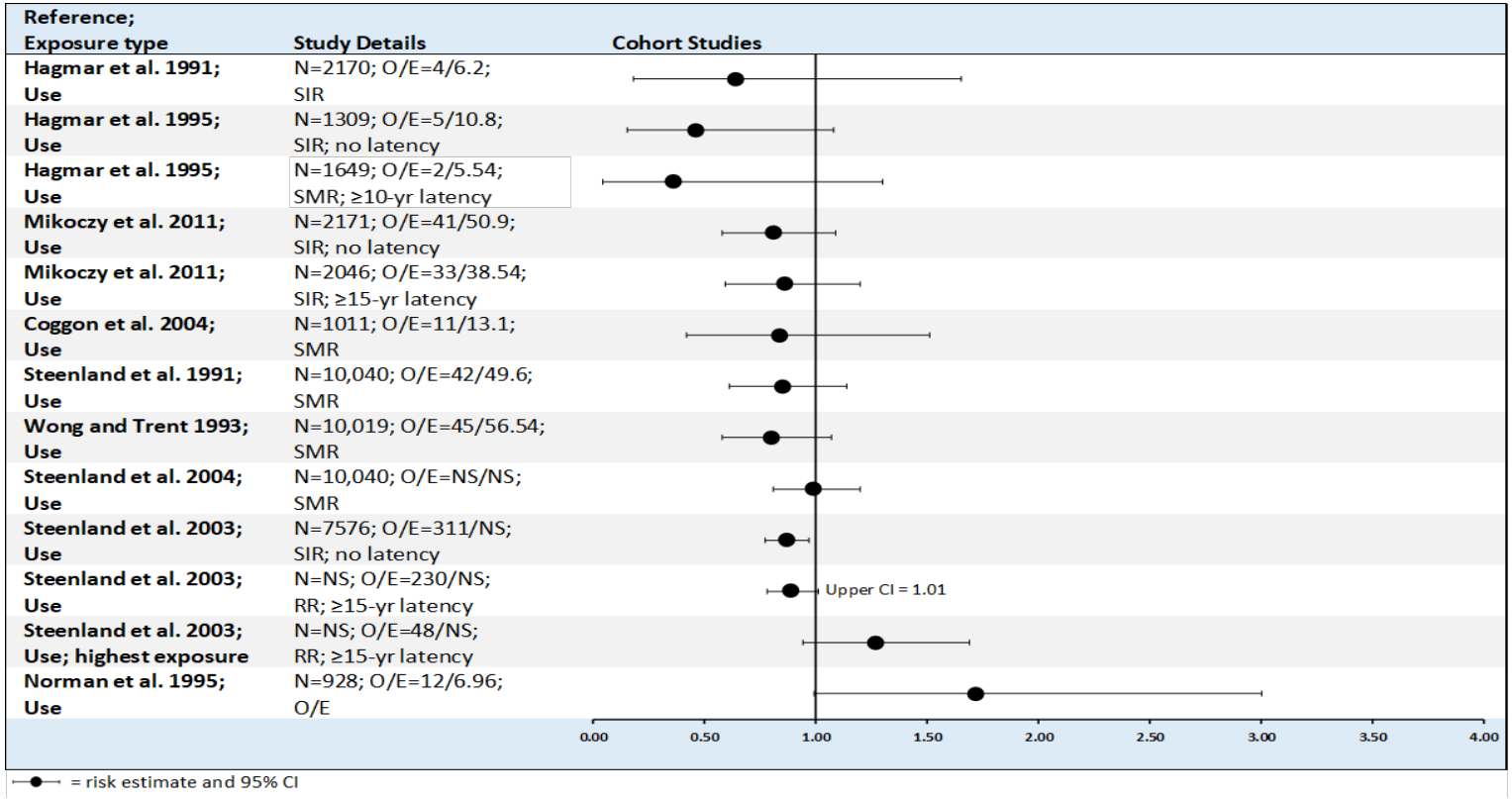
1 = production via chlorohydrin process; CI = confidence interval; EO = ethylene chloride; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene oxide production; Use = workers exposed via ethylene oxide sterilization process

Figure 2-5. Summary of Epidemiological Studies Evaluating Non-Hodgkin's Lymphoma in Workers Exposed to Inhaled Ethylene Oxide



CI = confidence interval; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene oxide production; Use = workers exposed via ethylene oxide sterilization process

Figure 2-6. Summary of Epidemiological Studies Evaluating Breast Cancer in Workers Exposed to Ethylene Oxide*



*SMRs/SIRs are presented in the figure for ease of comparison across multiple studies and datasets. Additional analyses below use internal comparisons, which may reduce potential confounding from the healthy worker effect.

Mikoczy et al. (2011)[a] found a positive association between inhaled ethylene oxide and breast cancer incidence: Incidence rate ratio (IRR) for upper exposure quartiles (Q) versus Q1-2: Q3: 2.76 (95% CI: 1.20, 6.33); Q4: 3.55 (95% CI: 1.58, 7.93).

Steenland et al. (2004) found a positive association between inhaled ethylene oxide and breast cancer mortality: Cox regression coefficient for cumulative exposure with 20-year lag, (trend: p=0.01); odds ratio for upper quartile (Q) versus unexposed: Q4 3.13 (95% CI: 1.42, 6.92).

Steenland et al. (2003) found positive associations between inhaled ethylene oxide and breast cancer incidence: Cox regression coefficient for log cumulative exposure with 15-year lag, (trend: p=0.05); odd ratio for upper quartile (Q) versus unexposed: Q5 1.87 (95% CI: 1.12–3.10).

CI = confidence interval; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; RR = rate ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene oxide production; Use = workers exposed via ethylene oxide sterilization process

Figure 2-7. Summary of Epidemiological Studies Evaluating Lympho-Hematopoietic Cancer in Workers Exposed to Inhaled Ethylene Oxide*

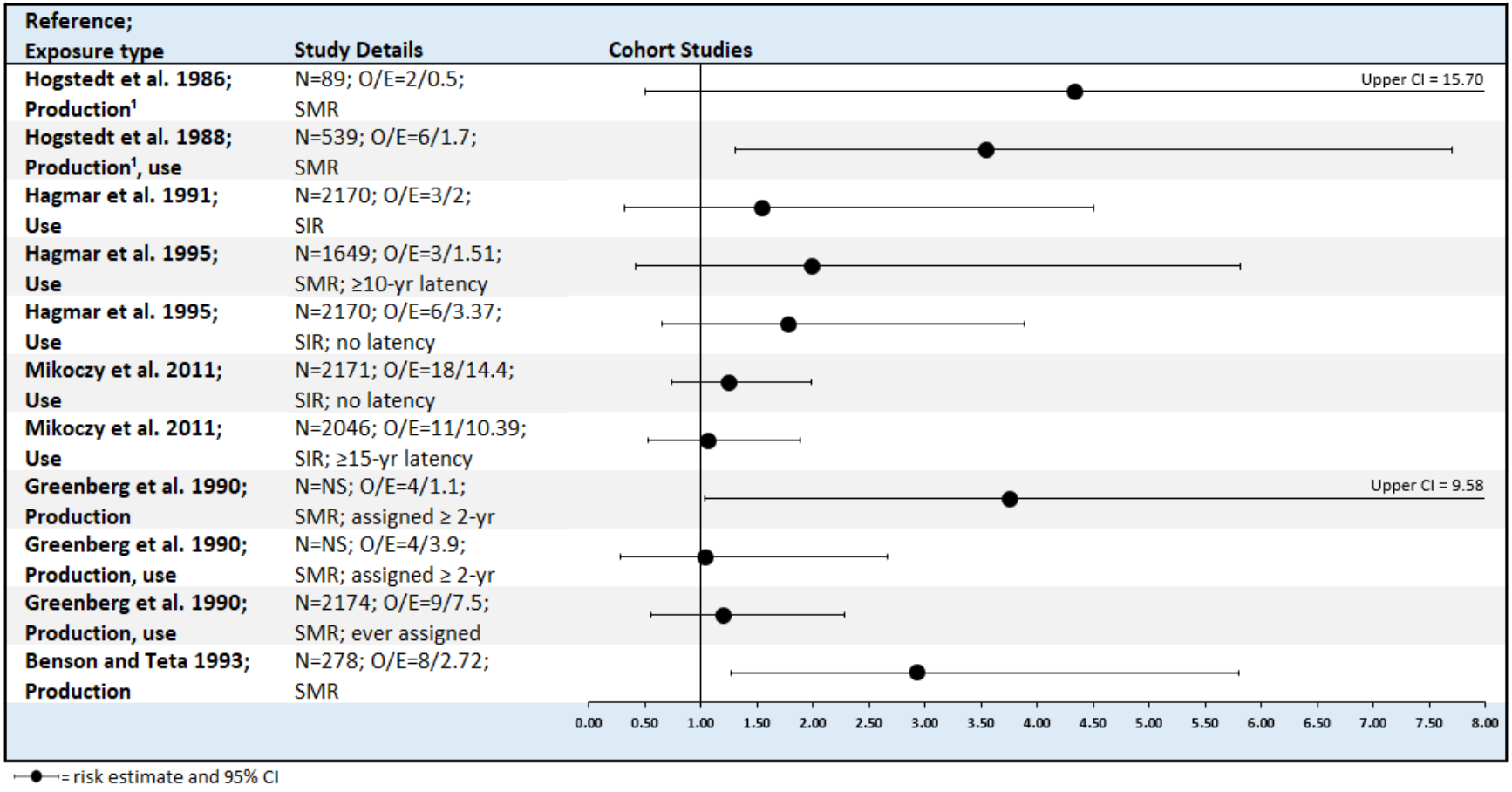
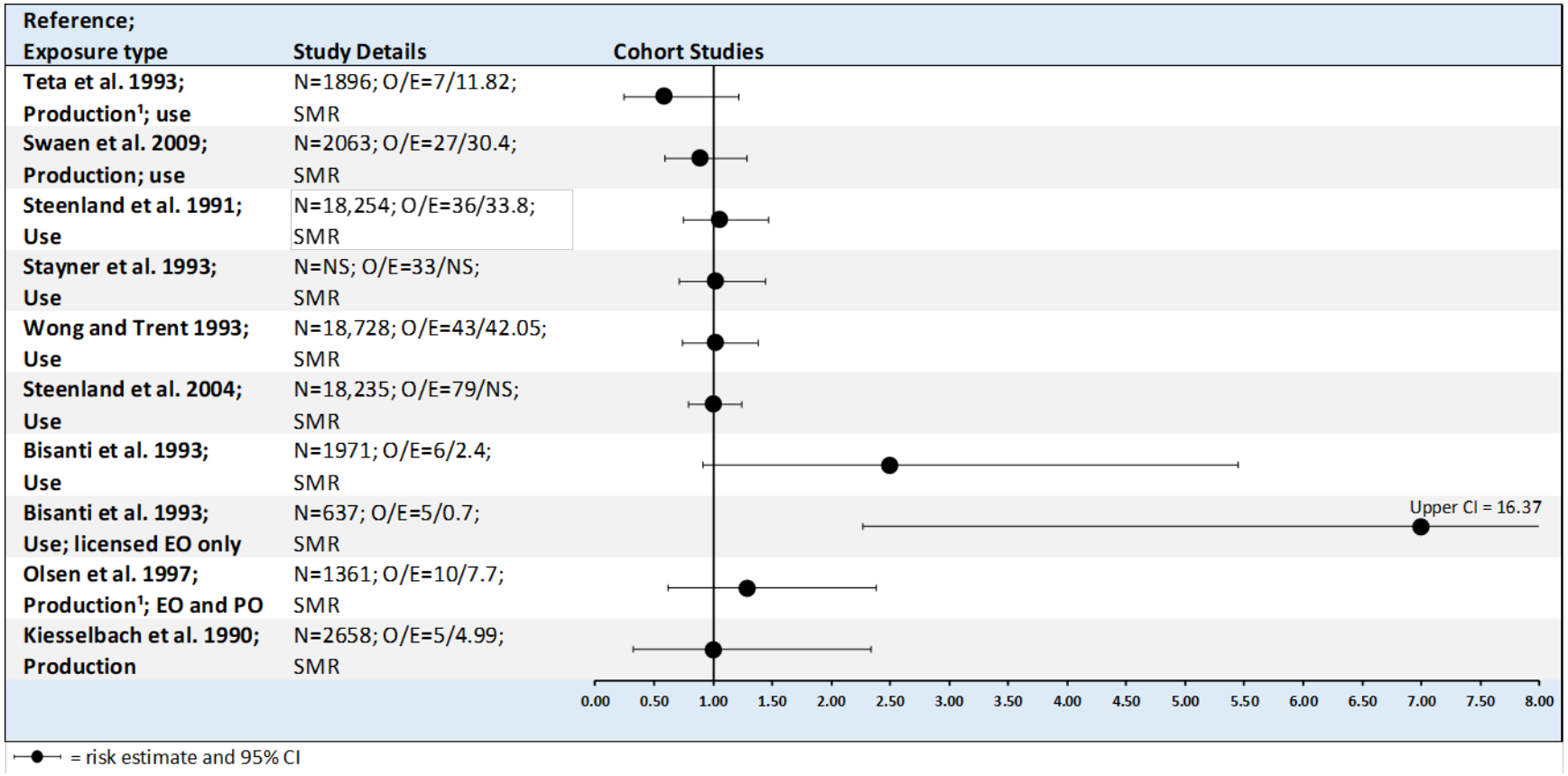


Figure 2-7. Summary of Epidemiological Studies Evaluating Lympho-Hematopoietic Cancer in Workers Exposed to Ethylene Oxide* (continued)

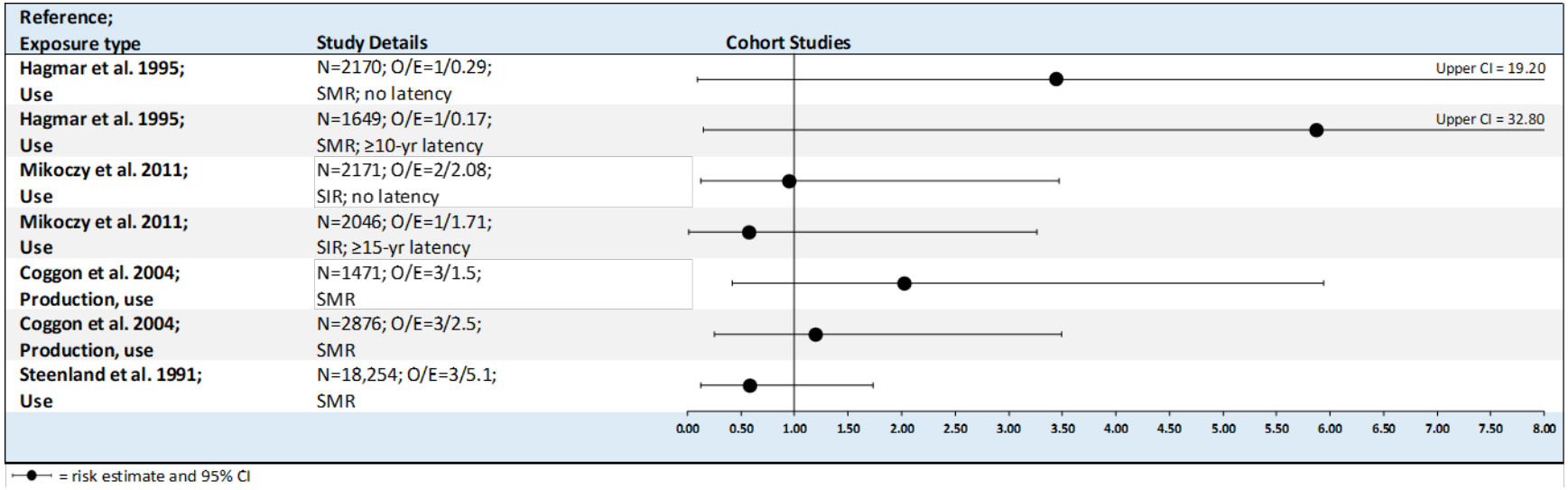


*SMRs/SIRs are presented in the figure for ease of comparison across multiple studies and datasets. Additional analyses noted below use internal comparisons, which may reduce potential confounding from the healthy worker effect.

Steenland et al. (2004) found a positive association between inhaled ethylene oxide and lympho-hematopoietic cancer: Cox regression coefficient for continuous log cumulative exposure (trend: p = 0.02); odds ratio for upper quartiles (Q) versus unexposed: Q4(males): 3.76 (95% CI: 1.03, 13.64).

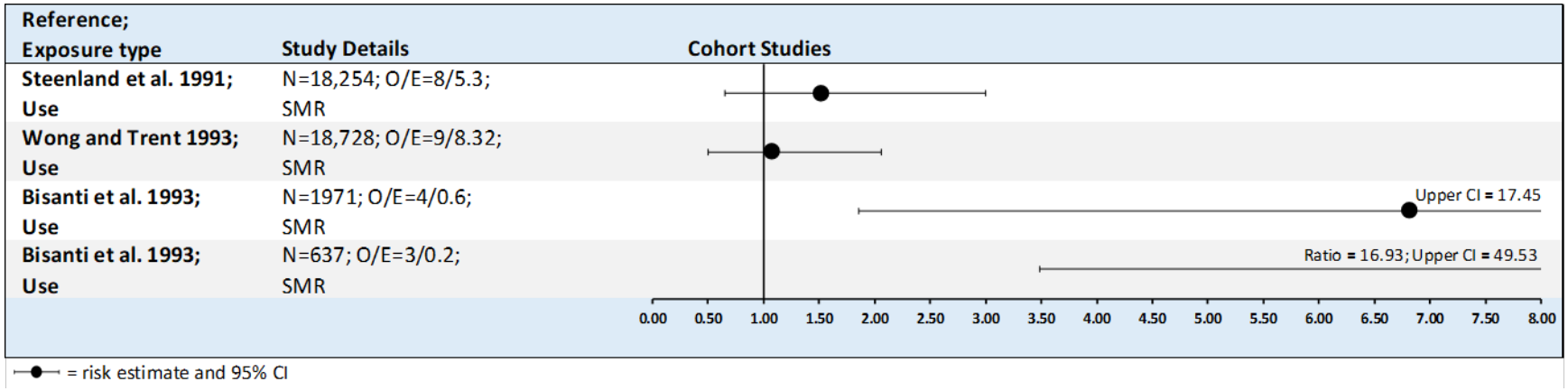
1 = production via chlorohydrin process; CI = confidence interval; EO = ethylene oxide; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; PO = propylene oxide; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene oxide production; Use = workers exposed via ethylene oxide sterilization process

Figure 2-8. Summary of Epidemiological Studies Evaluating Myeloma-Multiple Myeloma in Workers Exposed to Inhaled Ethylene Oxide



CI = confidence interval; N = cohort size; O/E = observed deaths (incidences)/expected; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene oxide production; Use = workers exposed via ethylene oxide sterilization process

Figure 2-9. Summary of Epidemiological Studies Evaluating Lymphosarcoma/Reticulosarcoma in Workers Exposed to Inhaled Ethylene Oxide



CI = confidence interval; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; SMR = standardized mortality ratio; Use = workers exposed via ethylene oxide sterilization process

Animal Studies. Animal studies examining the carcinogenicity of ethylene oxide have reported increased incidences of several tumor types. Significantly increased incidence of brain gliomas (5/79 versus 0/76 controls; $p<0.05$) and peritoneal mesotheliomas (21/79 versus 3/78 controls; $p<0.01$) were reported among male Fischer 344 rats intermittently exposed by inhalation for up to 2 years at 100 ppm (Lynch et al. 1984a, 1984b). An increase in the incidence of mononuclear cell leukemia was also observed at 50 ppm (38/79 versus 24/77 controls, $p<0.01$).

Neoplastic changes reported in rats following exposure to ethylene oxide vapor for up to 2 years included splenic mononuclear cell leukemia, peritoneal mesothelioma, subcutis fibroma, and primary brain neoplasms (Garman et al. 1985, 1986; Snellings et al. 1984b). Significantly increased incidence of spleen mononuclear cell leukemia was observed in female rats exposed to ethylene oxide vapor for up to 2 years at 100 ppm (58% versus 8 or 11% controls; $p<0.01$). Although the incidence was only statistically significantly elevated at 100 ppm, increased incidences were also observed at 10 ppm (11/54 versus 11/115 in controls) and 33 ppm (14/48). When incidences among rats dying early or killed in moribund condition were included, there were significant mortality-adjusted trends for mononuclear cell leukemia in males and females at ≥33 ppm (incidence data not reported). Male rats of the 100 ppm exposure group exhibited significant increases in peritoneal mesothelioma when rats that died or were killed in moribund condition were included (no incidence reported) and subcutis fibroma (36% versus 2 and 4% control; $0.01>p>0.001$). A significant trend for primary brain neoplasms was observed in males ($p<0.01$) and females ($p<0.05$).

In a 2-year inhalation study of male and female B6C3 F1 mice, ethylene oxide exposure at 100 ppm resulted in significantly increased incidence of alveolar/bronchiolar carcinoma (16/50 versus 6/50 controls, $p=0.048$ according to life table analysis) in males, and significantly increased incidences of alveolar/bronchiolar adenoma (17/49 versus 2/49 controls; $p=0.001$) and alveolar/bronchiolar carcinoma (7/49 versus 0/49 controls, $p=0.019$) in female mice (NTP 1987). Incidences of Harderian gland papillary cystadenoma were increased at 50 ppm in males (9/44, $p=0.014$) and females (6/46, $p=0.052$) and at 100 ppm in males (8/42, $p=0.021$) and females (8/47, $p=0.039$). The 100 ppm group of female mice also exhibited marginally significantly increased incidence of malignant lymphoma in the hematopoietic system (22/49 versus 9/49 controls; $p=0.049$) and uterine adenocarcinoma (5/49 versus 0/49 controls; $p=0.058$). The 50 ppm (but not 100 ppm) group of female mice also exhibited increased incidences of hepatocellular adenoma (8/48 versus 1/49; $p=0.021$) and mammary gland adenocarcinoma or adenosquamous carcinoma combined (8/48 versus 1/49 controls; $p=0.020$). Picut et al. (2003) re-evaluated the pathology and tumor incidence data from NTP (1987) and confirmed the results.

Significantly increased incidences of lung adenomas were reported among female A/J mice intermittently exposed to ethylene oxide vapor for 6 months at 70 or 200 ppm; lung adenoma incidences were 16/28 and 25/29, respectively, compared to 8/30 controls (Adkins et al. 1986). Incidences were statistically significantly increased in both ethylene oxide-exposed groups. In a replicate study that included controls and 200 ppm groups, incidences of lung adenomas in surviving mice were 9/29 (29%) and 12/28 (42%), respectively.

Dose-related increased incidence of malignant tumors of the forestomach (the application site for oral gavage) was reported among female rats administered ethylene oxide by gavage at 7.5 or 30 mg/kg/day for 2 days/week for 150 weeks; incidences were 8/50 and 31/50, respectively, compared to no stomach tumors among 50 vehicle and 50 untreated controls (Dunkelberg 1982). A total of 37 of the 39 tumors were squamous cell carcinomas.

In a lifetime skin painting study, application of a 10% solution of ethylene oxide to the backs of mice did not result in skin tumors (Van Duuren et al. 1965).

2.20 GENOTOXICITY

Ethylene oxide has been demonstrated to be genotoxic in human and animal studies *in vivo* and in a wide variety of test systems *in vitro*. Extensive reviews are available regarding the genotoxicity of ethylene oxide (see EPA 2016; IARC 1994, 2008, 2012). Studies evaluating the genotoxicity of ethylene oxide in humans and *in vivo* studies using experimental test species are summarized in Tables 2-4 and 2-5, respectively. Results from selected *in vitro* assays are summarized in Table 2-6. Available data collectively demonstrate the mutagenicity and clastogenicity of ethylene oxide both *in vitro* and *in vivo*. Ethylene oxide induced gene mutation, chromosomal aberrations, sister chromatid exchange, micronucleus formation, deoxyribonucleic acid (DNA) strand breaks, unscheduled DNA synthesis, and cell transformation *in vitro*. Ethylene oxide induced gene mutation, specific locus mutation, chromosomal aberrations, sister chromatid exchange, micronucleus formation, dominant lethal mutation, and heritable translocation in test species and/or occupationally-exposed humans. Although some conflicting results were observed in occupational studies, results of human studies support that ethylene oxide is genotoxic in humans. Preston (1999) noted that results may vary due to numerous confounding

factors, including the time of testing relative to exposure. However, despite some negative results in human studies, IARC (2012) concluded the following regarding the genotoxicity of ethylene oxide:

> "Ethylene oxide consistently acts as a mutagen and clastogen at all phylogenetic levels, it induces heritable translocations in the germ cells of exposed rodents, and a dose-related increase in the frequency of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes of exposed workers."

In addition to these genotoxic effects, *in vitro* studies in mammal tissues, *in vivo* studies in rats and mice, and studies in humans have demonstrated the formation of DNA adducts. Ethylene oxide is an alkylating agent that forms adducts with DNA, ribonucleic acid (RNA), and proteins. The primary DNA adduct formed is N7-(2-hydroxyethyl)guanine (7-HEG). Other DNA adducts have been found in lesser amounts, these include N3-(2-hydroxyethyl)adenine and O^6-(2-hydroxyethyl)guanine (EPA 2016; IARC 2012). 7-HEG has been detected in various tissues of rats exposed via inhalation to ethylene oxide for up to 4 weeks (Walker et al. 1990). Duration-related increases were observed in the brain, lungs, spleen, kidneys, leukocytes, liver, and testes. In addition to DNA adducts produced from exposure to exogenous ethylene oxide, DNA adducts can also form from endogenously produced ethylene oxide.

Table 2-4. Genotoxicity of Ethylene Oxide in Humans

Ethylene oxide exposure group	Test system	Endpoint	Result	Reference
Hospital nurses	Lymphocytes	Gene mutation	–	Major et al. 2001
Hospital, factory sterilization workers	Lymphocytes	Gene mutation	–	Tates et al. 1991
Chemical manufacturing workers	Lymphocytes	Gene mutation	–	Tates et al. 1995
Hospital workers	Lymphocytes	Gene mutation	–	Tomkins et al. 1993
Sterilization plant workers	Lymphocytes	Chromosomal aberrations	+	Galloway et al. 1986
Production workers	Lymphocytes	Chromosomal aberrations	+	Högstedt et al. 1990
Production, sterilization workers	Lymphocytes	Chromosomal aberrations	+	Karelová et al. 1987
Hospital sterilization workers	Lymphocytes	Chromosomal aberrations	+	Lerda and Rizzi 1992
Sterilization workers	Lymphocytes	Chromosomal aberrations	+, –	Richmond et al. 1985
Hospital, factory sterilization workers	Lymphocytes	Chromosomal aberrations	+	Tates et al. 1991
Chemical industry workers	Lymphocytes	Chromosomal aberrations	+	Thiess et al. 1981

Table 2-4. Genotoxicity of Ethylene Oxide in Humans

Ethylene oxide exposure group	Test system	Endpoint	Result	Reference
Sterilization plant workers	Lymphocytes	Chromosomal aberrations	(+)	Pero et al. 1981
Hospital sterilization workers	Lymphocytes	Chromosomal aberrations	(+)	Sarto et al. 1984
Chemical industry workers	Lymphocytes	Chromosomal aberrations	–	Clare et al. 1985
Hospital sterilization workers	Lymphocytes	Chromosomal aberrations	–	Mayer et al. 1991
Chemical production workers	Lymphocytes	Chromosomal aberrations	–	Ribeiro et al. 1994
Chemical industry workers	Lymphocytes	Chromosomal aberrations	–	van Sittert et al. 1985
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Garry et al. 1979
Highly-exposed sterilization workers	Lymphocytes	Sister chromatid exchange	+	Laurent 1988
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Laurent et al. 1984
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Lerda and Rizzi 1992
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Mayer et al. 1991
Hospital workers	Lymphocytes	Sister chromatid exchange	+	Richmond et al. 1985
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Sarto et al. 1984
Sanitary workers	Lymphocytes	Sister chromatid exchange	+	Sarto et al. 1987
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Schulte et al. 1992
Sterilization plant workers	Lymphocytes	Sister chromatid exchange	+	Stolley et al. 1984
Hospital, factory sterilization workers	Lymphocytes	Sister chromatid exchange	+	Tates et al. 1991
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	+	Yager et al. 1983
Sterilization plant workers	Lymphocytes	Sister chromatid exchange	(+)	Lambert and Lindblad 1980
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	±	Sarto et al. 1991
Hospital sterilization workers	Lymphocytes	Sister chromatid exchange	–	Hansen et al. 1984
Production workers	Lymphocytes	Sister chromatid exchange	–	Tates et al. 1995
Hospital workers	Lymphocytes	Sister chromatid exchange	–	Tomkins et al. 1993
Production workers	Lymphocytes	Micronucleus formation	+	Högstedt et al. 1990
Hospital, factory sterilization workers	Lymphocytes	Micronucleus formation	+	Tates et al. 1991
Hospital sterilization workers	Lymphocytes	Micronucleus formation	–	Mayer et al. 1991
Hospital sterilization workers	Lymphocytes	Micronucleus formation	–	Schulte et al. 1992
Hospital sterilization, preparation workers	Lymphocytes	Micronucleus formation	–	Sarto et al. 1991
Production workers	Lymphocytes	Micronucleus formation	–	Tates et al. 1995

Table 2-4. Genotoxicity of Ethylene Oxide in Humans

Ethylene oxide exposure group	Test system	Endpoint	Result	Reference
Chemical production workers	Buccal cells	Micronucleus formation	–	Ribeiro et al. 1994
Factory sterilization workers	Buccal cells	Micronucleus formation	–	Sarto et al. 1990
Hospital sterilization, preparation workers	Buccal cells	Micronucleus formation	–	Sarto et al. 1991
Factory sterilization workers	Nasal cells	Micronucleus formation	+	Sarto et al. 1990
Hospital sterilization workers	Granulocytes	DNA adducts	(+)	Yong et al. 2007
Hospital sterilization workers		DNA strand breaks	–	Mayer et al. 1991
Hospital sterilization workers		DNA cross-links	+	Popp et al. 1994
Commercial, hospital sterilization workers	Peripheral blood mononuclear cells	DNA damage	+	Fuchs et al. 1994

– = negative result; + = positive result; (+) = weakly positive result; ± = inconclusive

Table 2-5. Genotoxicity of Ethylene Oxide in Experimental Test Species *In Vivo*

Species (test system)	Endpoint	Results	Reference
Drosophila melanogaster	Sex-linked recessive lethal mutation	+	Bird 1952; Fahmy and Fahmy 1956; IARC 1994; Vogel and Nivard 1997, 1998; Watson 1966; Zijlstra and Vogel 1988
D. melanogaster	Somatic mutation	+	Fahmy and Fahmy 1970
D. melanogaster	Heritable translocation	+	IARC 1994
D. melanogaster	Heritable translocation	+	Watson 1966
D. melanogaster	DNA adducts	+	Nivard et al. 2003
Rat splenic, thymic T-lymphocytes	Gene mutation	+	Walker et al. 1997
Rat splenic T-lymphocytes	Gene mutation	(+)	Tates et al. 1999
Mouse splenic T-lymphocytes	Gene mutation	+	Walker and Skopek 1993
Mouse lung lymphocytes	Gene mutation	+	Sisk et al. 1997
Mouse bone marrow, germ cells	Gene mutation	+	Recio et al. 2004
Mouse bone marrow, splenic lymphocytes	Gene mutation	–	Sisk et al. 1997
Mouse germ cells	Gene mutation	–	Sisk et al. 1997
Mouse germ cells	Specific locus gene mutation	–	Russell et al. 1984
		+	Lewis et al. 1986, 1990
Rat lymphocytes	Chromosomal aberrations	–	Kligerman et al. 1983
Rat lymphocytes	Chromosomal aberrations	–	van Sittert et al. 2000
Mouse lymphocytes	Chromosomal aberrations	+	Donner et al. 2010
Rat bone marrow cells	Chromosomal aberrations	–	Union Carbide 1980
Mouse bone marrow cells	Chromosomal aberrations	+	Ribeiro et al. 1987; Farooqi et al. 1993

Table 2-5. Genotoxicity of Ethylene Oxide in Experimental Test Species *In Vivo*

Species (test system)	Endpoint	Results	Reference
Mouse spermatocytes	Chromosomal aberrations	+	Ribeiro et al. 1987
Monkey lymphocytes	Chromosomal aberrations	+	Lynch et al. 1984c
Rat lymphocytes	Sister chromatid exchange	+	Kligerman et al. 1983
Rat bone marrow, splenic cells	Sister chromatid exchange	+	Lorenti Garcia et al. 2001; Ong et al. 1993
Mouse bone marrow cells	Sister chromatid exchange	+	Farooqi et al. 1993
Rabbit lymphocytes	Sister chromatid exchange	+	Yager 1987; Yager and Benz 1982
Monkey lymphocytes	Sister chromatid exchange	+	Kelsey et al. 1988; Lynch et al. 1984c
Rat bone marrow cells	Micronucleus formation	+	IARC 1994
Rat bone marrow, splenic cells	Micronucleus formation	+	Hochberg et al. 1990; Lorenti Garcia et al. 2001
Mouse bone marrow cells	Micronucleus formation	+	Farooqi et al. 1993; IARC 1994; Jenssen and Ramel 1980
Rat splenic T-lymphocytes	Micronucleus formation	(+)	Tates et al. 1999
Rat lymphocytes	Micronucleus formation	–	van Sittert et al. 2000
Mouse sperm	Single strand breaks	+	Sega and Generoso 1988
Mouse spermatids	Single strand breaks	+	Sega et al. 1988
Mouse lymphocytes	Reciprocal translocation	(+)	Donner et al. 2010
Mouse (germ cells)	Heritable translocation	+	Generoso et al. 1980, 1990
Chinese hamster V79 cells	Heritable translocation	+	Generoso et al. 1980, 1990
Rat	Dominant lethal mutation	+	Embree et al. 1977
Mouse	Dominant lethal mutation	+	Generoso et al. 1980, 1983, 1986, 1990
Mouse	Dominant lethal mutation	–	Appelgren et al. 1977
Rat liver, testis DNA	DNA adducts	+	Osterman-Golkar et al. 1993
Rat DNA	DNA adducts	+	Potter et al. 1989
Rat brain, spleen, liver DNA	DNA adducts	+	Rusyn et al. 2005
Rat brain, lung, spleen, kidney, liver, testis DNA	DNA adducts	+	Walker et al. 1992b
Rat lymphocyte DNA	DNA adducts	(+)	van Sittert et al. 2000
Mouse DNA	DNA adducts	+	Ehrenberg et al. 1974
Rat brain, lung, spleen, kidney, liver, testis DNA	DNA adducts	+	Walker et al. 1990
Mouse germ cell DNA	DNA adducts	+	Sega et al. 1991
Mouse DNA	DNA adducts	+	Segerbäck 1983

– = negative result; + = positive result; (+) = weakly positive result

Table 2-6. Genotoxicity of Ethylene Oxide *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms:				
Salmonella typhimurium				
TA100, TA1535	Gene mutation		+	Agurell et al. 1991
TA100, TA1535	Gene mutation	+	+	De Flora 1981
TA98, TA1537, TA1538	Gene mutation	–	–	De Flora 1981
TA100, TA102	Gene mutation	+		Hughes et al. 1987
TA98, TA100, TA1535, TA1537	Gene mutation		+	Pfeiffer and Dunkelberg 1980
TA1535	Gene mutation		+	Rannug et al. 1976
TA100, TA1535	Gene mutation		+	Simmon 1981
TA100	Gene mutation	+	+	Victorin and Ståhlberg 1988
Escherichia coli				
WU36-10, WU36-10-89	Gene mutation		+	Kolman 1984; Kolman et al. 1989a
KMBL 3835	Gene mutation		+	Kolman 1985
WP2, WP2 uvrA, WP6	Gene mutation		+	Kolman and Näslund 1987
Bacillus subtilis				
HA101, TKJ5211, TKJ8201	Gene mutation		+	Tanooka 1979
Eukaryotic organisms:				
Saccharomyces cerevisiae RS112	Gene mutation		+	Agurell et al. 1991
Schizosaccaromyces pombe	Gene mutation	+	+	Migliore et al. 1982
Streptomyces griseoflavus	Gene mutation		–	Mashima and Ikeda 1958
Aspergillus nidulans	Gene mutation		(+)	Morpurgo 1963
Neurospora crassa	Gene mutation		+	de Serres and Brockman 1995; Kilbey and Kolmark 1968; Kolmark and Kilbey 1968; Kolmark and Westergaard 1953
Aspergillus nidulans	Somatic crossing-over	–		Morpurgo 1963
Mammalian cells:				
Chinese hamster				
V79 cells	Gene mutation		+	Hatch et al. 1986
SP5/V79 cells	Gene mutation		–	Zhang and Jenssen 1994
K1-BH4 ovary cells	Gene mutation	+	+	Tan et al. 1981
Mouse L5178Y TK cells	Gene mutation		+	Brown et al. 1979; Krell et al. 1979
Human fibroblasts	Gene mutation		+	Bastlová et al. 1993; Kolman et al. 1992; Lambert et al. 1994

Table 2-6. Genotoxicity of Ethylene Oxide *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Chinese hamster V79 cells	Chromosomal aberrations		+	Zhong et al. 1991
Monkey lymphocytes	Chromosomal aberrations		+	Lynch et al. 1984c
Human transformed amniotic cells	Chromosomal aberrations		+	Poirier and Papadopoulo 1982
Monkey lymphocytes	Sister chromatid exchange		+	Kelsey et al. 1989; Lynch et al. 1984c
Human lymphocytes	Sister chromatid exchange		+	Agurell et al. 1991; Garry et al. 1982; Hallier et al. 1993; Tucker et al. 1986
Chinese hamster V79 cells	Micronucleus formation		+	Zhong et al. 1991
Mouse C3H10T1/2 cells	Cell transformation		+	Kolman et al. 1989b, 1990
SA7/Syrian hamster embryo cells	Cell transformation		+	Hatch et al. 1986
Chinese hamster V79 cells	DNA single strand breaks		+	Herrero et al. 1997
Human fibroblasts			+	Nygren et al. 1994
Human fibroblasts	DNA double strand breaks		+	Nygren et al. 1994
Human lymphocytes			+	Hengstler et al. 1997
Human lymphocytes	Unscheduled DNA synthesis		+	Pero et al. 1981
Human peripheral blood mononuclear cells	DNA damage		+	Godderis et al. 2006
Calf thymus DNA	DNA adducts		+	Li et al. 1992
Calf thymus DNA	DNA adducts		+	Segerbäck 1990

– = negative result; + = positive result; (+) = weakly positive result

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Inhaled or ingested ethylene oxide is readily absorbed through the lung and by the gastrointestinal tract.
- Following absorption, ethylene oxide and its metabolites are rapidly distributed by the blood to a wide variety of tissues.
- As a reactive epoxide, ethylene oxide forms hydroxyethyl adducts with proteins (including hemoglobin) and deoxyribonucleic acid (DNA).
- Metabolism of ethylene oxide occurs by two separate pathways; hydrolysis and glutathione conjugation.
- Ethylene oxide metabolites are rapidly excreted, predominantly in urine.

Endogenous production of ethylene oxide occurs in the body via oxidation of ethylene; biological processes that produce endogenous ethylene include lipid peroxidation, methionine and heme oxidation, and metabolic activity of intestinal bacteria (Thier and Bolt 2000). Isotope labeling is one way to differentiate between absorbed ethylene oxide from exogenous sources and endogenously-produced ethylene oxide. The toxicokinetics of exogenous ethylene oxide is commonly measured using a radiolabeled isotope (typically ^{14}C-ethylene oxide). In such studies, the radiolabel is monitored to determine the extent of absorption, distribution, and excretion related to exogenous exposure to ^{14}C-ethylene oxide.

Levels of endogenously produced ethylene oxide in humans have not been quantified. Kirman and Hays (2017) compared levels of the hemoglobin adduct, N-(2 hydroxyethyl)-valine (HEV), in occupationally exposed workers and smokers (both unique groups described as representing significant exogenous ethylene oxide exposed human populations) with a low-exposure group (described as representing nonexposed human populations) that included nonsmokers and passive smoke-exposed subjects who had no occupational exposures to ethylene oxide. In studies on smokers and studies on occupationally exposed workers, mean HEV values ranged from 19.2 to 15,472 pmol/g hemoglobin. In the low-exposure group, mean HEV values ranged from 12.9 to 117 pmol/g hemoglobin. Based on an observed linear relationship between air exposure levels and HEV levels in workers (slope: 10.9 pmol HEV/g Hgb per ppb ethylene oxide) (Angerer et al. 1998), Kirman and Hays (2017) predicted air ethylene oxide levels

that could result in the HEV levels observed in the low-exposure group. The median was 1.6 ppb (5^{th}–95^{th} percentile range: 0.56, 4.5).

3.1.1 Absorption

In a study of hospital workers exposed to ethylene oxide in the workplace air at concentrations ranging from 0.2 to 24.1 mg/m^3 (0.11–13.2 ppm), approximately 75% of the inhaled ethylene oxide was absorbed into the bloodstream (Brugnone et al. 1985, 1986). Blood:air coefficients were 2.5–3.3 measured from venous blood samples collected 4 hours after the workshift.

Inhaled ethylene oxide was rapidly absorbed through the respiratory system of the rat (Filser and Bolt 1984; Koga et al. 1987; Matsuoka 1988; Nakashima et al. 1987; Tardif et al. 1987), mouse (Cumming et al. 1981; Ehrenberg et al. 1974; Tardif et al. 1987), and rabbit (Tardif et al. 1987). Absorption approached 100% among mice exposed to ethylene oxide for up to 2 hours at 2–55 mg/m^3 (1.1–30 ppm) (Ehrenberg et al. 1974).

No human or animal data were located regarding absorption of ethylene oxide after oral exposure. Available information regarding dermal absorption of ethylene oxide is limited to a reported permeation rate of 0.125 mg/(cm-hour) for absorption through excised human skin exposed to a 1% ethylene oxide solution (IARC 2008).

3.1.2 Distribution

No studies were located regarding the distribution of ethylene oxide in humans. However, studies in experimental animals demonstrate that absorbed ethylene oxide is readily distributed to a wide variety of tissues.

Brown et al. (1996) exposed rats and mice to ethylene oxide by 4-hour inhalation at 100 or 300 ppm and studied its distribution and elimination from blood, muscle, and brain. Tissue concentrations of ethylene oxide were calculated from headspace ethylene oxide concentrations using the appropriate air:tissue partition coefficient (Krishnan et al. 1992). For the 100 ppm exposure concentration, peak tissue concentrations averaged 0.57–0.60 µg/g for male rats, 0.56–0.72 µg/g for female rats, 0.29–0.36 µg/g for male mice, and 0.35–0.41 µg/g for female mice. Half-times of elimination of ethylene oxide from blood were 13.8 and 10.8 minutes for male and female rats, respectively, and 3.12 and 2.4 minutes for male and

female mice, respectively. Peak ethylene oxide concentrations in the testes were approximately 20% lower in rats and 50% lower in mice compared to concentrations in blood, muscle, and brain. Saturation kinetics were observed in mice (but not rats) exposed to ethylene oxide at 300 ppm for 4 hours. Brown et al. (1998) reported a linear increase in ethylene oxide levels in blood with increasing exposure concentrations in mice exposed to 50–200 ppm ethylene oxide for 4 hours; steady state was achieved within the first 2 hours of exposure. At higher concentrations (300 and 400 ppm), blood ethylene oxide levels increased sublinearly and continued to increase during the 4-hour exposure. The sublinear increase in blood levels correlated with tissue glutathione depletion. Ehrenberg et al. (1974) reported that 75 minutes after exposing mice to radiolabeled ethylene-[1,2-^{3}H] oxide, the highest levels of radioactivity were observed in the lungs, liver, and kidneys. Lesser amounts were found in the spleen, brain, and testes.

Krishnan et al. (1992) demonstrated relatively similar ethylene oxide tissue distribution for male Fischer rats based on calculated *in vitro* tissue:air partition coefficients for fat (44.1), brain (48.3), lung (60.9), liver (61.6), blood (64.1), and testes (83). Tyler and McKelvey (1982) reported the highest concentrations of ^{14}C-activity in urinary bladder, liver, packed blood cells, and adrenal glands, and the lowest concentration in fat from rats exposed to ^{14}C-ethylene oxide.

No studies were located regarding distribution of ethylene oxide after oral or dermal exposure.

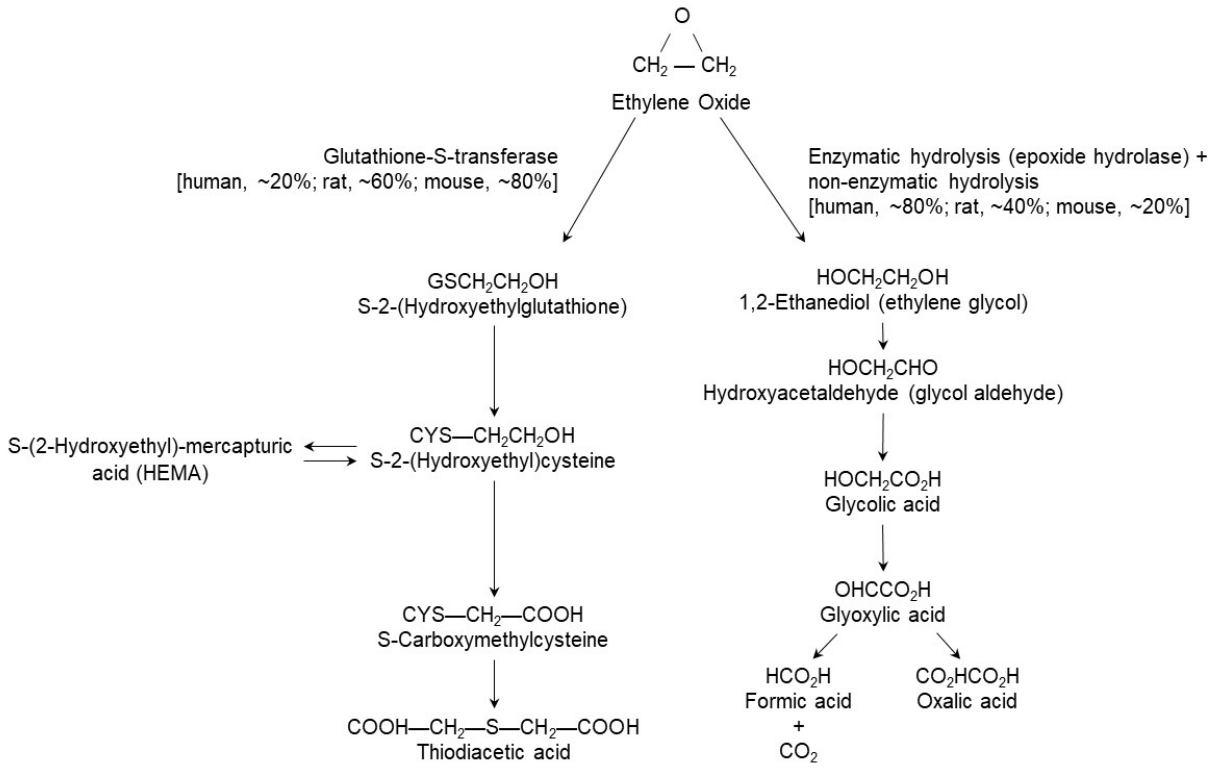
3.1.3 Metabolism

Ethylene oxide metabolism has been evaluated in a variety of experimental mammal systems *in vivo* and *in vitro*, and has resulted in the proposed metabolic scheme shown in Figure 3-1 (IARC 2008; Popp et al. 1994; Scheick et al. 1997). Metabolism is initiated via two separate pathways. One pathway involves enzymatic and nonenzymatic hydrolysis to ethylene glycol and subsequent conversion to oxalic acid, formic acid, and carbon dioxide. The other pathway involves glutathione conjugation to form mercapturic acid and meththio metabolites, some of which are converted to thiodiacetic acid. Metabolites recovered from the urine of ethylene oxide-exposed rats include ethylene glycol, 2-hydroxyethyl-mercapturic acid, and thiodiacetic acid (Scheick et al. 1997).

The relative contribution of each major pathway is species dependent. Results from a physiologically based pharmacokinetic (PBPK) model (Fennell and Brown 2001) designed to simulate the uptake and metabolism of ethylene oxide in rats, mice, and humans suggest that approximately 80% (rats), 60%

(mice), and 20% (humans) of metabolized ethylene oxide occurs via glutathione conjugation and 20% (rats), 40% (mice), and 80% (humans) occurs via the hydrolytic pathway. Although PBPK model simulations produced these species-specific differences in the relative contribution of each metabolic pathway, after accounting for species differences in uptake and metabolism, simulated peak blood concentrations were relatively similar for rats, mice, and humans (Fennell and Brown 2001). The order of area under the curve (AUC) values was humans>rats>mice.

Figure 3-1. Metabolism of Ethylene Oxide



Source: IARC 2008

3.1.4 Excretion

No studies were located regarding excretion in humans following inhalation, oral, or dermal exposure to ethylene oxide. No animal studies were located regarding excretion of ethylene oxide and/or its metabolites following oral or dermal exposure.

In a study of rats exposed to ^{14}C-ethylene oxide by inhalation, 59% of the ^{14}C-activity was recovered in the urine, 12% expired as $^{14}CO_2$, 4.5% in feces, and 1% expired unchanged (Tyler and McKelvey 1982). Ethylene oxide and its metabolites are 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 (Ehrenberg et al. 1974). Filser and Bolt (1984) found that ethylene oxide administered in a closed-system inhalation chamber exhibited first-order elimination kinetics. Metabolites recovered in urine from rats exposed to airborne ethylene oxide include ethylene glycol, 2-hydroxyethylmercapturic acid, and thiodiacetic acid (Scheick et al. 1997).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

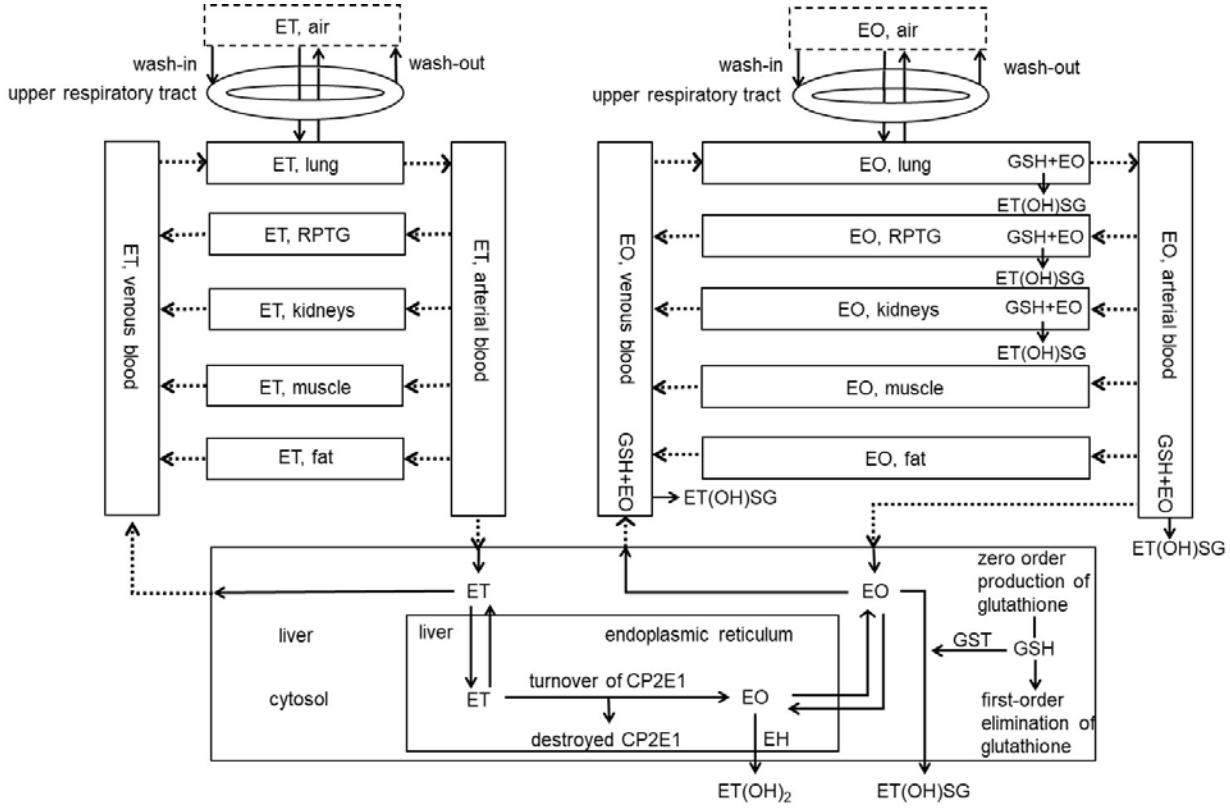
PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Several PBPK models of ethylene oxide have been reported. These include models of humans, mice, and rats (Csanady et al. 2000; Fennell and Brown 2001; Filser and Klein 2018a, 2018b; Krishnan et al. 1992; NIOSH 1987). The models simulate species differences in metabolism of ethylene oxide thought to contribute to interspecies differences in dose-response relationships for carcinogenicity. The model reported by Filser and Klein (2018a, 2018b) is an extension and enhancement of a model reported by Csanady et al. (2000) and includes simulations of adduct formation, thought to be important in the mechanism of carcinogenicity of ethylene oxide. The model reported by Fennell and Brown (2001) is an extension and enhancement of a model reported by Krishnan et al. (1992).

Filser and Klein (2018a, 2018b) Models of Human, Mouse, and Rat. Filser and Klein (2018a, 2018b) developed a model for simulating the kinetics of inhaled ethylene and ethylene oxide in humans, mice, and rats. The model is an extension and enhancement of a model reported by Csanady et al. (2000). The major enhancements made to the Csanady et al. (2000) model were as follows: (1) including glutathione transferase activity to extra-hepatic tissues; (2) including suicide substrate (ethylene) inhibition of hepatic

CYP2E1-mediated metabolism; (3) expanding metabolism pathways to include non-enzymatic hydrolysis and glutathione conjugation; and (4) updating some parameter values based on new data. The general structure of the model is depicted in Figure 3-2. Parameter values for the model are presented in Tables 3-1 and 3-2. Complete lists of parameters and parameter values and the basis for parameter values and evaluations of model predictions in comparison to observations are described in Filser and Klein (2018a, 2018b).

Figure 3-2. Physiologically Based Toxicokinetic Model for Inhaled Ethylene and Inhaled or Metabolically Formed Ethylene Oxide*



*Compartments in solid lines are characterized by defined volumes; the air compartment (dotted lines) can have a defined volume or can be infinitely large, depending on the exposure condition. Dashed arrows indicate transport in the blood; solid arrows indicate uptake or elimination

CYP2E1 = cytochrome P450 2E1; EH = microsomal epoxide hydrolase; EO = ethylene oxide; ET = ethylene; $ET(OH)_2$ = ethylene glycol; ET(OH)SG = S-(2-hydroxyethyl)glutathione; GSH = glutathione; GST = cytosolic glutathione S-transferase; RPTG = richly perfused tissue group

Source: Filser and Klein 2018a, 2018b (permission: Creative Commons CC BY 4.0, https://creativecommons.org/licenses/by/4.0/; minor revisions)

Table 3-1. Physiological and Physicochemical Parameters Used in the Physiologically Based Toxicokinetic Model

Parameter	Abbreviation	Mouse	Rat	Human
Body weight (kg)	BW	0.025	0.25	70
Alveolar ventilation at rest (L/hour)	Qalv	1.2	7.02	300
Cardiac output at rest (L/hour)	Qcard	1.02	5.04	372
Blood flow (L/hour)				
RPTG	Qr	0.355 x Qcard	0.355 x Qcard	0.285 x Qcard
Kidneys	Qk	0.155 x Qcard	0.155 x Qcard	0.155 x Qcard
Muscle	Qm	0.223 x Qcard	0.223 x Qcard	0.250 x Qcard
Fat	Qa	0.017 x Qcard	0.017 x Qcard	0.050 x Qcard
Liver	QL	0.250 x Qcard	0.250 x Qcard	0.260 x Qcard
Compartment volumes (L)				
Arterial blood	Vart	0.0159 x BW	0.0241 x BW	0.0257 x BW
Venous blood	Vvnb	0.0331 x BW	0.050 x BW	0.0533 x BW
RPTG	Vr	0.026 x BW	0.0377 x BW	0.038 x BW
Kidneys	Vk	0.0167 x BW	0.0073 x BW	0.0044 x BW
Lung	Vp	0.0073 x BW	0.005 x BW	0.0076 x BW
Muscle	Vm	0.66 x BW	0.676 x BW	0.541 x BW
Fat	Va	0.10 x BW	0.07 x BW	0.19 x BW
Liver	VL	0.055 x BW	0.04 x BW	0.026 x BW
Water content as fraction of compartment volume				
Blood	wfb	0.842	0.842	0.830
RPTG	wfr	0.783	0.783	0.76
Kidneys	wfk	0.771	0.771	0.827
Lung	wfp	0.842	0.842	0.790
Muscle	wfm	0.756	0.756	0.756
Fat	wfa	0.183	0.183	0.100
Liver	wfL	0.705	0.705	0.683
Partition coefficients of ET				
Blood:air	Pbair	0.48	0.48	0.22
RPTG:blood	Prb	1.04	1.04	2.18
Kidney:blood	Pkb	1.04	1.04	2.18
Lung:blood	Ppb	1.04	1.04	2.18
Muscle:blood	Pmb	1.31	1.31	2.95
Fat:blood	Pab	4.29	4.29	8.73
Liver:blood	PLb	1.19	1.19	2.05
Partition coefficients of EO				
Blood:air	PEObair	61	61	61
RPTG:blood	PEOrb	1.03	1.03	1.03
Kidney:blood	PEOkb	1.03	1.03	1.03
Lung:blood	PEOpb	1.03	1.03	1.03

Table 3-1. Physiological and Physicochemical Parameters Used in the Physiologically Based Toxicokinetic Model

Parameter	Abbreviation	Mouse	Rat	Human
Muscle:blood	PEOmb	1.08	1.08	1.08
Fat:blood	PEOab	0.70	0.70	0.70
Liver:blood	PEOLb	0.89	0.89	0.89
Wash-in–wash-out effect				
Fraction of inhaled ET reaching the alveoli	fET	0.6	0.6	1.0
Fraction of inhaled EO reaching the alveoli	fEO	0.6	0.6; 0.3	0.8

EO = ethylene oxide; ET = ethylene; RPTG = richly perfused tissue group

Source: Filser and Klein 2018a, 2018b (permission: Creative Commons CC BY 4.0, https://creativecommons.org/licenses/by/4.0/; minor revisions)

Table 3-2. Biochemical Parameters Used in the Physiologically Based Toxicokinetic Model

Parameter	Abbreviation	Mouse	Rat	Human
Metabolism of ET in the liver				
Rate constant of CYP2E1 catalyzed formation of EO from ET ($hour^{-1}$)	k3	260	420	50
Rate constant of suicide inhibition of CYP2E1 by ET ($hour^{-1}$)	k4	1.9	0.8	1.1
Apparent Michaelis constant of ET oxidation in venous liver blood (mmol/L)	Kmmo	0.001	0.003	0.003
Rate constant of physiological degradation of CYP2E1 ($hour^{-1}$)	ke	0.187	0.120	0.0139
Initial concentration of CYP2E1 (mmol/kg liver)	CYPo	0.00288	0.001074	0.002115
Metabolism of EO				
EH in the liver				
Maximum rate of hydrolysis of EO catalyzed by EH (mmol/hour/kg liver)	VmaxEOEH	2.70	3.60	25.83
Apparent Michaelis constant of EO hydrolysis in the liver (mmol/L)	KmapEO	0.2	0.2	0.46
Intrinsic Michaelis constant of EO hydrolysis in the endoplasmic reticulum (mmol/L)	KmihEO	0.1999	0.1999	0.31
GST in the liver				
Maximum metabolic elimination rate of EO catalyzed by GST in the liver (mmol/hour/kg liver)	VmaxgstL	1,431	272	58.4
Apparent Michaelis-constant of EO with GST in the liver (mmol/L)	KmEOL	9	9	9
Apparent Michaelis constant of GSH with GST in the liver (mmol/L)	KmgshL	0.1	0.1	0.1

Table 3-2. Biochemical Parameters Used in the Physiologically Based Toxicokinetic Model

Parameter	Abbreviation	Mouse	Rat	Human
Elimination rate constant for GSH turnover in the liver (hour^{-1})	kdgshL	0.2	0.2	0.2
Initial concentration of cytosolic GSH in the liver (mmol/L)	CgshoL	8.62	6.4	5.9
GST in the lung				
Maximum metabolic elimination rate of EO catalyzed by GST in the lung (mmol/hour/kg lung)	Vmaxgstp	97.6	27.5	5.84
Apparent Michaelis-constant of EO with GST in the lung (mmol/L)	KmEOp	9	9	9
Apparent Michaelis constant of GSH with GST in the lung (mmol/L)	Kmgshp	0.1	0.1	0.1
Elimination rate constant for GSH turnover in the lung (hour^{-1})	kdgshp	1.3	1.8	2.0
Initial concentration of cytosolic GSH in the lung (mmol/L)	Cgshop	1.86	1.7	1.95
GST in the kidneys				
Maximum metabolic elimination rate of EO catalyzed by GST in the kidneys (mmol/hour/kg kidney)	Vmaxgstk	264	172	5.0
Apparent Michaelis-constant of EO with GST in the kidneys (mmol/L)	KmEOk	9	9	9
Apparent Michaelis constant of GSH with GST in the kidneys (mmol/L)	Kmgshk	0.1	0.1	0.1
Elimination rate constant for GSH turnover in the kidneys (hour^{-1})	kdgshk	0.2	0.2	0.2
Initial concentration of cytosolic GSH in the kidneys (mmol/L)	Cgshok	3.06	2.6	0.5
GST in the RPTG				
Maximum metabolic elimination rate of EO catalyzed by GST in the RPTG (mmol/hour/kg RPTG)	Vmaxgstr	43	8.16	1.75
Apparent Michaelis-constant of EO with GST in the RPTG (mmol/L)	KmEOr	9	9	9
Apparent Michaelis constant of GSH with GST in the RPTG (mmol/L)	Kmgshr	0.1	0.1	0.1
Elimination rate constant for GSH turnover in the RPTG (hour^{-1})	kdgshr	0.2	0.2	0.2
Initial concentration of cytosolic GSH in the RPTG (mmol/L)	Cgshor	2.29	2.85	1.20
GST in blood				
Maximum metabolic elimination rate of EO catalyzed by GST in the blood (mmol/hour/L blood)	Vmaxgstb	57.24	10.88	2.33
Apparent Michaelis-constant of EO with GST in the blood (mmol/L)	KmEOb	9	9	9

Table 3-2. Biochemical Parameters Used in the Physiologically Based Toxicokinetic Model

Parameter	Abbreviation	Mouse	Rat	Human
Apparent Michaelis constant of GSH with GST in the blood (mmol/L)	Kmgshb	0.1	0.1	0.1
Elimination rate constant for GSH turnover in the blood ($hour^{-1}$)	kdgshb	0.2	0.2	0.2
Initial concentration of cytosolic GSH in the blood (mmol/L)	Cgshob	1.255	0.945	0.766
Non-enzymatic GSH conjugation of EO				
Rate constant of the conjugation reaction (L/(mmol GSHxhour))	kEOG	0.01248	0.01248	0.01248
Non-enzymatic hydrolysis of EO				
Rate constant of EO hydrolysis ($hour^{-1}$)	kEOh	0.06	0.06	0.06

CYP2E1 = cytochrome P450 2E1; EH = microsomal epoxide hydrolase; EO = ethylene oxide; ET = ethylene; SH = glutathione; GST = cytosolic glutathione S-transferase; RPTG = richly perfused tissue group

Source: Filser and Klein 2018a, 2018b (permission: Creative Commons CC BY 4.0, https://creativecommons.org/licenses/by/4.0/; minor revisions)

The ethylene oxide model includes compartments representing venous and arterial blood, lung, kidney, liver, muscle, fat, and a lumped compartment representing all other richly perfused tissues. Absorption from the respiratory tract is simulated as a flow-limited transfer from the upper respiratory tract governed by the fraction of inhaled ethylene oxide reaching the alveolar region of the lung, the alveolar-blood concentration difference, alveolar ventilation rate, cardiac output, and the blood:air partition coefficient. Reported blood:air partition coefficients are 61 for humans (Csanady et al. 2000) and 64.1 for rats (Krishnan et al. 1992). Exchanges between ethylene oxide in tissues and blood are assumed to be flow-limited (governed by blood flow) with equilibrium determined by the tissue:blood partition coefficient. Elimination of ethylene oxide is simulated as exhalation and metabolism. Four metabolism pathways are simulated: (1) conversion to ethylene glycol mediated by liver microsomal epoxide hydrolase in liver; (2) conversion to S-(2-hydroxyethyl)glutathione mediated by cytosolic glutathione S-transferase in lung, kidney, liver, and richly perfused tissue; (3) non-enzymatic conversion to ethylene glycol in all tissues; and (4) non-enzymatic conjugation with glutathione in all tissues.

The epoxide-hydrolase pathway is simulated as a capacity-limited process governed by a maximum rate (Vmax, mmol/hour/kg liver) and a Michaelis half-saturation constant (Km, mmol/L). The non-enzymatic hydrolysis pathway is unlimited and governed by a first-order rate constant ($hour^{-1}$). The glutathione transferase pathway is simulated as a capacity-limited process governed by a maximum (Vmax, mmol/hour/kg liver) and Michaelis constants (Km, mmol/L) for ethylene oxide and reduced glutathione

(GSH). Conjugation with glutathione is limited by availability of GSH, which is consumed by conjugation with ethylene oxide as well as physiologic GSH turnover unrelated to conjugation. Physiologic turnover of GSH is governed by a first-order elimination rate constant ($hour^{-1}$). The non-enzymatic glutathione conjugation pathway is unlimited and governed by a clearance constant (L/mmol GSH/hour). The Filser and Klein (2018a, 2018b) ethylene oxide model is connected to a similar model for ethylene. The ethylene model simulates production of ethylene oxide in the liver mediated by the microsomal CYP2E1 system and includes suicide inhibition of CYP2E1 by ethylene. Production of ethylene oxide is governed by a first-order rate constant ($hour^{-1}$) for the reaction with ethylene, a first-order rate constant for suicide inhibition of CYP2E1 by ethylene ($hour^{-1}$), and a first-order rate constant for physiologic turnover of CYP2E1 ($hour^{-1}$). The model simulates the formation of adducts between ethylene oxide and HEV and DNA guanine (N7-(2-hydroxyethyl)guanine; HEG). Adduct formation is governed by clearance terms (L/hour/g Hb or DNA).

Partition coefficients were estimated from *in vitro* head-space studies (Csanady et al. 2000). Parameters (Vmax, Km) for liver epoxide hydrolase and tissue-specific glutathione transferase activity were derived from *in vitro* studies, with Vmax scaled to whole tissue from estimates of rates per unit mass of protein (Filser and Klein 2018a, 2018b). Parameters for liver epoxide hydrase were subsequently calibrated to fit data on blood ethylene oxide concentration in mice, rats, or humans exposed to ethylene or ethylene oxide (Brugnone et al. 1986; Fennell et al. 2004; Filser et al. 2013). Calibration was achieved by visual inspection of plots of observed and predicted values. The rate of non-enzymatic conjugation with GSH was estimated from *in vitro* studies (Fennell and Brown 2001). The rate of non-enzymatic hydrolysis was estimated by model calibration to blood ethylene oxide concentrations measured in workers exposed to ethylene oxide (Fennell and Brown 2001). Adduct formation rates were derived from *in vitro* studies of adduct formation (Segerbäck 1990; Walker et al. 1992b).

The calibrated model was evaluated against observations of blood ethylene oxide concentrations and rates of uptake from closed space air obtained from studies in which mice, rats, or humans were exposed to ethylene or ethylene oxide (Brown et al. 1998; Brugnone et al. 1986; Filser and Bolt 1984; Filser et al. 1992, 2013, 2015). Exposures to ethylene oxide were 9–2,500 ppm in mice, 140–1,450 ppm in rats, and 2–10 ppm in humans. Goodness-of-fit was assessed by the sum of squared errors from observations and comparison of plotted predictions and observations.

The model predicts that, over a range of exposures (0.5–500 ppm for 6 hours), the epoxide hydrolase pathway will dominate metabolism in the human relative to the glutathione transferase pathway (EH/GST

ratio: 85/15). In mice and rats, the glutathione transferase pathway is predicted to dominate; however, depletion of the glutathione will limit the capacity for conjugation at concentrations exceeding 100 ppm in the mouse and 200 ppm in the rat. The model predicts that clearance of ethylene oxide in the mouse is capacity limited. At exposure concentrations below 200 ppm, rates of uptake of ethylene oxide from closed chambers (an indicator of systemic clearance) are predicted to be similar in mice and rats. However, at exposure concentrations exceeding 200 ppm, uptake rates in mice are slower than those predicted for rats, indicating slower clearance by mice. The model also predicts that exposure concentrations exceeding 200 ppm in mice would result in a super-linear increase in blood ethylene oxide concentrations (i.e., an increase in blood concentration larger than the proportional increase in exposure concentration). The predicted differences in the exposure-clearance and exposure-blood concentration relationship in mice agree with observations (Filser and Klein 2018a, 2018b). These differences in metabolic pathways and systemic clearance could contribute to species differences in dose-response relationships for toxicity endpoints that derive from metabolites of ethylene oxide. The model was applied to estimating exposure concentrations of ethylene and ethylene oxide that would result in the same HEV or HEG levels. The model predicts that an inhalation exposure of humans to 0.3 ppm ethylene oxide (8 hours/day, 5 days/week) would produce the same levels of HEV or HED as a similar exposure to 200 ppm ethylene.

Fennell and Brown (2001) Models of Human, Mouse, and Rat. Fennell and Brown (2001) developed a model for simulating the kinetics of inhaled ethylene oxide in humans, mice, and rats. The model is an extension and enhancement of a model reported by Krishnan et al. (1992). The major enhancements made to the Krishnan et al. (1992) model were as follows: (1) including a kidney compartment; (2) simulating enzymatic hydrolysis (liver) and glutathione conjugation (liver, kidney, testes) as capacity limited (Vmax, Km); (4) simulating exchanges between blood and testes as diffusion-limited; and (4) updating some parameter values based on new data. Complete lists of parameters and parameter values and the basis for parameter values and evaluations of model predictions in comparison to observations are described in Fennell and Brown (2001).

The model includes compartments representing venous and arterial blood, lung, kidney, liver, brain, testes, fat, and lumped compartments representing all other richly perfused tissues or slowly perfused tissues. Absorption from the respiratory tract is simulated as a flow-limited transfer from a gas exchange compartment of the lung to a metabolic lung compartment, governed by an uptake fraction, concentration difference across the lung compartments, alveolar ventilation rate, cardiac output, and the blood:air partition coefficient. Exchanges between ethylene oxide in blood and all tissues except testes are

assumed to be flow-limited (governed by blood flow) with equilibrium determined by a tissue:blood partition coefficient. Exchange between blood and testes was simulated as a diffusion-limited process governed by a permeability coefficient ($hour^{-1}$). The diffusion-limited assumption was needed to accurately predict the observed testes concentrations of ethylene oxide. Elimination of ethylene oxide is simulated as exhalation and metabolism. Three metabolism pathways are simulated: (1) conversion to ethylene glycol mediated by liver microsomal epoxide hydrolase in liver; (2) conversion to S-(2-hydroxy-ethyl)glutathione mediated by cytosolic glutathione S-transferase in lung, kidney, and testes; and (3) non-enzymatic hydrolysis in all other tissues except fat. The epoxide hydrolase pathway is simulated as a capacity-limited process governed by a maximum rate (Vmax, mmol/hour) and a Michaelis half-saturation constant (Km, mmol/L). The non-enzymatic hydrolysis pathway is unlimited and governed by a first-order rate constant ($hour^{-1}$). The glutathione transferase pathway is simulated as a capacity-limited process governed by a maximum (Vmax, mmol/hour) and Michaelis half-saturation constants (Km, mmol/L) for ethylene oxide and GSH. Conjugation with glutathione is limited by availability of GSH, which is consumed by conjugation with ethylene oxide as well as physiologic GSH turnover unrelated to conjugation. Physiologic turnover of GSH is governed by first-order synthesis and elimination rates ($hour^{-1}$). The model simulates the formation of adducts between ethylene oxide and the protein and DNA in kidney, liver, and testes, governed by first-order binding rates ($hour^{-1}$).

Partition coefficients were estimated from *in vitro* head-space studies (Csanady et al. 2000; Filser et al. 1992; Krishnan et al. 1992). Parameters (Vmax, Km) for liver epoxide hydrolase and tissue-specific glutathione transferase activity were derived from *in vitro* studies, with Vmax scaled to whole tissue from estimates of rates per unit mass of protein (Brown et al. 1996; Fennell and Brown 2001). Other parameters were calibrated to achieve better agreement with observations. These included the pulmonary uptake factor, the diffusion permeability coefficient for testes, partition coefficients, and various physiological parameters. The model was calibrated with observations made in mice and rats on kinetics of ethylene oxide concentrations in closed exposure chamber air, blood, and tissues; and blood GSH concentrations (Brown et al. 1996, 1998; Krishnan et al. 1992). The human model was calibrated with observations of blood ethylene oxide concentrations exposed to work room air (Brugnone et al. 1986).

The model predicts that, over a range of exposures (20–500 ppm for 4 hours), the hydrolysis pathway will dominate metabolism in the human relative to the glutathione transferase pathway (EH/GST ratio: 60/20). In mice and rats, the glutathione transferase pathway is predicted to dominate; however, depletion of the glutathione will limit the capacity for conjugation at concentrations exceeding 200 ppm in the mouse. The EH/GST ratio was relatively constant (30:60) in the rat. The model predicts that clearance of

ethylene oxide in the mouse is capacity limited. At exposure concentrations below 200 ppm, blood ethylene oxide concentrations are predicted to be similar in mice, rats, and humans. However, at exposure concentrations exceeding 200 ppm, blood ethylene oxide concentrations in mice exceed those predicted for rats and humans. The predicted differences in the exposure-blood concentration relationship in mice and rats agree with observations (Fennell and Brown 2001). These differences in metabolic pathways and clearance could contribute to species differences in dose-response relationships for toxicity endpoints that derive from metabolites of ethylene oxide. However, at exposure concentrations below 100 ppm, the models predict similar peak and blood ethylene oxide concentrations and areas under the curve (AUCs) in mice, rats, and humans (Fennell and Brown 2001).

3.1.6 Animal-to-Human Extrapolations

The disposition and metabolism of inhaled ethylene oxide is species dependent. Species differences exist regarding the relative contribution of the metabolic pathways discussed in Section 3.1.3 (the nonenzymatic hydrolysis pathway and the glutathione conjugation pathway) (Fennell and Brown 2001). Although ethylene oxide exposure concentrations <200 ppm are predicted to result in similar blood levels among rats, mice, and humans, higher exposure concentrations would result in higher blood levels in mice compared to rats and humans. The higher blood levels in mice are likely the result of glutathione depletion. Interspecies extrapolation would need to account for species differences in metabolic pathways, species-specific contribution of exposure concentration, and the identity of the toxicant or toxicants (ethylene oxide itself and/or its metabolite[s]) responsible for a particular toxic effect.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic

makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to ethylene oxide are discussed in Section 5.7, Populations with Potentially High Exposures.

No data were located regarding age-related differences in susceptibility to ethylene oxide toxicity or carcinogenicity. However, because detoxification of ethylene oxide occurs via hydrolytic and glutathione-S-transferase pathways, very young children with incomplete development of these detoxification pathways (McCarver and Hines 2002; Zhong et al. 2018) may exhibit increased susceptibility to ethylene oxide toxicity. Limited data do not suggest significant sex-related differences in ethylene oxide metabolism (Fennell and Brown 2001; Mertes et al. 1985). Individuals with genetic deficiencies in activities of detoxification enzymes would likely be at increased risk of ethylene oxide toxicity/carcinogenicity. For example, ethylene oxide hemoglobin adduct levels in occupationally-exposed workers were 2-fold greater among individuals expressing a null GSTT1 genotype than those expressing a nonnull GSTT1 genotype (Yong et al. 2001). Haufroid et al. (2007) reported increased urinary excretion of an ethylene oxide glutathione conjugate among nonnull GSTT1 genotype hospital workers, suggestive of increased ethylene oxide detoxification. People with DNA repair deficiencies might experience increased sensitivity to DNA-damaging effects of ethylene oxide.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to ethylene oxide are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/

exposurereport/). If available, biomonitoring data for ethylene oxide from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by ethylene oxide are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Ethylene oxide can be measured in blood and alveolar air (Brugnone et al. 1986). The urinary metabolite, HEMA (*S*-[2-hydroxyethyl]mercapturic acid), has been used as a biomarker of exposure to ethylene oxide (Alwis et al. 2012; Eckert et al. 2011; Popp et al. 1994), including occupational levels <1 ppm (Haufroid et al. 2007). However, HEMA is not specific to ethylene oxide; it is also a metabolite of acrylonitrile and vinyl chloride.

Ethylene oxide forms adducts with DNA and hemoglobin, which are considered markers of biological effects (Angerer et al. 1998; Boogaard 1999, 2002; Rusyn et al. 2005; Walker and Skopek 1993). However, these adducts also can implicate that exposure to ethylene oxide has occurred. Additional information is provided in Section 3.3.2 (Biomarkers of Effect).

3.3.2 Biomarkers of Effect

Ethylene oxide is a direct acting alkylating agent that can form adducts with macromolecules such as DNA and hemoglobin. The 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 (EPA 2016; IARC 2012). Studies in rats and mice have found concentration- and duration-related increases in 7-HEG levels following inhalation exposure (Rusyn et al. 2005; Walker and Skopek 1993). EPA (2016) notes that DNA adducts are less reliable measures of exposure because they can be repaired or fixed as mutations. The ethylene oxide hemoglobin adduct, hydroxylated *N*-terminal valine (HOEtVal), has been widely used as a biomarker for ethylene oxide (see Angerer et al. 1998; Boogaard 2002; Boogaard et al. 1999). Occupational exposure studies have found a correlation between ambient air levels of ethylene oxide and HOEtVal levels (Angerer et al. 1998; Boogaard 2002). Studies in rats and mice have reported increases in HOEtVal levels following a single inhalation exposure (Walker et al. 1992a) or intraperitoneal injection (Tates et al. 1999; Walker et al. 1992a) or repeated inhalation (Tates et al. 1999; Walker and Skopek 1993; Walker et al. 1992a) or drinking water (Tates et al. 1999) exposures. A 4-week inhalation exposure to 3–33 ppm resulted in a linear increase in HOEtVal levels; at 100 ppm, the slope estimated from the 3–33 ppm exposure underpredicted the HOEtVal levels by 20 and 25% in rats and mice, respectively (Walker et al. 1992a). In humans, HOEtVal blood levels are influenced by endogenous production of ethylene oxide, genetic status of the polymorphic glutathione transferases *hGSST1* (Fennell et al. 2000; Müller et al. 1998; Thier et al. 1999, 2001; Yong et al. 2001), and smoking status (Bono et al. 1999; Fennell et al. 2000; Müller et al. 1998; Thier et al. 1999). *hGSTM1* genotypes did not influence HOEtVal blood levels (Fennell et al. 2000; Müller et al. 1998; Thier et al. 1999).

3.4 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding toxicologically-relevant interactions between ethylene oxide and other substances.

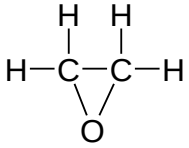
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Ethylene oxide is both a manmade substance and a natural substance produced in the body via oxidation of absorbed or endogenously produced ethylene during normal oxidation processes.

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for ethylene oxide.

Table 4-1. Chemical Identity of Ethylene Oxide

Characteristic	Information	Reference
Chemical name	Ethylene oxide	NLM 2021
Synonym(s) and registered trade name(s)	Oxirane; dihydro-oxirane; dimethylene oxide; epoxyethane; ETO; Anprolene; Oxyfume; T-Gas; 1,2-epoxyethane; ethene oxide; diethylene oxide; E.O.; oxane; oxidoethane	NLM 2021; Parod 2014; WHO 2003
Chemical formula	C_2H_4O	EPA 2017b
Chemical structure		
CAS Registry Number	75-21-8	WHO 2003

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Ethylene oxide is a colorless, flammable gas. It is highly soluble in water ($1x10^6$ mg/L at 20°C) and possesses a high vapor pressure ($1.095x10^3$ mm Hg at 20°C).

Table 4-2 lists important physical and chemical properties of ethylene oxide.

Table 4-2. Physical and Chemical Properties of Ethylene Oxide

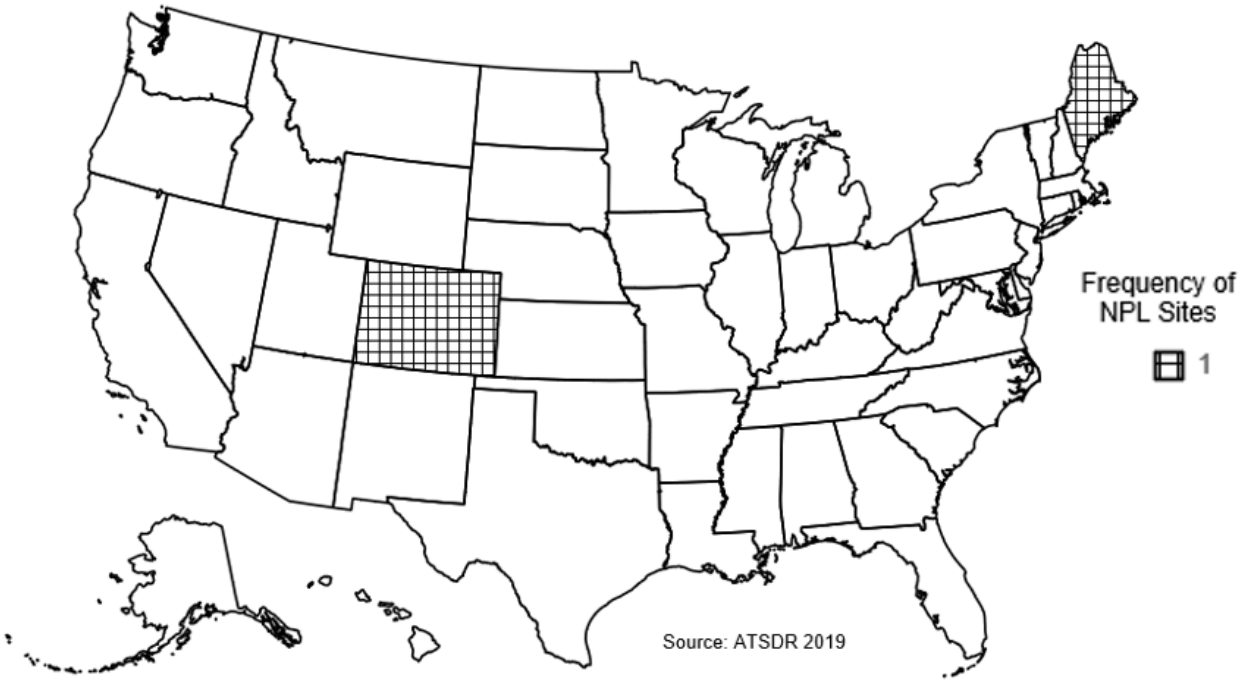
Property	Information	Reference
Molecular weight	44.05 g/mol	WHO 2003
Color	Colorless	WHO 2003
Physical state	Gas	NIOSH 2007
Melting point	-111.7°C	NLM 2021
Boiling point	51°F (10.6°C)	NIOSH 2016
Density at 10°C	0.8824	NLM 2021; Weast 1985
Odor	Sweet, olefinic; ether-like	NIOSH 2007; Verschueren 1983
Odor threshold:		
Water	140 mg/L	Amoore and Hautala 1983
Air	787 mg/m^3 (432.85 ppm)	Amoore and Hautala 1983
Solubility:		
Water at 20°C	1x10^6 mg/L	EPA 2017b
Organic solvents	Soluble in alcohol, ether, acetone, benzene	EPA 2017b
Partition coefficients:		
Log K_{ow}	-0.22	EPA 2017b
Log K_{oc}	1.204	WHO 2003
Vapor pressure at 20°C	1.095x10^3 mm Hg	EPA 2017b
Henry's law constant at 25°C	1.48x10^{-4} atm-m^3/mol	NLM 2021
Autoignition temperature	429°C	NLM 2021
Flashpoint	<-18°C (open cup)	NLM 2021
Flammability limits	Lower: 3.0% Upper: 100%	NLM 2021
Conversion factors at 20°C and 101.3 kPa	1 ppm=1.83 mg/m^3 1 mg/m^3=0.55 ppm	WHO 2003
Explosive limits	Lower: 3.0% Upper: 100%	NLM 2021

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Ethylene oxide has been identified in at least 2 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which ethylene oxide has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Ethylene Oxide Contamination



- People can be exposed to ethylene oxide through:
  - Inhalation of contaminated air near production and use facilities
  - Inhalation of contaminated air during sterilization/fumigation practices
  - Inhalation of tobacco smoke
  - Dermal contact during sterilization/fumigation practices
  - Use of medical devices and cosmetics sterilized with ethylene oxide
  - Preparation and ingestion of foods sterilized with ethylene oxide
  - During production of ethylene oxide and its involvement in the production of other chemicals
  - Following use of ethylene oxide in sterilization/fumigation operation
  - By breathing air contaminated with tobacco smoke

- In the environment, ethylene oxide is expected to:
  - Oxidize in the atmosphere
  - Evaporate or hydrolyze from water
  - Volatilize from soil
  - React with nucleophilic groups such as carboxyl, amino, and phenolic groups, as well as strong acids

Ethylene oxide is man-made chemical used as a sterilant, a fumigant, or an intermediate in the production of other synthetic chemicals such as ethylene glycol. Gaseous releases of ethylene oxide to the environment are the result of uncontrolled industrial emissions (WHO 2003). Less than 1% of global production of ethylene oxide is used for the sterilization of biomedical equipment and foods or as a fumigant (WHO 2003).

Ethylene oxide degrades in both the air and natural water. In the air, oxidation via free radical formation is the most probable degradation pathway; the estimated half-life of this reaction ranges from 2 to 5 months. The half-life estimates for other degradation pathways for atmospheric ethylene oxide vary widely. In water, ethylene oxide would likely degrade via radical formation and hydrolysis, leading to the formation of glycols, and halogenated alcohols (in the presence of sodium chloride), which in turn degrade into simpler molecules such as carbon dioxide and water. The half-lives of these reactions range from a few hours to <15 days, depending on environmental conditions. Ultraviolet-catalyzed oxidation (in the presence of oxygen and nitrogen dioxide) may also account for some of the ethylene oxide lost in the atmosphere. Ethylene oxide also degrades in wastewater treatment systems with a half-life of about 20 days.

No data are available on the fate of ethylene oxide in soil. Nonetheless, this chemical is expected to either volatilize or be leached due to its high vapor pressure, infinite solubility in water, and reaction with mineral surfaces. Soil microorganisms may also convert it to glycols.

Data on the levels of ethylene oxide in the environment are very limited. There is a limited amount of ethylene oxide air monitoring data in the United States; EPA has begun to measure ethylene oxide at the National Air Toxics Trends Stations and the Urban Air Toxics Monitoring Program networks. There are no data to indicate that ethylene oxide is a common constituent of water sources of any type in any geographic location within the United States. 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. There are no data on ethylene oxide bioaccumulation in marine organisms.

There are limited data to evaluate the general population's exposure levels to ethylene oxide. Environmental exposures may include ethylene oxide from tobacco smoke. The populations with potentially higher than average risk of exposure to ethylene oxide include sterilization technicians and industrial workers involved in the manufacture and/or use of ethylene oxide.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Ethylene oxide is primarily produced through ethylene oxidation with silver catalyst (Khan et al. 2002; Parod 2014). Ethylene and oxygen combine at 10–30 atmospheres and 400–500°F in a fixed bed catalytic reactor, which contains tubes with silver catalyst. The off-gas from the reactor is processed by CO_2 scrubbers followed by ethylene oxide scrubbers. Ethylene oxide is recovered from the resulting liquid by a desorber and then distilled (Khan et al. 2002). The EPA Chemical Data Reporting tool lists eight manufacturers of ethylene oxide in the United States at 11 different locations (EPA 2014, 2017a). Only two manufacturers (LG America and Shell Petroleum Inc.) reported actual production volume data with the other manufacturers declaring their production volumes confidential business information (CBI). In 2010 and 2011, LG Chemicals America reported production volumes of 3,368 and 26,479 pounds (1.5 and 12.0 metric tons), respectively. Shell Petroleum reported production volumes of 1,012,190,974, 925,329,789, and 1,012,190,974 pounds (0.45, 0.42, and 0.46 million metric tons) in 2009, 2010, and 2011, respectively. For 2015, the national domestic aggregate production of ethylene oxide was estimated to range from 5,000,000,000 to 10,000,000,000 pounds (2.3–4.6 million metric tons) (EPA 2014, 2017a). According to the American Chemistry Council (ACC) Economics and Statistics Department, in 2018, it was reported that there were 15 process plants in the United States that produced ethylene oxide with a total production volume of 2.92 million metric tons (6,400 million pounds) (ACC 2019). Total production capacity is about 3.5 million metric tons (7,700 million pounds) but is expected to increase by another 1.8 million metric tons (4,000 million pounds) by 2023 due to market demand (ACC 2019).

Ethylene oxide is produced naturally in negligible quantities by degradation of ethylene in certain plants and microorganisms. It can also emanate from water-logged soil, manure, and sewage sludge (WHO 2003).

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of ethylene oxide in 2019 (TRI19 2021). Based on reported company names, seven of the companies were likely involved in sterilization processes; another nine companies were associated with medical devices. Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Ethylene Oxide[a]

State[b]	Number of facilities	Minimum amount on site in pounds[c]	Maximum amount on site in pounds[c]	Activities and uses[d]
AR	2	10,000	99,999	12
AZ	1	1,000	9,999	11
CA	1	1,000,000	9,999,999	6
CO	1	1,000	9,999	11
CT	1	1,000	9,999	12
DE	1	1,000,000	9,999,999	1, 3, 6, 7
GA	2	1,000	9,999	12
IA	5	1,000	9,999,999	6, 11, 12
IL	1	1,000,000	9,999,999	6
IN	4	100,000	9,999,999	6, 7
KS	2	100	9,999	9, 11, 12, 14
KY	1	1,000,000	9,999,999	6
LA	1	1,000,000	9,999,999	6
MD	14	100	49,999,999	1, 3, 4, 5, 6, 9, 10, 12
MI	2	1,000	9,999	12
MN	3	1,000	9,999,999	6, 11, 12
MO	2	10,000	9,999,999	6, 9, 12
MS	1	100,000	999,999	6
NC	4	1,000	49,999,999	6, 7, 11
NE	2	1,000	9,999	12
NJ	2	1,000	9,999,999	6, 11
NV	1	100	999	12
NY	1	10,000	99,999	9
OH	1	100	999	12
OK	1	10,000,000	49,999,999	6
PA	5	1,000	9,999,999	6, 9, 11, 12
PR	3	1,000	9,999	2, 3, 6, 12
SC	7	100,000	9,999,999	6, 9
TN	2	1,000	999,999	6, 12
TX	26	100	999,999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
UT	2	1,000	9,999	2, 3, 11, 12

Table 5-1. Facilities that Produce, Process, or Use Ethylene Oxide[a]

State[b]	Number of facilities	Minimum amount on site in pounds[c]	Maximum amount on site in pounds[c]	Activities and uses[d]
VA	3	1,000	999,999	6, 11
WI	3	100,000	999,999	6
WV	6	1,000	9,999,999	6, 9, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI19 2021 (Data are from 2019)

Estimated total production of ethylene oxide in the United States for the year 2004 was nearly 9 billion pounds (IARC 2008).

5.2.2 Import/Export

Due to its high reactivity, most ethylene oxide that is produced is also used onsite to create other products (ethylene oxide derivatives). There are little import or export volumes of ethylene oxide; however, there is substantial trade involving ethylene oxide derivatives such as monoethylene glycol (MEG) (ACC 2019). In 2018, approximately one-third of the MEG produced in the United States from ethylene oxide was exported to other nations. In 2018, the United States exported 0.831 million metric tons (1,800 million pounds) of ethylene oxide derivatives and also imported 1.2 million metric tons (2,600 million pounds) of ethylene oxide derivatives. Shell Petroleum exported 825,320 pounds of ethylene oxide in 2010; however, the other U.S. producers reported either zero export and import volumes or declared this as CBI (EPA 2014, 2017a).

5.2.3 Use

Greater than 97% of ethylene oxide production involves its use as a chemical intermediate for the production of other chemicals. The ACC reported the following consumption patterns of ethylene oxide in 2018: 34% to produce MEG; 28% in the production of ethoxylates; 16% used to produce

ethanolamines; 6% in the production of glycol ethers; 4% to produce polyether polyols; and 12% for other uses, which includes sterilization of medical and surgical devices, microbial reduction in spices, and refining of corn (ACC 2019). At one time, ethylene oxide was used in the production of acrylonitrile, but that process was discontinued in 1966 (EPA 1984a, 1985; NIOSH 1981; WHO 1985). Ethylene oxide is used as a fumigant, a sterilant for food (spices) and cosmetics, and in hospital sterilization of surgical equipment and plastic devices that cannot be sterilized by steam (EPA 2017b; Parod 2014; Ribeiro et al. 1994; WHO 2003). 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 (EPA 2004). Ethylene oxide is the primary fumigation/sterilization method for reducing bacteria levels in spices/herbs and black walnuts. According to the EPA (2008) RED, approximately 8.2 million pounds of ethylene oxide are used annually in the United States for commercial fumigation/sterilization. Of the 8.2 million pounds, approximately 7.4 million pounds are used annually for sterilization of medical and laboratory items/equipment; an estimated 800,000 pounds are used annually for fumigation of herbs and spices (EPA 2008).

5.2.4 Disposal

Because ethylene oxide is listed as a hazardous substance, disposal of wastes containing this compound is controlled by a number of federal regulations.

The production processes for ethylene oxide do not generate solid wastes, and the waste waters are treated or recycled. The production process is a closed system; however, vent gases and fugitive emissions may contain some ethylene oxide. Waste gases may be removed from the air by scrubbers. Wastes containing ethylene oxide may be incinerated by rotary kiln or fluidized bed incineration methods (EPA 1989; WHO 1985).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005c). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust

coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005c).

5.3.1 Air

Estimated releases of 174,455 pounds (~79 metric tons) of ethylene oxide to the atmosphere from 114 domestic manufacturing and processing facilities in 2019, accounted for about 84% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2021). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chemical Ethylene Oxide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	2	9,173	0	0	0	0	9,173	0	9,173
AZ	1	308	0	0	0	0	308	0	308
CA	1	15	0	0	0	0	15	0	15
CO	1	325	0	0	0	0	325	0	325
CT	1	124	0	0	0	8	124	8	132
DE	1	1,293	0	0	0	0	1,293	0	1,293
GA	2	107	0	0	0	0	107	0	107
IA	5	2,415	380	0	0	0	2,415	380	2,795
IL	1	2,121	338	0	0	0	2,121	338	2,459
IN	4	1,035	0	0	0	0	1,035	0	1,035
KS	2	198	0	0	30,224	0	198	30,224	30,422
KY	1	612	0	0	0	0	612	0	612
LA	1	1,950	8	0	0	0	1,958	0	1,958
MD	14	40,723	120	0	5	0	40,843	5	40,848
MI	2	139	0	0	0	0	139	0	139
MN	3	356	2	0	5	0	363	0	363
MO	2	5,691	0	0	0	0	5,691	0	5,691

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chemical Ethylene Oxide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
MS	1	1	0	0	0	0	1	0	1
NC	4	165	0	0	0	0	165	0	165
NE	2	40	0	0	0	0	40	0	40
NJ	2	402	0	0	0	0	402	0	402
NV	1	15	0	0	0	0	15	0	15
NY	1	8	0	0	0	0	8	0	8
OH	1	0	0	0	0	0	0	0	0
OK	1	1,456	0	0	0	0	1,456	0	1,456
PA	5	8,980	0	0	0	0	8,980	0	8,980
PR	3	340	0	0	0	0	340	0	340
SC	7	2,594	12	0	53	0	2,594	65	2,659
TN	2	202	0	0	0	0	202	0	202
TX	26	85,730	1,782	0	436	10	87,078	879	87,957
UT	2	42	0	0	0	0	42	0	42
VA	3	4,628	14	0	0	0	4,628	14	4,642
WI	3	314	9	0	0	0	314	9	323
WV	6	2,954	0	0	0	0	2,954	0	2,954
Total	114	174,455	2,665	0	30,723	18	175,938	31,923	207,861

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI19 2021 (Data are from 2019)

Ethylene oxide is a synthetically produced gas used primarily in the production of other chemicals by the chemical industry. As a result, most of the releases of ethylene oxide to the atmosphere occur during its

storage and handling in industrial settings. Industrial emissions of ethylene oxide are due to uncontrolled fugitive emissions or venting with other gases (EPA 1980, 2017b).

Other known sources of ethylene oxide air emissions include its production from combustion of hydrocarbon fuels and its release from commodity-fumigated materials, estimated to be about 10 million pounds annually (EPA 1980), and losses during disinfection of hospital equipment (EPA 2017b).

Ethylene oxide could be released to the atmosphere during catastrophic events. In 1987, an explosion in an ethylene oxide purification column in Antwerp, Germany occurred due to decomposition of ethylene oxide (Khan et al. 2002).

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. This database documents and estimates emission data from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Ethylene oxide emissions estimated from the 2014 inventory are summarized in Table 5-3.

Table 5-3. Ethylene Oxide Emissions from the National Emissions Inventory

Emission sector	Amount of ethylene oxide emitted to air (pounds)
Fuel combustion, commercial/institutional, natural gas	17
Fuel combustion, commercial/institutional, oil	0.0009
Fuel combustion, electric generation, natural gas	45
Fuel combustion, industrial boilers, ICEs, natural gas	33
Fuel combustion, industrial boilers, ICEs, other	8
Industrial processes, chemical manufacturing	123,520
Industrial processes, not elsewhere classified	86,367
Industrial processes, petroleum refineries	0.040
Industrial processes, pulp and paper	125
Industrial processes, storage and transfer	6,707
Solvent, degreasing	1,368
Solvent, graphic arts	23

Table 5-3. Ethylene Oxide Emissions from the National Emissions Inventory

Emission sector	Amount of ethylene oxide emitted to air (pounds)
Solvent, industrial surface coating and solvent use	2,502
Waste disposal	2,386

ICE = internal combustion engine

Source: EPA 2020a

Some older studies have suggested that ethylene oxide may be formed when fuels are burned in an engine or in other combustion conditions. However, these decades-old studies used methods that are considered outdated today and that contain significant uncertainties. No peer-reviewed studies are available that have used state-of-the-art analytic methods to measure ethylene oxide in emissions from combustion sources.

The World Health Organization (WHO 2003) reported that the estimated air emissions due to sterilization and fumigation operations, production, medical facility use, and ethoxylation resulted in 57, 31, 8, and 4% of total ethylene oxide emissions, respectively.

5.3.2 Water

Estimated releases of 2,665 pounds (~1.2 metric tons) of ethylene oxide to surface water from 114 domestic manufacturing and processing facilities in 2019, accounted for about 1.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2021). This estimate includes releases to waste water treatment and publicly owned treatment works (POTWs) (TRI19 2021). These releases are summarized in Table 5-2.

Although recent data were not located, historically, ethylene oxide discharges into water appeared to be primarily industry-related. WHO (1985) indicated that biological treatment of waste waters containing ethylene oxide appeared to be successful in removing and preventing this chemical from reaching waterways. Recent data concerning discharge of ethylene oxide to water were not located.

5.3.3 Soil

Estimated releases of 30,723 pounds (~13.94 metric tons) of ethylene oxide to soil from 114 domestic manufacturing and processing facilities in 2019, accounted for about 14.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2021). These releases are summarized in Table 5-2.

No discharges of ethylene oxide into the soil are reported in the literature. Although ethylene oxide is a potent fumigant and will kill fungi, viruses, and insects, it is not approved as a soil fumigant. However, since ethylene oxide is infinitely soluble in water, it is likely that the soil environment is exposed to this chemical as a result of the atmospheric scrubdown of rainfall and some uncontrolled discharges of liquid wastes containing this chemical. Data concerning levels of ethylene oxide in soil were not found.

5.3.4 Other Sources

Solid or liquid wastes containing measurable amounts of ethylene oxide, as defined in Part 261 of CFR 40 (EPA 1984c), can be classified as hazardous with ignitable and toxic properties. However, according to EPA (1980), no specific wastes containing large amounts of ethylene oxide associated with the manufacture of ethylene oxide have been identified.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. The primary mode of transport of ethylene oxide is via air emissions into the atmosphere. At atmospheric pressure and room temperature, ethylene oxide exists as a gas due to its very high vapor pressure (1,095 mm Hg at 20°C) and low boiling point (51°F [10.6°C]) (NIOSH 2016). A fugacity model estimated that ethylene oxide will persist in the atmosphere over a densely populated area of Canada for approximately 3 days, localized to the area of discharge (WHO 2003).

Water. Although ethylene oxide dissolves in water in any proportion, it also has the tendency to volatilize due in part to its high vapor pressure. Conway et al. (1983) reported that about 95% of ethylene oxide mixed with water volatilizes within 4 hours (its half-life is about 1 hour), and thus is not prevalent in environmental water sources.

Sediment and Soil. The reported log of the octanol/water partition coefficient (K_{ow}) for ethylene oxide is -0.30 (Hansch and Leo 1979), indicating that ethylene oxide is a very polar chemical. From its chemical and physical properties, it can be inferred that ethylene oxide in soil will volatilize as water evaporates, leach through the soil, or be removed by runoff during rainstorms. It is, therefore, unlikely that ethylene oxide will accumulate in soils or sediments (WHO 2003). No data on the accumulation and/or fate of ethylene oxide in the soil environment are available.

Other Media. EPA (1984b) indicated that there are no data on the bioaccumulation of ethylene oxide in animal tissue.

Ethylene oxide is used as a fumigant for some food commodities. EPA has set tolerances of 7 ppm on herbs and spices, licorice roots, dried peppermint tops, sesame seeds, dried spearmint tops, and dried vegetables. A 50 ppm tolerance was set for walnuts (EPA 2018a).

Staples and Gulledge (2006) used a level III multi-media fate model to calculate ethylene oxide concentrations in air, water, soil, and sediment given an estimated annual emission rate using six different environmental scenarios meant to represent different climatic regions of the United States. Mass transport parameters such as the erosion and runoff mass transport velocities as well as rainfall rates and composition of the four main environmental compartments were varied in these six scenarios. The modeled output concentrations in air, water, and sediment were not highly sensitive to the changes in environmental parameters. However, modeled soil levels were shown to be fairly sensitive to changes in the input parameters, most likely the 10-fold changes in the soil erosion and runoff mass transport parameters. In all cases, hazard quotients calculated for target species were much lower than 1, suggesting low adverse risk to aquatic and terrestrial wildlife at the given emissions used in the model.

5.4.2 Transformation and Degradation

Ethylene oxide undergoes numerous reactions. It hydrolyzes in water and reacts with other nucleophiles with a half-life of approximately 10 days, forming ethylene glycol and ethylene chlorohydrin in saltwater (e.g., oceans). It also undergoes biodegradation, some of the measurable biological oxygen demand (BOD) is likely from the degradation of its reaction products. These rates have been measured in closed systems to prevent volatilization. Under most environmental conditions, volatilization from water or soil will be more rapid than hydrolysis, biodegradation, or reaction with other nucleophiles.

Air. There is limited information on the fate of ethylene oxide in the atmosphere. EPA (1984b) reported that the most probable path of atmospheric degradation of ethylene oxide is oxidation via free-radical formation, and estimated its half-life in air at 25°C to range from 69 to 149 days, based on data (rate constants and the concentration of OH radicals) obtained by Fritz et al. (1982). Atmospheric half-lives based on reaction with hydroxyl radicals were also estimated as ranging from 38 to 382 days (WHO 2003).

According to EPA (1984b), measurements of the absolute rate constant, determined to be about $6x10^{-16}$ cm^3/mole/second by Bogan and Hand (1978) for the reaction between oxygen and ethylene oxide at 27°C, indicate an ethylene oxide half-life of about 1,400 years, assuming an atmospheric oxygen concentration of 25,000 molecules/cm^3. Bogan and Hand (1978) determined the final products of ethylene oxide oxidation to be hydrogen, water, carbon monoxide, carbon dioxide, and formaldehyde. Joshi et al. (1982) determined ethylene oxide to have a low reactivity with atmospheric nitrogen dioxide under W radiation and at 25°C. Using ethylene oxide:nitrogen dioxide ratios similar to those found in urban and rural air, these researchers reported the ethylene oxide half-life to be >53 hours.

In summary, the few available studies on the photodecomposition of ethylene oxide in the atmosphere suggest that it undergoes measurable rates of degradation into simpler products. However, laboratory estimates of the half-life of ethylene oxide in the atmosphere vary widely.

Water. If released to water, ethylene oxide would likely evaporate, hydrolyze, or biodegrade aerobically (and to a lesser extent, anaerobically) (WHO 2003). Ethylene oxide hydrolyzes in water to form glycols (Long and Pritchard 1956). EPA (1980) reported the hydrolysis rate constant (acid catalyzed) to be about $19.9x10^{-3}$ L/mol-second at 30°C. According to the same report, all epoxides, including ethylene oxide, can react with anions such as chloride and bromide in aqueous solutions, forming halogenated alcohols. The hydrolysis half-life of ethylene oxide ranges from 12 to 14 days in sterile, deionized, and natural river water (Conway et al. 1983; EPA 2017b; WHO 2003). Increased water salinity (up to 3% sodium chloride) was found to decrease the half-life of ethylene oxide to 9 days (Conway et al. 1983), producing ethanediol and chloroethanol. The volatilization half-life is estimated to be approximately 1 hour (WHO 2003). According to Anbar and Neta (1967), the degradation of ethylene oxide in water via hydroxyl radicals is very slow, with a computed half-life of about 50 years. Conway et al. (1983) reported that the half-life measurements for ethylene oxide in sterile and natural river water were not appreciably different.

This may be because hydrolytic degradation of ethylene oxide is more rapid than biodegradation of this compound in aqueous media.

The estimated aerobic biodegradation half-life for ethylene oxide in water is expected to be 20 days to 6 months, while the anaerobic biodegradation half-life is estimated as 4 months to 2 years (WHO 2003). The aqueous aerobic biodegradation half-life from a BOD test was about 20 days. A 5-day BOD was 3% of the theoretical oxygen demand (1.82 g/g) (WHO 2003). With an initial concentration of 100 mg/L, ethylene oxide was found to hydrolyze in water over a 4-week period (J-CHECK 2019).

Sediment and Soil. No studies on the degradation of ethylene oxide in the soil environment have been located. However, it is likely that ethylene oxide would be found in both the water and vapor phases of the soil environment due to its high vapor pressure and very low octanol/water partition coefficient. Thus, ethylene oxide in the soil is likely to undergo at least some degradation via the same types of mechanisms as those that predominate in aquatic environments and via reactivity with mineral surfaces.

Ethylene oxide is expected to volatilize rapidly from soil, with estimated hydrolysis half-lives of 10.5 and 11.9 days for soil and groundwater, respectively. While volatilization is expected to be the predominant mechanism by which ethylene oxide is removed from soil, it may also undergo fairly rapid hydrolysis and biodegradation. It is not expected to be sorbed by soil or sediment (WHO 2003).

Other Media. While no reports of ethylene oxide in biota were located, bioaccumulation of ethylene oxide is not expected, based on the very low log K_{ow} (WHO 2003).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to ethylene oxide depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of ethylene oxide in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on ethylene oxide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	NA[b]	EPA 2019a
Drinking water	9 µg/L	EPA 2007

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Method detection limits are regularly updated.

Table 5-5. Summary of Environmental Levels of Ethylene Oxide

Media	Low	High	For more information
Outdoor air	0.4 µg/m^3 (0.22 ppb)	11 µg/m^3 (6.05 ppb)	Parod 2014
Surface water	Not applicable	2 mg/L	EPA 1984b
Food	<0.05 µg/g	1,800 µg/g	WHO 2003

Historical ambient air levels are shown in Table 5-6. The samples were collected in areas with no known industrial ethylene oxide sources and ranged from below the reporting level to 5.3 µg/m^3 (2.92 ppb).

Table 5-6. Historical Ambient Air Monitoring Data from Selected States[a]

Location (sampling time frame)	Number of valid samples[b]	Median(s)[c]	Range
California (1989–1990)	58	0.08 µg/m^3 (0.044 ppb)	0.03–0.54 µg/m^3 (0.017–0.30 ppb)
Colorado[d]	16	0.276 µg/m^3 (0.153 ppb)[e]	<RL–1.05 µg/m^3 (<RL–0.580 ppb)
Illinois (2018)	72	0.19–0.20 µg/m^3 (0.105–0.11 ppb)[f]	<RL–1.1 µg/m^3 (<RL–0.61 ppb)
Massachusetts (1999–2016)	1,433	0.15–0.18 µg/m^3 (0.083–0.099 ppb)[g]	<RL–5.3 µg/m^3 (<RL–2.92 ppb)
New Hampshire (2002–2008)	578	0.22–0.27 µg/m^3 (0.12–0.15 ppb)[g]	<RL–1.61 µg/m^3 (<RL–0.89 ppb)

Table 5-6. Historical Ambient Air Monitoring Data from Selected States[a]

Location (sampling time frame)	Number of valid samples[b]	Median(s)[c]	Range
Rhode Island (1999–2010)	11,280	0.14–0.20 µg/m^3 (0.077–0.11 ppb)[g]	<RL–1.68 µg/m^3 (<RL–0.92 ppb)

[a]Different analytical methods with different detection limits were used.
[b]Samples were reported be nonvalid by the instrument operators for reasons including, but not limited to, instrument malfunction or collection error.
[c]Non-detect values and values below the RL may have been substituted with the detection limit/2.
[d]Post-control samples only from background sites.
[e]Reported average assuming ½ MDL for non-detected samples.
[f]Ranges reflect 12-hour and grab sampling.
[g]Ranges reflect estimates at different sampling locations.

MDL = minimum detection level; NA = not applicable; RL = reporting level

Sources: CARB 1992; CDPHE 2018; EPA 2018a; Ramboll 2019

No data are available on levels of ethylene oxide in air, water, or soil at NPL sites (ATSDR 2019).

5.5.1 Air

The National Air Toxics Assessment (NATA) program is a comprehensive screening assessment released by EPA in 2018 (EPA 2018b). NATA uses emissions data compiled for a single year as inputs to air quality models; model outputs provide a snapshot of outdoor air toxic emissions. The data are used by public health officials to screen air toxic concentrations for further evaluation of public health risk and reduction activities in areas where concentrations are elevated. This assessment utilized emission estimates from the 2014 NEI discussed in Section 5.3.1 to calculate ambient concentrations of air toxics across the United States, Puerto Rico, and the Virgin Islands (EPA 2018c). A statistical breakdown of the calculated annual concentrations of ethylene oxide in ambient outdoor air at the census tract level is provided in Table 5-7. The mean calculated national concentration of ethylene oxide in ambient air was 2.92×10^{-4} µg/m^3 (1.61×10^{-4} ppb) and the maximum level measured was 0.144 ug/m^3 (0.079 ppb).

Table 5-7. Ethylene Oxide Ambient Air Levels from NATA[a]

Mean level	5th percentile	25th percentile	50th percentile	75th percentile	95th percentile
2.9×10^{-4} µg/m^3 (1.0×10^{-4} ppb)	5.7×10^{-6} µg/m^3 (3.2×10^{-6} ppb)	4.0×10^{-5} µg/m^3 (2.2×10^{-5} ppb)	8.7×10^{-5} µg/m^3 (4.8×10^{-5} ppb)	1.5×10^{-4} µg/m^3 (8.2×10^{-4} ppb)	9.5×10^{-4} µg/m^3 (5.2×10^{-4} ppb)

[a]Ambient levels were derived by arithmetically averaging census tract concentrations and are primarily from stationary point sources; emissions estimates from 2014 NEI.

NATA = National Air Toxics Assessment; NEI = National Emission Inventory

Source: EPA 2018b

EPA conducted a limited sampling of ethylene oxide in ambient air in both residential areas and locations in close proximity to the Sterigenics commercial sterilizing facility in Willowbrook, Illinois. The maximum 12-hour residential sample concentration was 2.1 µg/m^3 (1.56 ppb) and the maximum 12-hour for a general workplace concentration was 9.09 µg/m^3 (5.0 ppb). ATSDR reviewed the data to assess potential health risks to the surrounding community in a health consultation document (ATSDR 2018). The EPA Office of Air Quality Planning and Standards Office of Air and Radiation released a risk assessment report for this facility, which consisted of both monitoring data and modeled levels of ethylene oxide from the Gaussian dispersion model AERMOD (EPA 2019b). Sampling was conducted at eight locations in Willowbrook, two locations approximately 100 meters from the facility and six locations in the surrounding community, from November 2018 to March 2019. Ethylene oxide levels at the two locations near the facility reached maximum 24-hour values of 26.4 and 17.3 µg/m^3 (14.5 and 9.5 ppb), respectively, for samples collected on February 5, 2019, while the background level 1.7 km away for this location was 0.174 µg/m^3 (0.096 ppb) (EPA 2019b).

The Georgia Environmental Protection Division collected monitoring data from sites (September 2019–November 2020) located near three facilities that utilize ethylene oxide to sterilize medical equipment (Georgia EPD 2021). The average ethylene oxide air levels near the three facilities were 0.452, 0.489, and 1.149 µg/m^3; the average levels at two "background sites" were 0.337 and 0.552 µg/m^3. Recent monitoring data (samples collected in April–May 2020) from 12 sites in Lake County, Illinois reported air levels of 0.06–0.83 µg/m^3 (0.0313–0.459 ppb) (LakeCounty 2020).

LaMontagne et al. (2004) studied the long-term trends in ethylene oxide worker exposures from 1984 to 2001 to document the effects that the Occupational Safety and Health Administration (OSHA) 1984 and 1988 standards had on workplace exposures. In this study, data from 87,582 8-hour personal samples and 46,097 short-term (15-minute) samples from 2,265 U.S. hospitals were analyzed. The number of

hospitals that exceeded the 1 ppm permissible exposure limit (PEL) declined from roughly 20% in 1984 to about 1% in 2001. The number of hospitals that exceeded the 8-hour action level of 0.5 ppm decreased from about 40% in 1988 to about 5% in 2001. These results suggest that work shift exposures declined after the implementation of the new OSHA standards, continued to taper off, and have remained low and constant through 2001; however, the authors stated that since 1996, the probability of exceeding the short-term excursion limit has increased as enforcement of the standards decreased.

In 1993, it was estimated that the average ground-level ethylene oxide concentrations could be >12 μg/m^3 (>6.6 ppb) for 17 hours/year around a Canadian production facility, although no measured data were provided (WHO 2003). Ethylene oxide was detected in only 1 of 50 samples of indoor air in a study of residences by Health Canada; the concentration was determined to be 4 μg/m^3 (2.2 ppb) in the 24-hour sample (WHO 2003). It was also detected at levels of 5 μg/m^3 in 3 of 24 personal air samples collected from an occupant of each of the 50 residences.

Parod (2014) reported that mean and maximum concentrations of ethylene oxide in ambient air were <0.2 and 2 ppb (0.37 and 4.37 μg/m^3), respectively, based on measured and estimated data. The average concentration may be slightly higher (≤11 μg/m^3 [≤6.05 ppb]) near production and sterilization facilities utilizing ethylene oxide (Parod 2014). Limitations of the report include lack of information regarding the number of samples evaluated, limit of detection, number of samples below the limit of detection, and whether the mean value was geometric or arithmetic.

EPA (2020b) reported ethylene oxide average concentrations from ambient air samples collected at 8 National Air Toxics Trends Stations (NATTS) and 10 Urban Air Toxics Monitoring Program (UATMP) sampling sites between October 2018 and March 2019. Results are summarized in Table 5-8. Measured average ethylene oxide concentrations ranged from 0.185 μg/m^3 (0.103 ppb) in Grayson Lake, Kentucky to 0.397 μg/m^3 (0.220 ppb) in Phoenix, Arizona. EPA has added ethylene oxide to pollutants to be measured at all existing, longstanding monitoring sites in the NATTS and the UATMP networks (a total of 34 sites).

Table 5-8. Ethylene Oxide Ambient Air Concentrations at National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program Stations October 2018 to March 2019

Location	AQS Site ID	Station ID	Average concentration in µg/m^3 (ppb)
Phoenix, Arizona	04-013-9997 04-013-4003	National Air Toxics Trend Urban Air Toxics	0.397 (0.220) 0.345 (0.191)
Grand Junction, Colorado	08-077-0018	National Air Toxics Trend	0.261 (0.145)
Northbrook, Illinois	17-031-4201	National Air Toxics Trend	0.294 (0.163)
Chicago, Illinois	17-031-3103	Urban Air Toxics	0.365 (0.203)
Ashland, Kentucky	21-019-0017	Urban Air Toxics	0.286 (0.159)
Grayson lake, Kentucky	21-043-0500	National Air Toxics Trend	0.185 (0.103)
Smithland, Kentucky	21-139-0004	Urban Air Toxics	0.312 (0.173)
Calvert City, Kentucky	21-157-0014	Urban Air Toxics	0.363 (0.201)
Dearborn, Michigan	26-163-0033	National Air Toxics Trend	0.242 (0.134)
St Louis, Missouri	29-510-0085	National Air Toxics Trend	0.270 (0.150)
Camden, New Jersey	34-007-0002	Urban Air Toxics	0.350 (0.194)
E. Brunswick, New Jersey	34-023-0011	Urban Air Toxics	0.298 (0.165)
Chester, New Jersey	34-027-3001	Urban Air Toxics	0.361 (0.200)
Elizabeth, New Jersey	34-039-0004	Urban Air Toxics	0.305 (0.169)
Bountiful, Utah	49-011-0004	National Air Toxics Trend	0.338 (0.188)
Seattle, Washington	53-033-0080	National Air Toxics Trend	0.185 (0.103)
Lacey, Washington	53-067-0013	Urban Air Toxics	0.192 (0.107)

AQS = Air Quality System; ID = identification

Source: EPA 2020b

5.5.2 Water

There are very limited data on the presence or absence of ethylene oxide in water (drinking water supplies, groundwater, etc.) on a national scale. EPA (1984b) reported a survey showing ethylene oxide at a concentration of 2 mg/L in the effluent of a chemical plant in Bandenburg, Kentucky. The intake fraction (*iF*) is the modeled portion of chemical mass releases into the environment that will be inhaled, ingested, or absorbed by the population. The water *iF* for ethylene oxide is 1.32×10^{-5} compared to the air intake fraction of 1.99×10^{-5}, suggesting similar efficiency of population intake via water compared to air (Bennett et al. 2002).

5.5.3 Sediment and Soil

No data are available on the presence or absence of any significant levels of ethylene oxide in soil. However, De Bont and Albers (1976) reported that ethylene oxide is produced by the metabolism of ethylene by an ethylene-oxidizing bacterium. Also, ethylene is a relatively common volatile hydrocarbon in wet soil, where it can be produced by several species of fungi, bacteria, and actinomycetes (Alexander 1977). Therefore, small but constant levels of ethylene oxide may be present in soils under wet conditions. No data are available on ethylene oxide in soils resulting from uncontrolled releases of ethylene oxide liquid waste or from atmospheric depositions of any kind.

5.5.4 Other Media

Ethylene oxide may be found in tobacco, some food and spices, skin care products, and medical devices as a result of its use as a fumigant and a sterilizing agent. Measurable amounts of ethylene oxide were detected in both fumigated and unfumigated tobacco and its smoke; the ethylene oxide concentration in smoke from unfumigated tobacco was 1 µg/g (EPA 1980). More recently, it was also detected in smoke from fumigated and unfumigated tobacco at 0.3 and 0.02 µg/mL (0.17 and 0.011 ppm), respectively (WHO 2003). Skin care products may contain up to 1 µg/g of ethylene oxide (WHO 2003). As a result of sterilization, medical devices have been found to contain ethylene oxide concentrations of 1–2%, which generally decrease rapidly upon aeration; however, levels >180 mg/m^3 (>99 ppm) have been identified after aeration (WHO 2003). There is evidence that some foods such as flour and spices retain measurable ethylene oxide and byproducts several months after fumigation (NIOSH 1981; Parod 2014; EPA 2017b).

Residual ethylene oxide may be found in foods temporarily, following fumigation. The July 2006 Tolerance Reassessment and Risk Management Decision (TRED) for ethylene oxide required the use of sterilization methods that have been demonstrated to result in residue levels that are lower than those that result from sterilization using conventional sterilization methods (EPA 2006). All ethylene oxide product labels have been revised accordingly to require a single chamber sterilization process (where pre-conditioning and aeration occur in the same chamber as the sterilization) that yields less residues of ethylene oxide and its reaction products on spices. This was effective August 1, 2008. Based on product labels, the only food commodities that can be treated with ethylene oxide products in the United States are spices, dried vegetables, and seasonings. In addition, tolerances (the maximum amount of a pesticide allowed to remain in or on a food) are established in the Code of Federal Regulations for residues of

ethylene oxide (and ethylene chlorohydrin) on commodities in the United States. The following commodities have established tolerances for ethylene oxide: dried herbs and spices (except basil), licorice roots, dried peppermint and spearmint tops, sesame seeds, dried vegetables, and walnuts. If any commodity other than those listed are found to have residues of ethylene oxide, it is considered to be adulterated and is subject to be seized and removed from the channels of trade. Scudamore and Heuser (1971) reported that ethylene oxide may react with water and inorganic halides (chloride and bromide) from foods and produce glycols and halohydrins. The same researchers concluded that the persistence or disappearance of ethylene oxide and its byproducts in fumigated commodities depends on the grain size, type of foods, aeration procedures, temperature, and storage and cooking conditions. According to Scudamore and Heuser (1971), most commodities experimentally fumigated (to kill microorganisms) had levels of ethylene oxide <1 ppm after 14 days in normal storage conditions. No residues of ethylene oxide were found in commercially fumigated flour or tobacco.

Rajendran and Muthu (1981) reported that concentrations of ethylene oxide in 24-hour aerated foods (wheat, rice, spices, dates, and peas), following a 24-hour fumigation period, ranged from 0 to 3.5 ppm. IARC (1976) indicated that food fumigated with ethylene oxide generally had negligible levels of ethylene oxide within a few hours after fumigation, due primarily to loss by volatilization. However, in spices, ethylene oxide levels of 53–116 mg/kg (ppm) and ~25 mg/kg (ppm) at 2 and 26 days after fumigation, respectively, have been reported (WHO 1985). As reported by EPA (2006), a 2005 study examining ethylene oxide residues in herbs and spices that were sterilized using an improved process that is used in all domestic spice sterilization work found that the ethylene oxide dissipated rapidly and would be unlikely to be found in spices available for consumption.

Food product samples obtained from retail stores in Denmark in 1985 were found to contain ethylene oxide in concentrations ranging from <0.05 to 1,800 µg/g (in 96 of 204 samples). Spice samples also contained ethylene oxide at a maximum concentration of 580 µg/g (mean: 84 µg/g) (WHO 2003).

5.6 GENERAL POPULATION EXPOSURE

The general population's exposure to ethylene oxide occurs primarily via inhalation and food ingestion. There is no information to indicate that ethylene oxide is a common contaminant of drinking water supplies.

Some foods retain ethylene oxide after fumigation (EPA 2017b; NIOSH 1981; Parod 2014), thereby resulting in exposure to the general population. Ethylene oxide is naturally occurring in the body, as it is formed from ethylene conversion during metabolic processes (Bono et al. 2002; Parod 2014). WHO estimated that potential maximum exposure levels of ethylene oxide for the general population are about 0.34 and 0.17 μg/m^3 (0.19 and 0.094 ppb) for outdoor and indoor air, respectively. For those residing near point sources, the levels may be significantly higher (estimated as 2, 11, and 20.1 μg/m^3 [1.1, 6.05, and 11.06 ppb) near hospitals, sterilization facilities, and production facilities of ethylene glycol, respectively (WHO 2003).

Exposure to ethylene oxide from environmental tobacco smoke and via maternal transfer has been demonstrated in several studies. In a study of 3–13-year-old children, the levels of HOEtVal (ethylene oxide hemoglobin adduct) was correlated to the number of cigarettes passively smoked by the children (Bono et al. 2005). The levels of HOEtVal were also correlated to urinary cotinine (a nicotine metabolite) levels. Similarly, studies of newborns of mothers have found correlations between HOEtVal levels in maternal blood and cord blood (Farmer et al. 1996; Von Stedingk et al. 2011) or newborn blood levels (Tavares et al. 1994). The cord blood levels were 5 times higher in smokers than nonsmokers (Farmer et al. 1996) and newborn blood levels were about 3 times higher in smokers (Tavares et al. 1994).

Monitoring data on ethylene oxide biomarkers (blood hemoglobin adducts, HEV) were collected during the 2013–2014 and 2015–2016 National Health and Nutrition Examination Survey (NHANES). The hemoglobin adduct levels for nonsmoking and smoking populations are presented in Tables 5-9 and 5-10, respectively. At occupational exposure levels, a relationship exists between exposure to ethylene oxide and increased levels of HEV. However, data to demonstrate that background HEV levels in nonsmoking populations are a direct indicator of internal exposures to ethylene oxide are not available.

Kirman et al. (2021) predicted air ethylene oxide levels that could result in the HEV levels observed in the NHANES 2013–2016 data. The prediction was based on an observed linear relationship between air exposure levels and HEV levels in workers (combined smokers and nonsmokers; slope: 10.9 pmol HEV/g Hgb per ppb ethylene oxide; Angerer et al. 1998). The arithmetic mean HEV level in nonsmokers was estimated to be 31.4 pmol/g Hgb (SD: 24.8, n=3841), and the mean level in smokers was estimated to be 236 pmol/g Hb (SD: 220, n=936). The corresponding equivalent air ethylene oxide levels were 2.9 ppb (SD: 1.3) in nonsmokers and 21.7 ppb (SD: 20.2) in smokers. Kirman et al. (2021) calculated HEV levels that would be associated with typical U.S. air levels of ethylene oxide. Based on a linear slope of 10.9 pmol HEV/g Hgb per ppb ethylene oxide, a concentration of 0.2 ppb in air would correspond to an

Table 5-9. Geometric Mean and Selected Percentiles of Blood Ethylene Oxide Hemoglobin Adduct Levels (pmol/g hemoglobin) Among Nonsmokers in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2013–2016

	Survey years[a]	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2013–2014	28.5 (27.0-30.1)	29.1 (27.6-30.5)	37.5 (35.4-39.7)	50.1 (46.8-52.9)	60.8 (55.9-69.7)	1,945
	2015–2016	27.7 (26.1-29.5)	26.5 (25.2-27.7)	34.7 (32.7-36.6)	47.8 (44.0-53.4)	63.8 (54.0-80.1)	1,896
Age 6–11 years	2013–2014	33.9 (31.6-36.4)	33.2 (30.2-36.8)	42.9 (37.9-47.9)	52.6 (48.8-56.2)	62.9 (55.8-76.1)	321
	2015–2016	33.1 (31.8-34.4)	32.2 (30.7-33.7)	39.9 (37.8-42.0)	52.0 (46.6-58.6)	60.3 (56.0-64.2)	301
Age 12–19 years	2013–2014	29.3 (27.4-31.2)	29.6 (27.4-31.2)	36.4 (34.4-40.0)	49.0 (44.1-56.8)	60.3 (48.0-79.8)	358
	2015–2016	27.6 (25.1-30.3)	27.0 (25.2-29.3)	35.3 (31.3-39.1)	46.3 (40.7-53.9)	54.0 (46.3-60.4)	328
Age 20+ years	2013–2014	27.8 (26.2-29.5)	28.6 (26.9-30.1)	36.8 (34.6-38.8)	49.2 (44.5-54.1)	60.8 (54.1-69.7)	1,266
	2015–2016	27.2 (25.5-29.0)	25.7 (24.1-27.2)	33.7 (32.0-36.2)	47.5 (43.1-54.0)	65.8 (54.0-82.7)	1,267
Males	2013–2014	29.0 (27.2-31.0)	30.2 (28.3-31.3)	38.4 (35.9-40.4)	50.5 (45.3-52.9)	60.4 (52.9-71.1)	897
	2015–2016	29.1 (27.5-30.8)	27.3 (25.7-28.7)	36.4 (34.4-37.8)	51.2 (45.8-56.9)	80.1 (60.5-83.0)	882
Females	2013–2014	28.1 (26.5-29.8)	28.6 (26.9-29.7)	36.6 (34.9-38.6)	49.6 (45.7-55.6)	60.8 (54.7-69.7)	1,048
	2015–2016	26.6 (24.7-28.6)	25.8 (24.1-27.3)	33.2 (31.7-35.6)	46.6 (40.5-52.6)	56.9 (49.0-68.1)	1,014
Non-Hispanic blacks	2013–2014	31.3 (29.1-33.7)	30.8 (28.7-33.7)	43.9 (38.0-47.9)	58.3 (51.7-69.2)	78.4 (61.9-109)	376
	2015–2016	31.8 (30.1-33.6)	30.7 (28.0-33.6)	40.6 (38.0-44.4)	53.9 (47.6-63.7)	65.6 (55.2-79.2)	340
Non-Hispanic whites	2013–2014	27.2 (25.0-29.5)	28.1 (26.2-30.2)	35.9 (32.6-39.1)	48.0 (42.1-52.9)	59.2 (49.6-69.7)	680
	2015–2016	26.1 (24.0-28.4)	25.0 (23.6-26.6)	32.2 (29.7-34.3)	43.1 (39.9-48.9)	63.8 (46.4-83.1)	569
All Hispanics	2013–2014	30.2 (28.9-31.6)	30.0 (29.2-31.3)	37.2 (35.1-39.5)	49.1 (44.4-53.7)	59.2 (52.6-73.1)	585
	2015–2016	29.0 (27.7-30.4)	27.6 (26.4-29.4)	35.7 (34.1-37.4)	47.4 (42.0-58.3)	62.7 (49.4-95.4)	654

[a]The limits of detection (LODs) for survey years 2013–2014 and 2015–2016 were 13.13 and 13.13 pmol/g hemoglobin, respectively.

CI = confidence interval

Source: CDC 2022

Table 5-10. Geometric Mean and Selected Percentiles of Blood Ethylene Oxide Hemoglobin Adduct Levels (pmol/g hemoglobin) Among Cigarette Smokers in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2013–2016

			Selected percentiles (95% CI)				
	Survey years[a]	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total	2013–2014	199 (177-224)	227 (208-244)	354 (325-391)	526 (464-612)	676 (610-894)	416
	2015–2016	192 (160-230)	228 (191-258)	374 (308-419)	533 (458-585)	675 (577-800)	377
Age 18–49 years	2013–2014	197 (175-221)	215 (177-250)	354 (314-399)	535 (439-649)	725 (535-926)	271
	2015–2016	151 (113-202)	180 (135-243)	296 (246-387)	464 (341-585)	585 (446-754)	220
Age 50+ years	2013–2014	204 (155-268)	243 (183-306)	345 (304-438)	510 (438-675)	657 (447-1250)	145
	2015–2016	290 (245-342)	300 (228-381)	444 (375-565)	606 (513-806)	806 (577-1530)	157
Males	2013–2014	200 (174-229)	214 (182-250)	383 (307-438)	578 (435-747)	742 (578-1060)	231
	2015–2016	176 (133-234)	227 (175-272)	360 (294-446)	540 (452-604)	606 (569-685)	231
Females	2013–2014	199 (159-248)	230 (185-264)	335 (290-388)	503 (404-649)	651 (490-926)	185
	2015–2016	214 (179-256)	228 (173-266)	383 (296-432)	531 (392-922)	763 (434-1530)	146

[a]The limits of detection (LODs) for survey years 2013–2014 and 2015–2016 were 13.13 and 13.13 pmol/g hemoglobin, respectively.

CI = confidence interval

Source: CDC 2022

HEV level of 2.2 pmol/Hgb. This level of HEV was approximately 7% of the arithmetic mean level in the U.S. nonsmoking population, based on NHANES 2013–2016 (31.4 pmol/g Hgb).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational groups exposed to ethylene oxide include workers in ethylene oxide manufacturing or processing plants, sterilization technicians, workers involved in the fumigation of foods, clothing, and cosmetics, and indoor fumigators (EPA 2017b; OSHA 1988;). Reported odor threshold concentrations of ethylene oxide in air are in the range of 430–700 ppm (786.9–1,281 mg/m^3) (Amoore and Hautala 1983; OSHA 2018a), which is well above the OSHA permissible exposure limit (PEL) of 1 ppm (1.83 mg/m^3) (OSHA 2018a, 2018b, 2018c). Thus, odor does not provide adequate warning of hazardous concentrations. Worker exposure to ethylene oxide can be determined through routine air monitoring and biomonitoring (see Sections 3.3.1 and 3.3.2 for additional details). The TWA concentration for ethylene oxide exposure in hospital settings near sterilization equipment was determined to be around 90 mg/m^3 (49.5 ppm) (WHO 2003).

Hospital workers and patients may be exposed to residual levels of ethylene oxide during procedures where medical supplies that have been sterilized with ethylene oxide are used. During sterilization, plastics can absorb ethylene oxide and release it when the product is used, resulting in exposure by inhalation, dermal contact, or direct release to the blood stream (Chien et al. 2009). Some sterilized plastics may retain concentrations of ethylene oxide ranging from 3 to 443 mg/kg (ppm) even after 7 days of aeration (WHO 1985). Medical equipment such as adhesive dressings and cotton wool pads may also retain ethylene oxide at ≤2 mg/kg (ppm) for 7–8 days after sterilization (Dauvois et al. 1982). Technicians involved in routine disinfection of medical equipment in hospitals may be exposed to relatively high levels of ethylene oxide. The temporal trends in U.S. hospital settings have indicated that exposure to hospital workers has shown a steady decline since implementation of OSHA standards in 1984 and 1988 (see Section 5.5.1) (LaMontagne et al. 2004). The number of hospitals that exceeded the 1-ppm PEL declined from roughly 20% in 1984 to about 1% in 2001 and the number of hospitals that exceeded the 8-hour action level of 0.5 ppm decreased from about 40% in 1988 to about 5% in 2001.

Short-term area concentrations of ethylene oxide were detected in the air of a central supply department of a Midwestern U.S. hospital at levels up to 77 ppm (141 mg/m^3) (measured at breathing zone height). TWA personal exposure concentrations in this proximity were determined to be 0.23–0.56 ppm (0.42–1.0 mg/m^3). Adjustment of the ventilation system, added exhaust hoods, and addition of an ethylene

oxide monitoring system mitigated the elevated air levels of ethylene oxide (Zey et al. 1994). Similarly, an intervention study conducted in 10 medical supply manufacturing facilities in Taiwan found that worker exposure to ethylene oxide was reduced by increasing the number of post-sterilization purge cycles and increased ventilation (Chien et al. 2007). A study of 9 hospital workers and 15 factory workers exposed to ethylene oxide during sterilization of medical equipment showed that elevated concentrations typically occurred in short bursts. Concentrations ranged from 22 to 72 ppm (40–132 mg/m^3) for hospital settings and from 14 to 400 ppm (26–732 mg/m^3) in factories (Tates et al. 1991). Instantaneous environmental air concentrations from the breathing zone near a hospital sterilizer unit ranged from 0.4 to 22.5 mg/m^3 (0.22–12.38 ppm) (Brugnone et al. 1986). An analysis of historical data pertaining to occupational exposure in various United Kingdom industries concluded that ethylene oxide concentrations ranged from <0.1 to 16 mg/m^3 (<0.055–8.8 ppm), with a mean concentration of 2.0 mg/m^3 (1.1 ppm) for 17 measurements (Cherrie et al. 2001).

Air samples collected at two commercial sterilization facilities contained ethylene oxide in concentrations ranging from 0.7 to 32 ppm (1.3–59 mg/m^3) and from 0.5 to 1.6 ppm (0.9–2.9 mg/m^3) for 15-minute and 8-hour durations, respectively (Cummins et al. 1993). A composite study presented airborne ethylene oxide concentrations in hospital sterilization facilities in various countries, with data collection ranging from 1977 to 1987. TWAs ranged from not detectable to 72 mg/m^3 (39.6 ppm), with peak levels ranging from not detectable to 1,431 mg/m^3 (787 ppm). The study also reported 8-hour TWAs and peak levels, measured in 1987 for six Dutch and Belgian hospitals, ranging from not detectable to 28 mg/m^3 (15.4 ppm) and from not detectable to 700 mg/m^3 (385 ppm), respectively (Florack and Zielhuis 1990). Air concentrations, measured in seven Swiss hospitals with sterilization units from March 2003 to March 2004, ranged from not detectable to 0.59 ppm (1.08 mg/m^3) (Haufroid et al. 2007).

In facilities utilizing ethylene oxide in sterilizing applications, concentrations in air are typically high for very short time periods (i.e., after opening a sterilizer), thereby resulting in low TWA exposures despite high initial concentrations. A survey of 26 exposure scenarios at 18 hospitals with ethylene oxide sterilizers determined that air concentrations peak within 20 seconds of opening portable sterilizers and within 78 seconds of opening built-in sterilizers. In a confined space, a peak ethylene oxide value of 24 ppm (43.9 mg/m^3) was reported following the opening of a built-in sterilizer (Yoshida et al. 1989). A 2005 study by the Taiwan Institute of Occupational Safety and Health of the medical supplies manufacturing industry monitored ethylene oxide concentration and exposure at 10 factories. Ethylene oxide concentrations in air were determined by collecting samples on hydrobromic acid (HBr)-coated charcoal tubes, followed by analysis with gas chromatography/mass spectrometry (GC/MS). It was

determined that workers operating sterilizers were exposed to short-term ethylene oxide air concentrations of 27.61 ppm (50.53 mg/m^3), with mean TWA workshift exposures of 7.35 ppm (13.45 mg/m^3). Additional measurements were obtained near the aeration, sterilizer, and warehouse areas of the facility, where mean ethylene oxide air concentrations were 10.19, 5.75, and 8.78 ppm (18.65, 10.52, and 16.07 mg/m^3), respectively (Chien et al. 2007).

A study of an Egyptian facility using ethylene oxide for sterilization of medical products found concentrations ranging from 4.20 to 7.10 ppm (7.87–12.9 mg/m^3) in the sterilization and aeration room and from 0.70 to 2.50 ppm (1.3–4.58 mg/m^3) in the final inspection room. The mean concentration in the assembly and injection room was reported as 0.21 ppm (0.38 mg/m^3) (Kamel et al. 2011).

Studies of worker exposures in five hospital sterilization rooms in the United States indicate that the time-averaged exposures range from <0.1 to 4.3 ppm (<0.183–7.87 mg/m^3), with peaks as high as 795 ppm (1,455 mg/m^3) (Hansen et al. 1984). In New Zealand fumigators and workers handling container cargo, the maximum 8-hour exposure levels (personal breathing zone) were 0.13 ppm (0.23 mg/m^3) and 0.005 ppm (0.009 mg/m^3), respectively (Hinz et al. 2020). Brugnone et al. (1985) reported alveolar concentrations of ethylene oxide to be about 75% of the environmental concentrations of ethylene oxide in a hospital sterilizing unit (0.1–7.8 ppm or 0.183–14.27 mg/m^3).

Ethylene oxide concentrations were monitored in a facility in Brazil that utilizes the chemical in the production of polyethylene glycol. Ambient air concentrations, determined using passive air sampling pumps with activated charcoal tubes, were analyzed for over a 3-month period. TWAs for an 8-hour working day were determined to be 2–5 ppm (4–10 mg/m^3) (Ribeiro et al. 1994).

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.

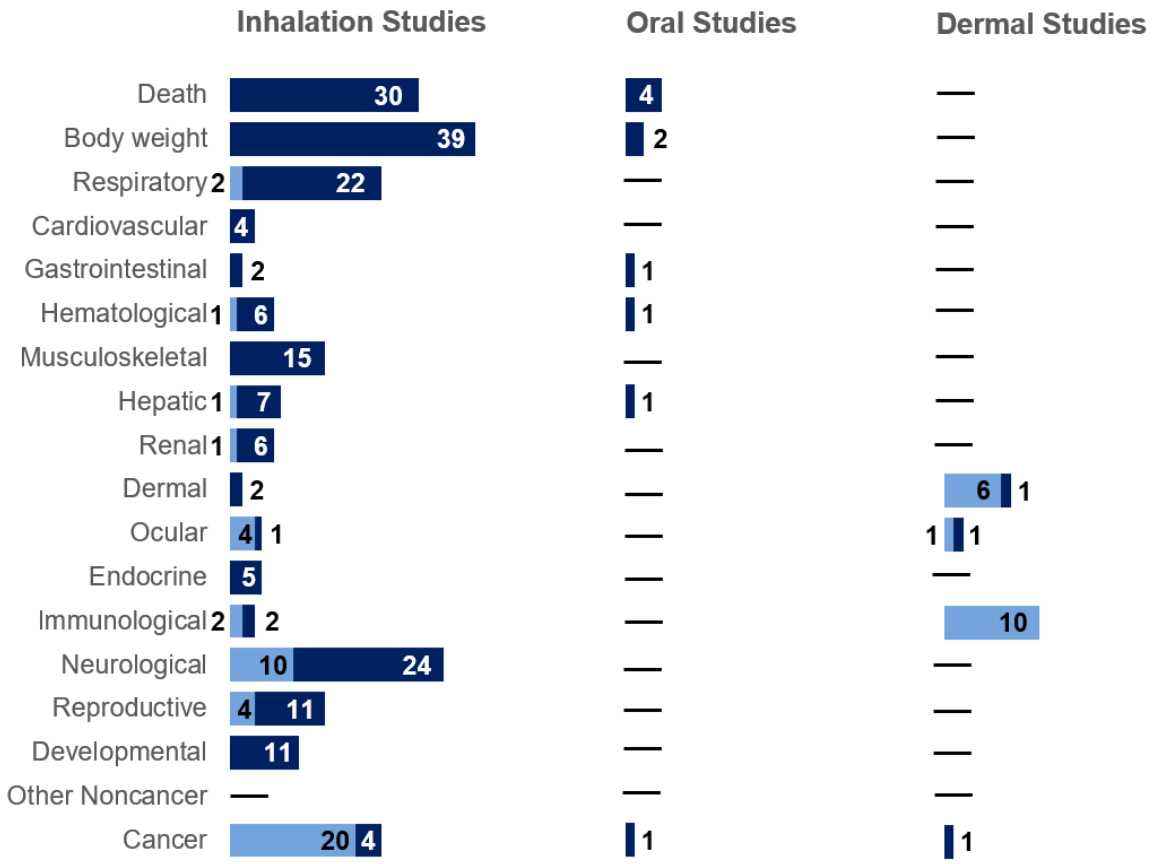
6.1 INFORMATION ON HEALTH EFFECTS

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.

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

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

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

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

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.

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

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).

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding ethylene oxide in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for ethylene oxide.

Table 7-1. Regulations and Guidelines Applicable to Ethylene Oxide

Agency	Description	Information	Reference
		Air	
EPA	RfC	Not assessed	EPA 2016, IRIS 2021
OEHHA	RfC (chronic)	30 µg/m^3 (18 ppb)	OEHHA 2008
WHO	Air quality guidelines	No data	WHO 2010
		Water & Food	
EPA	Drinking water standards and health advisories	Not listed	EPA 2018d
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	Not assessed	EPA 2016, IRIS 2021
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances added to food	No longer FEMA GRAS[a]	FDA 2021
		Cancer	
HHS	Carcinogenicity classification	Known to be a human carcinogen	NTP 2016
EPA	Carcinogenicity classification	Carcinogenic to humans	EPA 2016
	Inhalation unit risk (lifetime-based for lymphoid and female breast cancer combined)	5.0x10^{-3} per µg/m^3 (9.1x10^{-3} per ppb) for environmental ethylene oxide exposures up to about 40 µg/m^3 (20 ppb)	
	Inhalation unit risk (adult-based for lymphoid and female breast cancer combined)	3.0x10^{-3} per µg/m^3 (5.5x10^{-3} per ppb) for environmental ethylene oxide exposures up to about 40 µg/m^3 (20 ppb)	
IARC	Carcinogenicity classification	Group 1[b]	IARC 2012, IARC 2021

Table 7-1. Regulations and Guidelines Applicable to Ethylene Oxide

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	1 ppm (1.83 mg/m^3)	OSHA 2021a, 2021b, 2021c
	Excursion limit[c] (15-minute) for general industry, shipyards, and construction	5 ppm (9.15 mg/m^3)	
NIOSH	REL (up to 10-hour TWA)	<0.1 ppm[d] (<0.183 mg/m^3)	NIOSH 2019
	Ceiling REL (10-minute/day)	5 ppm (9.15 mg/m^3)	
	IDLH	800 ppm (1,464 mg/m^3)	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air[e]		EPA 2018e
	AEGL 2[f]		
	10-minute	80 ppm (146.4 mg/m^3)	
	30-minute	80 ppm (146.4 mg/m^3)	
	60-minute	45 ppm (82.35 mg/m^3)	
	4-hour	14 ppm (25.62 mg/m^3)	
	8-hour	7.9 ppm (14.46 mg/m^3)	
	AEGL 3[f]		
	10-minute	360 ppm (658.8 mg/m^3)	
	30-minute	360 ppm (658.8 mg/m^3)	
	60-minute	200 ppm (366 mg/m^3)	
	4-hour	63 ppm (115.29 mg/m^3)	
	8-hour	35 ppm (64.05 mg/m^3)	

Table 7-1. Regulations and Guidelines Applicable to Ethylene Oxide

Agency	Description	Information	Reference
DOE	PACs-air		DOE 2018a
	PAC-1[g]	5 ppm (9.15 mg/m^3)	
	PAC-2[g]	45 ppm (82.35 mg/m^3)	
	PAC-3[g]	200 ppm (366 mg/m^3)	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group 1: carcinogenic to humans.
[c]Exposure not to exceed 5 ppm as averaged over a sampling period of 15 minutes.
[d]Potential occupational carcinogen.
[e]No recommendations for AEGL 1 due to insufficient data.
[f]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018f).
[g]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline level; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FAO = Food and Agricultural Organization of the United Nations; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OEHHA = California's Office of Environmental Health Hazard Assessment; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene Oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL: 0.4 ppm
Critical Effect: Depressed fetal weight
Reference: Snellings et al. 1982a
Point of Departure: $BMCL_{RD05}$ of 45.50 ppm ($BMCL_{HEC}$ of 11.38 ppm)
Uncertainty Factor: 30
LSE Graph Key: 11
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 0.4 ppm has been derived for ethylene oxide based on depressed mean male fetal weight following exposure of pregnant Fischer 344 rats to ethylene oxide vapor for 6 hours/day during gestation days 6–15 (Snellings et al. 1982a). The $BMCL_{05}$ of 45.50 ppm was adjusted for intermittent exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 11.38 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No adequate exposure-response human data are available. Two rat studies were designed to evaluate acute lethality following single 1- or 4-hour exposure (Jacobson et al. 1956; Snellings et al. 2011). NTP (1987) evaluated the effects of repeated inhalation exposure of rats and mice for 2 weeks or up to 2 weeks during 14-week studies. Several studies were designed to evaluate the effects of maternal exposure during periods of gestation (Neeper-Bradley and Kubena 1993; NIOSH 1982; Rutledge and Generoso 1989; Saillenfait et al. 1996; Snellings et al. 1982a).

Selected results from the studies that evaluated sublethal effects (potential candidates for MRL derivation) are summarized in Table A-1. Several studies were considered inadequate for the purpose of deriving an acute-duration inhalation MRL for ethylene oxide. NTP (1987) reported a respiratory effect (rhinitis) at an exposure level (71.4 ppm) resulting in 90% mortality during 2 weeks of repeated exposures. The study of Rutledge and Generoso (1989) employed only a single high ethylene oxide exposure concentration (1,200 ppm) for an exposure period of 1.5 hours. The studies of Saillenfait et al. (1996) employed short exposure durations (30 minutes/day or three 30-minute periods/day).

In two developmental toxicity studies, pregnant rats were exposed to ethylene oxide vapors for 6 hours/day during gestation days 6–15. The studies reported fetal weight data as mean of litter means. Sprague-Dawley rats were used in the study of Neeper-Bradley and Kubena (1993); the study identified a NOAEL of 50 ppm and a LOAEL of 125 ppm for 5% depressed mean fetal weight. Fischer 344 rats were used in the study of Snellings et al. (1982a); the study identified a NOAEL of 33 ppm and a LOAEL of 100 ppm for up to 9% depressed mean fetal weight.

Table A-1. Summary of Selected NOAELs and LOAELs from Acute-Duration Studies in Animals Exposed to Ethylene Oxide by Inhalation

Species	Exposure scenario	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$[a] (ppm)	$LOAEL_{ADJ}$[a] (ppm)	Effect	Reference
Respiratory effects							
B6C3F1 mouse	Up to 2 weeks during a 14-week study 5 days/week 6 hours/day	ND	400[b]	ND	71.4	Rhinitis	NTP 1987
Developmental effects							
Fischer 344 rat	GDs 6–15 6 hours/day	33 F	100 F	8.3 F	25 F	Up to 9% depressed mean fetal weight	Snellings et al. 1982a
Sprague-Dawley rat	GDs 6–15 30 minutes/day	800 F	1,200 F	16.7	25 F	Increased incidence of dilation in renal pelvis and ureter of fetuses	Saillenfait et al. 1996
Sprague-Dawley rat	GDs 6–15 6 hours/day	50	125	12.5	31.3	5% depressed mean fetal weight	Neeper-Bradley and Kubena 1993
Sprague-Dawley rat	GDs 7–16 7 hours/day	ND	150 F	ND	43.8 F	5–6% depressed mean fetal weight; decreased crown-rump length; delayed ossification (skull, sternebrae)	NIOSH 1982
Sprague-Dawley rat	GDs 6–15 3x30 minutes/day	ND	800 F	ND	50 F	4–7% depressed mean fetal weight at maternally toxic exposure level	Saillenfait et al. 1996
Hybrid mouse	Once for 1.5 hours	ND	1,200 F	ND	75 F	Selected fetal defects (mostly hydrops and eye defects)	Rutledge and Generoso 1989

[a]Duration-adjusted from intermittent exposure to a continuous exposure scenario.
[b]Lethal exposure level.

ADJ = adjusted; F = female(s); GD = gestation day; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The mean fetal weight data in the developmental toxicity study of Fischer 344 maternal rats (Snellings et al. 1982a) were selected to represent the critical effect of acute-duration inhalation exposure to ethylene oxide because the fetal weight data represent the lowest LOAEL (100 ppm); the corresponding NOAEL was 33 ppm. As shown in Table A-1, duration adjustment (to account for a continuous exposure scenario) of NOAELs and LOAELs from the various studies did not result in a more appropriate principal study or critical effect.

Summary of the Principal Study:

Snellings WM, Maronpot RR, Zelenak JP, et al. 1982a. Teratology study in Fischer 344 rats exposed to ethylene oxide by inhalation. Toxicol Appl Pharmacol 64:476-481.

Groups of 22 pregnant Fischer 344 rats were exposed to 0, 0, 10, 33, or 100 ppm ethylene oxide 6 hours/day on gestation days 6–15 and sacrificed on gestation day 20. Parameters used to assess toxicity included number of implantation sites, viable fetuses, dead fetuses, early resorption sites, and late resorption sites, number of corpora lutea, fetal body weight, sex, crown-to-rump length, external fetal abnormalities, and internal and skeletal abnormalities in both control and 100 ppm groups (examined in 10 and 33 ppm groups if effects were noted at 100 ppm).

No overt signs of toxicity were observed in the dams. No alterations in preimplantation loss or embryo or fetal resorptions were observed. Significant decreases in fetal body weight were observed at 100 ppm (approximately 6–9% in males and 3–6% in females), but there were no differences in crown-rump length. An increase in the occurrence of vertebrae ossification variations was observed at 100 ppm, but the incidence was not significantly different from controls. No other developmental alterations were observed. The fetal weight data are presented in Table A-2. Although there are no established guidelines as to what minimal change in a continuous endpoint such as body weight is biologically significant, a 10% change is generally used for adult body weight. However, because fetal or neonatal organisms may be more susceptible than adults, a ≥5% decrease in fetal body weight relative to controls was selected to represent an adverse effect.

Table A-2. Fetal Weight Data (Mean of Litter Means) for Fetuses of Maternal Fischer 344 Rats Exposed to Ethylene Oxide Vapor for 6 Hours/Day During Gestation Days 6–15

	Ethylene oxide exposure level (ppm)				
	0 (control I)	0 (control II)	10	33	100
Number of litters	21	17	20	21	19
Mean fetal weight (g)	M: 3.4±0.4[a] F: 3.1±0.3	M: 3.3±0.2 F: 3.0±0.2	M: 3.3±0.3 F: 3.0±0.3	M: 3.3±0.3 F: 3.1±0.3	M: 3.1[b]±0.2 F: 2.9[b]±0.1

[a]Mean of litter means ± standard deviation.
[b]Significantly different from each sex-matched control group by Duncan's multiple range test ($p<0.05$).

F = female; M = male

Source: Snellings et al. 1982a

Selection of the Point of Departure for the MRL: A benchmark dose (BMD) approach was applied to derive the acute-duration inhalation MRL for ethylene oxide. Fetal body weight data from Snellings et al. (1982a; Table A-2) were fit to all available continuous variable models in the EPA Benchmark Dose

Software (BMDS, version 3.2) using a benchmark response (BMR) of 5% relative deviation from control and the assumption of constant variance. However, continuous Hill models were not considered viable because the model has five parameters, requiring a minimum of six data points (including control), and these data sets have only four or five data points. For remaining models, adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value ≥0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among models providing adequate fit to the data, the lowest BMCL was selected as the point of departure (POD) when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen.

BMD modeling results for male fetal weight data reported by Snellings et al. (1982a; see Table A-2) are summarized in Table A-3. Data were a fit to constant variance. Among models providing viable results, the 4-degree Polynomial model-predicted $BMCL_{RD05}$ of 45.50 ppm was selected as a potential POD because it provided the lowest AIC.

Table A-3. Results from BMD Analysis (Constant Variance) of Male Fetal Weight Following Maternal Exposure of Fischer 344 Rats to Ethylene Oxide Vapor for 6 Hours/Day During Gestation Days 6–15 (Snellings et al. 1982a)

					Scaled residuals[c]	
Model	BMC_{RD05}[a]	$BMCL_{RD05}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	67.70	43.83	0.81	40.98	0.47	-0.13
Exponential (model 3)[d]	74.58	44.00	0.55	42.91	0.22	-0.03
Exponential (model 4)[d]	67.69	43.83	0.81	40.98	0.47	-0.13
Exponential (model 5)[d]	73.93	44.00	0.55	42.91	0.24	-0.04
Polynomial (2-degree)[e]	76.38	45.43	0.58	42.86	0.19	-0.02
Polynomial (3-degree)[e]	79.24	45.51	0.87	40.84	0.15	-0.01
Polynomial (4-degree)[e,f]	**81.48**	**45.50**	**0.87**	**40.83**	**0.14**	**-0.002**
Linear[e]	68.39	45.14	0.82	40.96	0.45	-0.11
Power	74.61	54.00	0.56	42.90	0.22	-0.03

[a]BMCLs <10 times the lowest non-zero dose and their corresponding BMCs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. Using constant variance, all models provided adequate fit. BMCLs for all models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (4-degree Polynominal).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD05 = dose associated with a 5% relative deviation)

Table A-4 summarizes the results of BMD modeling for female fetal weight data reported by Snellings et al. (1982a; see Table A-2). None of the models provided adequate fit to the data using constant variance. Therefore, the data were fit to all models using nonconstant variance. The Power model and Polynomial models (2-, 3-, and 4-degree) provided viable results. Among these models, the 4-degree Polynomial

model-predicted $BMCL_{RD05}$ of 87.00 ppm was selected as a potential POD because the model provided the lowest AIC.

Table A-4. Results from BMD Analysis (Nonconstant Variance) of Female Fetal Weight Following Maternal Exposure of Fischer 344 Rats to Ethylene Oxide Vapor for 6 Hours/Day During Gestation Days 6–15 (Snellings et al. 1982a)

					Scaled residuals[c]	
Model	BMC_{RD05}[a]	$BMCL_{RD05}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]			0.01	5.97	1.46	0.41
Exponential (model 3)[d]			0.03	2.00	0.40	0.93
Exponential (model 4)[d]			0.01	5.97	1.46	0.41
Exponential (model 5)[d]			0.03	2.00	0.40	0.93
Polynomial (2-degree)[e]	97.62	82.74	0.31	-2.54	1.00	-0.02
Polynomial (3-degree)[e]	96.02	84.98	0.68	-5.37	0.68	0.28
Polynomial (4-degree)[e,f]	**99.07**	**87.00**	**0.83**	**-6.00**	**0.75**	**0.07**
Linear[e]			0.01	4.41	1.59	-0.23
Power	99.98	98.35	0.39	-2.14	0.76	0.003

[a]BMCLs <10 times the lowest non-zero dose and their corresponding BMCs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. Using nonconstant variance, the polynomial and power models provided adequate fit to the data. BMCLs for these models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (4-degree Polynomial).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD05 = dose associated with a 5% relative deviation)

Fetal weight data (per litter) reported by Neeper-Bradley and Kubena (1993; see Table A-5) were also modeled for comparison. Table A-6 summarize the results of BMD modeling for this data set. Data were a fit to constant variance. All models provided adequate fit to the data. The Exponential model 3 was selected as the best-fitting model (lowest AIC) and provided a $BMCL_{RD05}$ of 92.09 ppm.

Table A-5. Fetal Weight per Litter Following Maternal Exposure of Sprague-Dawley Rats to Ethylene Oxide Vapor for 6 Hours/Day on Gestation Days 6–15

	Ethylene oxide concentration (ppm)			
	0	50	125	225
Number of litters	23	20	20	24
Fetal weight per litter (g)	5.161±0.2480[a]	4.972±0.2766[b]	4.891±0.2745[b]	4.644±0.2899[c]

[a]Mean ± standard deviation.
[b]Significantly different from control group by t- test ($p<0.05$).
[c]Significantly different from control group by t- test ($p<0.01$).

Source: Neeper-Bradley and Kubena 1993

Table A-6. Fetal Weight per Litter Following Maternal Exposure of Sprague-Dawley Rats to Ethylene Oxide Vapor for 6 Hours/Day on Gestation Days 6–15 (Neeper-Bradley and Kubena 1993)

					Scaled residuals[c]	
Model	BMC_{RD05}[a]	$BMCL_{RD05}$[a]	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Exponential (model 2)[d]	115.38	92.07	0.54	23.92	-0.88	0.52
Exponential (model 3)[e]	**115.38**	**92.09**	**0.54**	**23.92**	**-0.88**	**0.52**
Exponential (model 4)[d]	112.35	59.62	0.27	25.91	-0.85	0.58
Exponential (model 5)[d]	115.38	59.50	0.27	25.92	-0.88	0.52
Polynomial (2-degree)[f]	118.32	95.58	0.53	23.95	-0.91	0.46
Polynomial (3-degree)[f]	118.32	95.58	0.53	23.95	-0.91	0.46
Linear[f]	118.32	95.58	0.53	23.95	-0.91	0.46
Power[d]	118.32	95.59	0.53	23.95	-0.91	0.46

[a]BMCLs <10 times the lowest non-zero dose and their corresponding BMCs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. Using constant variance, all models provided adequate fit. BMCLs for all models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential model 3).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., RD05 = dose associated with a 5% relative deviation)

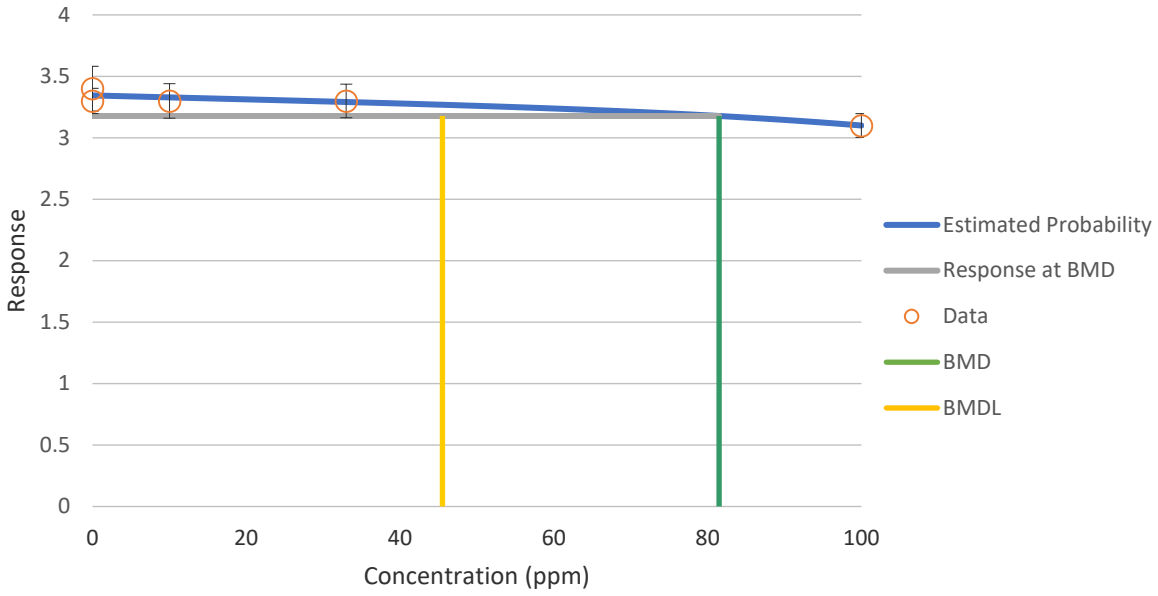
Potential PODs for deriving an acute-duration inhalation MRL for ethylene oxide include:

- $BMCL_{RD05}$ of 92.09 ppm from the fetal weight data of Neeper-Bradley and Kubena (1993)
- $BMCL_{RD05}$ of 87.00 ppm from the female fetal weight data of Snellings et al. (1982a)
- $BMCL_{RD05}$ of 45.50 ppm from the male fetal weight data of Snellings et al. (1982a)

The $BMCL_{RD05}$ of 45.50 ppm from the male fetal weight data of Snellings et al. (1982a) was selected as the POD for deriving an acute-duration inhalation MRL for ethylene oxide because it represents the most

conservative (health-protective) POD. The 4-degree Polynomial model fit to the male fetal weight data is presented in Figure A-1.

Figure A-1. Fit of 4-Degree Polynominal Model to Data on Male Fetal Weight Following Maternal Exposure of Fischer 344 Rats to Ethylene Oxide Vapor



Calculations

Intermittent Exposure: The $BMCL_{RD05}$ of 45.50 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$BMCL_{ADJ}$ = $BMCL_{RD05}$ of 45.50 ppm x (6 hours/24 hours) = 11.38 ppm

Human Equivalent Concentration: A PBPK modeling approach was initially considered to calculate a human equivalent to the rat $BMCL_{ADJ}$. However, a PBPK modeling approach was rejected due to a lack of experimental data regarding the proper dose metric (proximate toxicant) for ethylene oxide-induced developmental toxicity. Therefore, a human equivalent concentration was calculated by multiplying the duration adjusted BMCL by the regional gas dose ratio (RGDR). The RGDR for extrarespiratory tract effects is the ratio of animal to human blood:gas partition coefficients:

$BMCL_{HEC}$ = $BMCL_{ADJ}$ x $RGDR_{ER}$
$BMCL_{HEC}$ = $BMCL_{ADJ}$ x ($[H_{b/g}]_A/[H_{b/g}]_H$)

$[H_{b/g}]_A$ = animal blood/air partition coefficient = 64.1 for rats (Krishnan et al. 1992)
$[H_{b/g}]_H$ = human blood/air partition coefficient = 61 for humans (Csanady et al. 2000)

A default value of 1 is used for the ratio of blood/air partition coefficients because the animal value is greater than the human value.

$BMCL_{HEC}$ = 11.38 ppm x 1 = 11.38 ppm

Uncertainty Factor: The $BMCL_{HEC}$ of 11.38 ppm was divided by a total uncertainty factor (UF) of 30:

- 3 for extrapolation from animals to humans using dosimetric adjustment
- 10 for human variability

$MRL = BMCL_{HEC} \div UF$
$MRL = 11.38 \text{ ppm} \div (3 \times 10) = 0.379 \text{ ppm} \approx 0.4 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Other acute-duration developmental toxicity studies in rats identified fetal body weight effects as well (Neeper-Bradley and Kubena 1993; NIOSH 1982; Saillenfait et al. 1996), although LOAELs were higher than the LOAEL of Snellings et al. (1982a). Reduced fetal body weight was also observed in rats exposed to inhaled ethylene oxide for intermediate exposure durations (EPA 1994; NIOSH 1982)

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene Oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.07 ppm
Critical Effect: Decreased pup body weight
Reference: EPA 1994
Point of Departure: NOAEL of 10 ppm ($NOAEL_{HEC}$ of 2.1ppm)
Uncertainty Factor: 30
LSE Graph Key: 22
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.07 ppm has been derived based on decreased body weight in F1 male pups on postnatal day (PND) 21 in CD rats exposed to ethylene oxide vapor for 6 hours/day, 5.85 days/week in a 2-generation reproduction study (EPA 1994). The MRL is based on a NOAEL of 10 ppm that was adjusted to continuous exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 2.1 ppm, divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: No adequate exposure-response human data are available. Case studies of workers have reported a number of neurological effects including headache, neuropathy, impaired hand-eye coordination, hand numbness, cognitive dysfunction, and memory loss (Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Zampollo et al. 1984). These effects were seen at estimated average exposure levels as low as 3 ppm; however, short-term exposures may have been as high as 700 ppm for some of these workers. These case studies are insufficient to establish a causal relationship between exposure to ethylene oxide and neurological effects in humans.

Several animal studies evaluated sublethal effects of intermediate-duration inhalation exposure in laboratory animals (EPA 1994, 2005b; Fujishiro et al. 1990; Matsuoka et al. 1990; Mori et al. 1991a, 1991b; NIOSH 1982; NTP 1987; Ohnishi et al. 1985, 1986; Snellings et al. 1982b, 1984a). Adverse effects were observed in the respiratory, hematological, renal, neurological, and reproductive systems, and in the developing fetus; the most sensitive NOAELs and LOAELs for these effects are summarized in Table A-7. EPA (1994) reported the lowest LOAEL of 33 ppm, with a NOAEL of 10 ppm, for developmental effects (decreased PND pup weight in F1 males) and reproductive effects (increased post-implantation loss in F0 rats). For other systems, the lowest LOAELs were as follows: 100 ppm for renal effects (renal tubular degeneration) (NTP 1987); 200 ppm for respiratory effects (rhinitis) (NTP 1987); and 200 ppm for neurological effects (decreased hindlimb strength) (EPA 2005b); and 250 ppm for hematological effects (decreases in hemoglobin, erythrocyte count, packed cell volume, and/or mean corpuscular hemoglobin) (Snellings et al. 1984a)

Table A-7. Summary of Selected NOAELs and LOAELs from Intermediate-Duration Studies in Animals Exposed to Ethylene Oxide by Inhalation

Species	Exposure scenario	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$[a] (ppm)	$LOAEL_{ADJ}$[a] (ppm)	System: effect	Reference
CD rat	10 weeks premating (6 hours/day, 5 days/week) and during mating, gestation, and lactation (6 hours/day, 7 days/week)	10	33	2.1[b]	6.89[b]	***Developmental:*** Decreased pup body weight in F1 males on PND 21	EPA 1994
CD rat	10 weeks premating (6 hours/day, 5 days/week) and during mating, gestation, and lactation (6 hours/day, 7 days/week)	10	33 (SLOAEL)	2.1[b]	6.89[b]	***Reproductive:*** Increased post-implantation loss in F0 rats	EPA 1994
B6C3F1 mouse	Up to 14 weeks (6 hours/day, 5 days/week)	NR M 100 F	100 M 200 F	ND M 17.9 F	17.9 M 35.7 F	***Renal:*** Renal tubular degeneration	NTP 1987
Sprague-Dawley rat	14 weeks (6 hours/day, 5 days/week)	100	200	17.8	35.7	***Neurological:*** Decreased hindlimb grip strength	EPA 2005b
B6C3F1 mouse	Up to 14 weeks (6 hours/day, 5 days/week)	100	200	17.9	35.7	***Respiratory:*** Rhinitis	NTP 1987
B6C3F1 mouse	10–11 weeks (6 hours/day, 5 days/week)	100	250	17.9	44.6	***Hematological:*** Decreases in hemoglobin, erythrocyte count, packed cell volume, and/or mean corpuscular hemoglobin	Snellings et al. 1984a

[a]Duration-adjusted from intermittent exposure to a continuous exposure scenario.
[b]Duration-adjusted to continuous exposure using the time-weighted average for the exposure frequency (5.85 days/week, 6 hours/day).

ADJ = adjusted; F = female(s); LOAEL = lowest observed adverse effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NR = not reported; PND = postnatal day; SLOAEL = serious LOAEL

Selection of the Principal Study: Among available intermediate-duration inhalation studies in laboratory animals, EPA (1994) identified the lowest NOAEL and LOAEL of 10 and 33 ppm, respectively. Therefore, EPA (1994) was selected as the principal study for derivation of the intermediate-duration inhalation MRL.

Summary of the Principal Study:

EPA. 1994. Data evaluation report: Ethylene oxide (EtO): Range-finding/developmental studies in rats (MRID #427977-01 and -02). D192811. Two generation reproduction study in rats (MRID #427881-01). D192453 (Previous 189547). Washington, DC: U.S. Environmental Protection Agency.

Groups CD rats (28/sex/group) were exposed by inhalation (whole body) to 0, 10, 33, or 100 ppm of ethylene oxide for 10 weeks premating (6 hours/day, 5 days/week), and during mating (2 weeks), gestation days 0–21, and lactation days 5–28 (6 hours/day, 7 days/week). The time-weighted exposure frequency for the study is 5.85 days/week for 6 hours/day. Parental animals were evaluated mortality, clinical signs, body weight, food consumption, organ weights (liver and lung), gross pathology, and histopathology, including reproductive organs. Uteri were examined to determine the total number of implantation sites. Litters were examined for numbers of live and stillborn pups, number of live and dead pups, sex, external anomalies, and pup body weight.

In F0 and F1 parents, no mortality or clinical signs were observed. Significant decreases in body weight gain were observed in F0 males in the 100 ppm group during the first 3 weeks of the pre-mating period (13–23%) and in F1 males in the 100 ppm group during the first (13%) and fifth (24%) weeks in the pre-mating period. A decrease in body weight was also reported in F1 males (7–11%) in the 33 ppm group "throughout study," but data were not provided. No consistent treatment-related alterations in body weight gain were observed in the F0 or F1 females during the pre-mating period. Significant decreases in body weight gain were observed in F0 and F1 females in the 100 ppm group during gestation; the decreases in body weight in the F1 group were considered to be due to the reduced litter size in this group. Decreases in food consumption were observed in F0 and F1 lactating females. No treatment-related effects were observed for organ weights, or on gross pathological or histopathological examinations in males or females.

Reproductive and developmental effects were observed in F0 parents and F1 offspring at 33 and 100 ppm and in F1 parents and F2 offspring at 100 ppm. In F0 parents, post-implantation loss was increased to 14 and 41% in the 33 and 100 ppm groups respectively, compared to 7% in controls. The mean number of live births per litter was decreased by 36% in the 100 ppm group, compared to control. In F1 offspring, pup body weight on PND 21 was decreased by 7 and 13% in males in the 33 and 100 ppm groups, respectively. In female pups, body weight on PND 21 was decreased by 13% in the 100 ppm group. In F1 parents, post-implantation loss was increased to 42% in the 100 ppm group, compared to 11% in controls. The mean number of live births per litter were also decreased by 45% in the 100 ppm group, compared to control. In the 100 ppm group, alterations in F2 pup body weight were observed on PNDs 1 and 21. On PND 1, male and female body weights were increased by 10 and 9%, respectively, compared to controls; this was attributed to reduced litter size. In contrast, on PND 21, male and female body weights were decreased by 11%.

Selection of the Point of Departure for the MRL: Among intermediate-duration inhalation studies in laboratory animals, the 2-generation reproduction study in rats summarized by EPA (1994) identified the lowest LOAEL of 33 ppm for decreased F1 pup body weight in males on PND 21; data are presented in Table A-8. As noted in discussions above, post-implantation loss exposed to 33 and 100 ppm was also observed in this study. However, in a companion gestation-only exposure study (conducted by the same researchers using the same strain of rats with daily exposures on gestation days 6–15), post-implantation

loss was not observed at exposure levels up to 250 ppm (EPA 1994). Additionally, the reproductive NOAEL and LOAEL values in a 1-generation study in F-344 rats were 33 and 100 ppm, respectively, based on a significant decrease in the ratio of the number of fetuses born per number of implantation sites (Snellings et al. 1982b). Due to observed discrepancies regarding the LOAEL for post-implantation loss, this endpoint was not selected as a co-critical effect for the intermediate-duration inhalation MRL. Data for pup body weight was not amenable to BMD analysis because measures of variance (e.g., standard deviation or standard error) for pup body weights were not reported. Therefore, the NOAEL of 10 ppm was selected as the POD.

Table A-8. Male Pup Body Weight in F1 Offspring of CD Rats Exposed to Ethylene Oxide in a 2-Generation Reproduction Study

	Ethylene oxide exposure level (ppm)			
Effect	0	10	33	100
Body weight PND 21 (g)	40.8	41.7[a] (↑ 2.2%)	38.0[b] (↓6.9%)	35.3[c] (↓13.5%)

↑ = increase; ↓ = decrease; PND = postnatal day

[a]Values are means (% change from control)
[b]Significantly different from control ($p<0.05$)
[c]Significantly different from control ($p<0.01$)

Source: EPA 1994

Calculations

Intermittent Exposure: The NOAEL of 10 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$NOAEL_{ADJ}$ = NOAEL of 10 ppm x (6 hours/24 hours) x (5.85 days/7 days) = 2.1 ppm.

Human Equivalent Concentration: A PBPK modeling approach was initially considered to calculate a human equivalent to the rat $NOAEL_{ADJ}$. Available PBPK models for ethylene oxide are described in Section 3.1.5. However, a PBPK modeling approach was rejected due to a lack of experimental data regarding the proper dose metric (proximate toxicant) for ethylene oxide-induced developmental effects. Therefore, a human equivalent concentration was calculated by multiplying the duration adjusted BMDL by the RGDR. The RGDR for extrarespiratory tract effects is the ratio of animal to human blood:gas partition coefficients.

$NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ER}$
$NOAEL_{HEC} = NOAEL_{ADJ} \times ([H_{b/g}]_A/[H_{b/g}]_H)$

$[H_{b/g}]_A$ = andecreaseimal blood/air partition coefficient = 64.1 for rats (Krishnan et al. 1992)
$[H_{b/g}]_H$ = human blood/air partition coefficient = 61 for humans (Csanady et al. 2000)

A default value of 1 for the ratio of blood/air partition coefficients for rats and humans was used because the rat blood/air partition coefficient was greater than the value for humans.

$NOAEL_{HEC}$ = 2.1 ppm x 1 = 2.1 ppm

Uncertainty Factor and Modifying Factor: The $NOAEL_{HEC}$ of 2.1 ppm was divided by a total uncertainty factor (UF) of 30:

- 3 for extrapolation from animals to humans using dosimetric adjustment
- 10 for human variability

$MRL = NOAEL_{HEC} \div UF$
$MRL = 2.1 \text{ ppm} \div (3 \times 10) = 0.07 \text{ ppm}$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Gestational exposure studies in rats provide supporting evidence for developmental effects, specifically decreased pup body weight in dams exposed to inhaled ethylene oxide (Neeper-Bradley and Kubena 1993; NIOSH 1982; Saillenfait et al. 1996; Snellings et al. 1982a). LOAELs in these studies range from 100 ppm (Snellings et al. 1982a) to 800 ppm (Saillenfait et al. 1996).

The pre-public version of the ethylene oxide profile developed a provisional intermediate-duration inhalation MRL based on neurological effects. However, newly available data indicate that developmental effects are more sensitive than neurological effects. Therefore, the final intermediate-duration MRL for ethylene oxide was revised based on these developmental effects. The provisional neurological MRL in the pre-public version applied a modifying factor to address the insufficient assessment of functional neurological endpoints. However, since the endpoints in the developmental study were assessed thoroughly, ATSDR determined that no additional modifying factor was needed.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene Oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: Available chronic-duration inhalation data were not considered adequate for derivation of a chronic-duration inhalation MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No adequate exposure-response data were available for humans. Case studies of neurological effects in workers exposed to ethylene oxide have been reported. These studies are insufficient to establish a causal relationship between exposure to ethylene oxide and neurological effects in humans. Neuropathy, impaired hand-eye coordination, cognitive dysfunction, memory loss, headache, and hand numbness were reported after occupational exposure to ethylene oxide (Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Zampollo et al. 1984). Sural nerve biopsies performed on two occupational groups revealed axonal degeneration and regeneration (Kuzuhara et al. 1983; Schröder et al. 1985).

The effects of chronic-duration inhalation exposure studies have been evaluated in monkeys (Lynch et al. 1984a), rats (Lynch et al. 1984a, 1984b; Snellings et al. 1984b), and mice (NTP 1987). Studies in monkeys and mice were not considered as potential principal studies. In cynomolgus monkeys intermittently exposed to ethylene oxide vapor for 2 years, decreased sperm count (28% less than controls) and motility (32% less than controls) were noted at the lowest exposure level tested (50 ppm) (Lynch et al. 1984a). However, evaluation of sperm parameters at cessation of exposures at 24 months included only two monkeys per group. Therefore, data are not adequate for derivation of the chronic-duration MRL. The NTP (1987) study in mice did not identify any noncancer effects at the highest exposure level tested (100 ppm); therefore, data from this study cannot be considered as the basis of the MRL.

The rat studies (Lynch et al. 1984b; Snellings et al. 1984b) were considered as principal studies for derivation of the chronic-duration inhalation MRL; however, ATSDR determined that they are inadequate to support derivation of an MRL. Exposure concentrations in these studies ranged from 10 to 100 ppm. Observed effects included decreased body weight (Lynch et al. 1984b; Snellings et al. 1984b) and alterations in the hematological, musculoskeletal, and endocrine systems (Lynch et al. 1984b). The NOAEL and LOAEL values for these effects are summarized in Table A-9. Lynch et al. (1984b) identified the lowest LOAEL of 50 ppm based on splenic extramedullary hematopoiesis and histopathological changes to the adrenal gland (multifocal vacuolization and hyperplasia). NOAEL values for these effects were not identified. However, ATSDR deemed the study inappropriate for MRL derivation because the rat colony experienced a *Mycoplasma pulmonis* infection during the study period. This infection was treated with antibiotics but did not appear to resolve and resulted in decreased survival. The potential contribution of the infection and stress associated with infection to adverse health effects is unknown, particularly regarding adrenal gland findings. Adrenal findings are further confounded by evidence that administration of antibiotics may induce adrenal hyperplasia in rats (Dickson et al. 1954; Dietz et al. 1991). Therefore, effects reported by Lynch et al. (1984b) at ≥50 ppm are of uncertain toxicological relevance due to concurrent infection. The other available rat study (Snellings et al. 1984b) identified a higher LOAEL of 100 ppm based on decreased body weight. However, potential non-

Table A-9. Summary of Selected NOAELs and LOAELs from Chronic-Duration Studies in Animals Exposed to Ethylene Oxide by Inhalation

Species	Exposure scenario	NOAEL (ppm)	LOAEL (ppm)	$NOAEL_{ADJ}$[a] (ppm)	$LOAEL_{ADJ}$[a] (ppm)	Effect	Reference
Body weight effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/day	50	100	10.4	20.8	13% depressed body weight gain	Lynch et al. 1984b
Fischer 344 rat	2 years 5 days/week 6 hours/day	33	100	5.9	17.9	Depressed body weight gain in males (up to 12%) and females (12–18%)	Snellings et al. 1984b
Hematological effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/day	ND	50	ND	10.4	Splenic extramedullary hematopoiesis	Lynch et al. 1984b
Musculoskeletal effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/day	50	100	10.4	20.8	Multifocal myopathy	Lynch et al. 1984b
Endocrine effects							
Fischer 344 rat	104 weeks 5 days/week 7 hours/days	ND	50	ND	10.4	Multifocal cortical vacuolation and hyperplasia in adrenal gland	Lynch et al. 1984b

[a]Duration-adjusted from intermittent exposure to a continuous exposure scenario.

ADJ = adjusted; LOAEL = lowest observed adverse effect level; ND = not determined; NOAEL = no-observed-adverse-effect level

neoplastic changes in the spleen may have been masked at 33 ppm due to increased incidence of mononuclear cell leukemia that was associated with marked splenomegaly in these rats. Therefore, an MRL based on body weight effects observed at 100 ppm may not be protective of potential nonneoplastic effects at lower exposure levels.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: Available acute-duration oral data were not considered adequate for derivation of an acute-duration oral MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available 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).

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: The intermediate-duration oral data were not considered adequate for derivation of an intermediate-duration oral MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available 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 NOAEL was 30 mg/kg/day (Hollingsworth et al. 1956). The lack of quantitative data precludes derivation of an intermediate-duration oral MRL for ethylene oxide.

Agency Contacts (Chemical Managers): Jennifer Przybyla

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Ethylene oxide
CAS Numbers: 75-21-8
Date: August 2022
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The chronic-duration oral data were not considered adequate for derivation of a chronic-duration oral MRL for ethylene oxide.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Available 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 application site for oral gavage) was reported at 7.5 mg/kg/day (Dunkelberg 1982).

Agency Contacts (Chemical Managers): Jennifer Przybyla

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ETHYLENE OXIDE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to ethylene oxide.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for ethylene oxide. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of ethylene oxide have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of ethylene oxide are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for ethylene oxide released for public comment in 2020; thus, the literature search was restricted to studies published between Month YEAR and Month YEAR. The following main databases were searched in January 2021:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for ethylene oxide. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to ethylene oxide were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
01/2021	(75-21-8 [rn] AND (((("ethylene oxide/toxicity"[mh] OR "ethylene oxide/adverse effects"[mh] OR "ethylene oxide/poisoning"[mh] OR "ethylene oxide/pharmacokinetics"[mh] OR "ethylene oxide/blood"[mh] OR "ethylene oxide/cerebrospinal fluid"[mh] OR "ethylene oxide/urine"[mh] OR "ethylene oxide/antagonists & inhibitors"[mh]) OR ("ethylene oxide"[mh] AND ("environmental exposure"[mh] OR "chemically induced"[sh])) OR ("ethylene oxide"[mh] AND toxicokinetics[mh:noexp]) OR ("ethylene oxide"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("ethylene oxide"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("ethylene oxide/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("ethylene oxide"[mh] AND cancer[sb]) OR ("ethylene oxide/pharmacology"[majr])) AND (2018:3000[dp] OR 2018:3000[mhda] OR 2018:3000[crdt] OR 2018:3000[edat]))) OR ((("1,2-Epoxyethane"[tw] OR "Amprolene"[tw] OR "Anprolene"[tw] OR "dihydrooxirene"[tw] OR "Epoxyethane"[tw] OR "Ethene oxide"[tw] OR "ethylene oxide"[tw] OR "Ethyleneoxy"[tw] OR "Ethylenoxid"[tw] OR "Merpol"[tw] OR "Oxacyclopropane"[tw] OR "Oxane"[tw] OR "Oxidoethane"[tw] OR "Oxiran"[tw] OR "Oxirane"[tw] OR "Oxyfume"[tw] OR "Anproline"[tw] OR "Dimethylene oxide"[tw] OR "Emulsifier-Ethylene oxide"[tw] OR "Ethylene oxide-ionene copolymer"[tw] OR "Mirror Ox"[tw] OR "1,2,3,4-tetrahydro-1,1,6-trimethyl-Naphthalene polymer with oxirane"[tw] OR "Naphthalene, 1,2,3,4-tetrahydro-1,1,6-trimethyl-, polymer with oxirane"[tw] OR "Oxirane, polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene"[tw] OR "polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene oxirane"[tw] OR "Oxirene, dihydro-"[tw] OR "Oxyfume 12"[tw] OR "Oxyfume 2002"[tw]) NOT medline[sb]) AND (2018:3000[crdt] OR 2018:3000[edat] OR 2018:3000[dp]))

Table B-2. Database Query Strings

Database search date	Query string
NTRL	
01/2021	"1,2-Epoxyethane" OR "Amprolene" OR "Anprolene" OR "dihydrooxirene" OR "Epoxyethane" OR "Ethene oxide" OR "ethylene oxide" OR "Ethyleneoxy" OR "Ethylenoxid" OR "Merpol" OR "Oxacyclopropane" OR "Oxane" OR "Oxidoethane" OR "Oxiran" OR "Oxirane" OR "Oxyfume" "Anproline" OR "Dimethylene oxide" OR "Emulsifier-Ethylene oxide" OR "Ethylene oxide-ionene copolymer" OR "Mirror Ox" OR "1,2,3,4-tetrahydro-1,1,6-trimethyl-Naphthalene polymer with oxirane" OR "Naphthalene, 1,2,3,4-tetrahydro-1,1,6-trimethyl-, polymer with oxirane" OR "Oxirane, polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene" OR "polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene oxirane" OR "Oxirene, dihydro-" OR "Oxyfume 12" OR "Oxyfume 2002"
Toxcenter	
01/2021	FILE 'TOXCENTER' ENTERED AT 13:04:37 ON 26 JAN 2021 CHARGED TO COST=EH038.06.01.LB.03 L1 10178 SEA 75-21-8 L2 9971 SEA L1 NOT TSCATS/FS L3 6793 SEA L1 NOT PATENT/DT L4 6586 SEA L2 NOT PATENT/DT L5 283 SEA L4 AND PY>=2018 ACTIVATE TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (NONHUMAN MAMMALS)/ORGN
	L36 QUE L34 OR L35
	L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L38 QUE L36 OR L37

	L39 194 SEA L5 AND L36
	L40 191 SEA L5 AND L31
	L41 27 SEA L40 AND MEDLINE/FS
	L42 29 SEA L40 AND BIOSIS/FS
	L43 132 SEA L40 AND CAPLUS/FS
	L44 3 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L45 169 DUP REM L41 L42 L44 L43 (22 DUPLICATES REMOVED)
	L*** DEL 27 S L40 AND MEDLINE/FS
	L*** DEL 27 S L40 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L46 27 SEA L45 L*** DEL 29 S L40 AND BIOSIS/FS L*** DEL 29 S L40 AND BIOSIS/FS L47 22 SEA L45 L*** DEL 132 S L40 AND CAPLUS/FS L*** DEL 132 S L40 AND CAPLUS/FS L48 117 SEA L45 L*** DEL 3 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 3 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 3 SEA L45 L50 142 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS D SCAN L50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
01/2021	Compounds searched: 75-21-8
NTP	
01/2021	Limited to 2010 – present "Epoxyethane" "Ethene oxide" "ethylene oxide" "Ethyleneoxy" "Oxidoethane" "Oxiran" "Oxirane" "Oxyfume" "75-21-8" "1,2-Epoxyethane" "Amprolene" "Anprolene" "dihydrooxirene" "Ethylenoxid" "Merpol" "Oxacyclopropane" "Oxane"
Regulations.gov	
01/2021	Documents limited to: date 2018-Present; Notice; U.S. EPA 75-21-8 Ethylene oxide Docket limited to: U.S. EPA 75-21-8 Ethylene oxide"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
07/2021	Active projects, Text Search: "1,2-Epoxyethane" OR "Amprolene" OR "Anprolene" OR "dihydrooxirene" OR "Epoxyethane" OR "Ethene oxide" OR "ethylene oxide" OR "Ethyleneoxy" OR "Ethylenoxid" OR "Merpol" OR "Oxacyclopropane" OR "Oxane" OR "Oxidoethane" OR "Oxiran" OR "Oxirane" OR "Oxyfume" OR "Anproline" OR "Dimethylene oxide" OR "Emulsifier-Ethylene oxide" OR "Ethylene oxide-ionene copolymer" OR "Mirror Ox" OR "1,2,3,4-tetrahydro-1,1,6-trimethyl-Naphthalene polymer with oxirane" OR "Naphthalene, 1,2,3,4-tetrahydro-1,1,6-trimethyl-, polymer with oxirane" OR "Oxirane, polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene" OR "polymer with 1,2,3,4-tetrahydro-1,1,6-trimethylnaphthalene oxirane" OR "Oxirene, dihydro-" OR "Oxyfume 12" OR "Oxyfume 2002" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2021 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 934
- Number of records identified from other strategies: 22
- Total number of records to undergo literature screening: 956

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on ethylene oxide:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

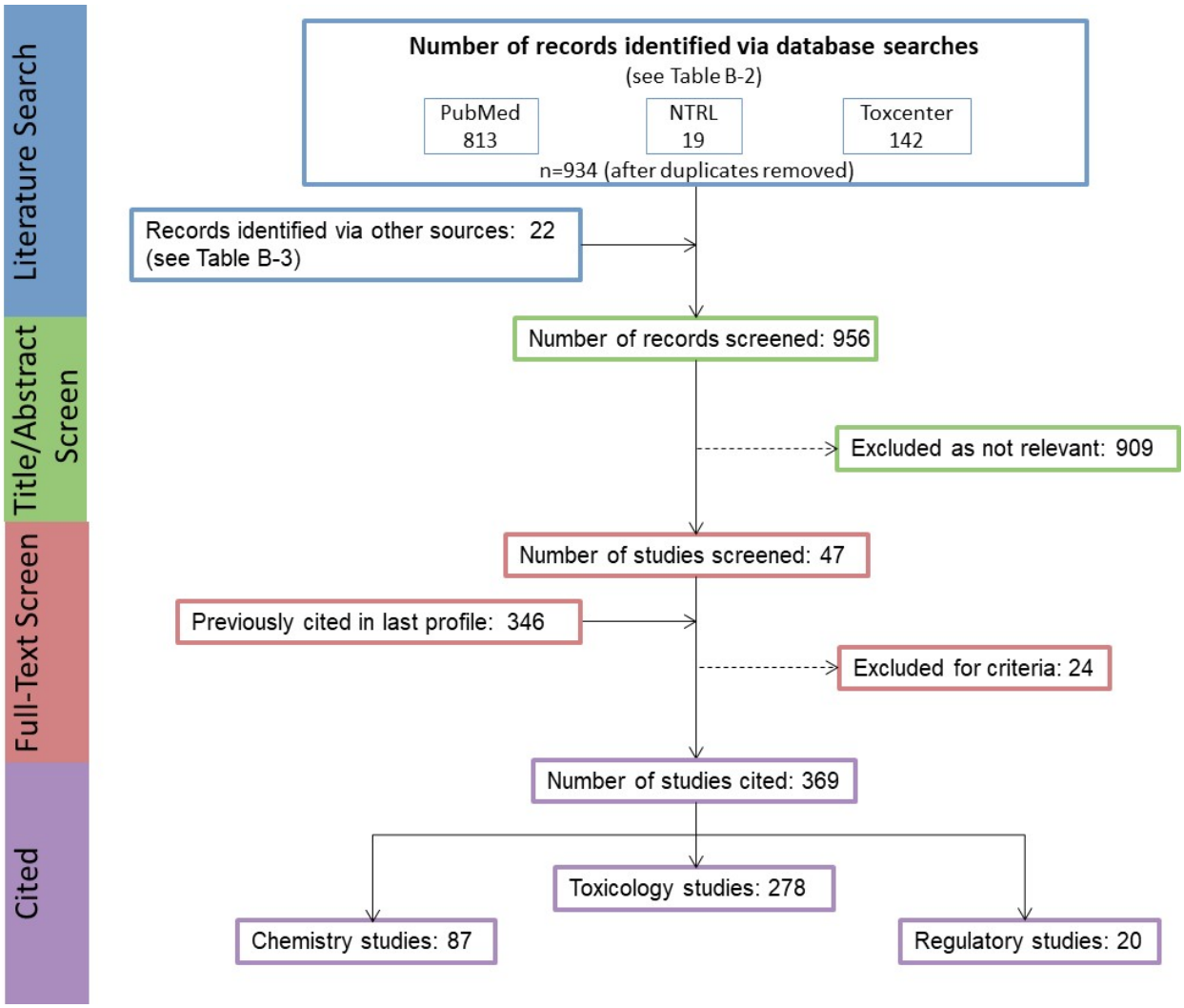
- Number of titles and abstracts screened: 956
- Number of studies considered relevant and moved to the next step: 47

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 47
- Number of studies cited in the pre-public draft of the toxicological profile: 346
- Total number of studies cited in the profile: 369

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. January 2021 Literature Search Results and Screen for Ethylene Oxide



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ETHYLENE OXIDE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to ethylene oxide, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to ethylene oxide:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to ethylene oxide. The inclusion criteria used to identify relevant studies examining the health effects of ethylene oxide are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of ethylene oxide. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for ethylene oxide released for public comment in 2020. See Appendix B for the databases searched and the search strategy.

A total of 956 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of ethylene oxide.

Title and Abstract Screen. In the Title and Abstract Screen step, 956 records were reviewed; 2 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 90 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 90 documents, 127 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Ethylene Oxide and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile; results from inhalation and oral exposure studies are presented in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for ethylene oxide identified in human and animal studies are presented in Tables C-3 and C-4, respectively. A number of occupational cohorts were evaluated for possible associations between ethylene oxide and risk of death from selected noncancer endpoints; these studies were not included in the systematic review since they did not evaluate specific respiratory endpoints. Animal studies examined a number of endpoints following inhalation exposure. These studies examined most endpoints; the most sensitive endpoints were hematological, endocrine (adrenal gland), and neurological effects.

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Table C-3. Overview of the Health Outcomes Ethylene Oxide Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		9	10	4	1		1	1	7	4		12		4			23
		2	0	0	0		0	0	7	4		10		4			13
Case control																	
Population																	
Case series													13				
													13				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

APPENDIX C

Table C-4. Overview of the Health Outcomes for Ethylene Oxide Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	9 5	6 6					2 2		2 2	1 1	2 2	1 1	1 1		8 6		
Intermediate-duration	26 9	14 6	1 0		4 4	13 6	3 0	1 0			1 0	1 0	19 13	8 7	3 2		1 1
Chronic-duration	3 2	2 1	3 0	2 0	2 1	2 1	2 0	2 0	1 0	1 0	2 1		3 1	3 1			3 3
Oral studies																	
Acute-duration	1 0																
Intermediate-duration	1 1			1 1	1 0		1 1										
Chronic-duration																	1 1
Dermal studies																	
Acute-duration										1 1							
Intermediate-duration																	
Chronic-duration																	1 0

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

Studies examining these potential outcomes (as well as respiratory, reproductive, and developmental outcomes) were carried through to Steps 4–8 of the systematic review. Oral data were not available for humans. Animal data were limited to results from a solitary study with limited study details. Gavage dosing of rats at 30 mg/kg/day, 2 times/week for up to 150 weeks resulted in decreased survival; forestomach squamous cell carcinoma (at the application site for oral gavage) was reported at 7.5 mg/kg/day (Dunkelberg 1982). This study was not subjected to systematic review because it could not be used as basis for deriving a chronic-duration oral MRL for ethylene oxide. There were 127 studies (published in 90 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies and animal experimental studies are presented in Tables C-5 and C-6, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of ethylene oxide health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-7 and C-8, respectively.

Table C-7. Summary of Risk of Bias Assessment for Ethylene Oxide—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Respiratory effects							
Case series							
Deschamps et al. 1992	+	–	+	na	–	+	Second
Thiess 1963	+	–	+	na	–	+	Second
Outcome: Neurological effects							
Case series							
Blackwood and Erskine 1938	na	–	+	na	–	+	Third
Brashear et al. 1996	na	–	+	na	–	+	Third
Crystal et al. 1988	na	–	+	na	–	+	Third
Dretchen et al. 1992	na	–	+	na	–	+	Third
Estrin et al. 1987	na	–	+	na	–	+	Third
Finelli et al. 1983	na	–	+	na	–	+	Third
Gross et al. 1979	na	–	+	na	–	+	Third
Kuzuhara et al. 1983	na	–	+	na	–	+	Third
Salinas et al. 1981	na	–	+	na	–	+	Third
Schröder et al. 1985	na	–	+	na	–	+	Third
Sexton and Henson 1949	na	–	+	na	–	+	Third
Von Oettingen 1939	na	–	+	na	–	+	Third
Zampollo et al. 1984	na	–	+	na	–	+	Third

Table C-7. Summary of Risk of Bias Assessment for Ethylene Oxide—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in the exposure characterization?***	**Confidence in the outcome assessment?***	All measured outcomes reported?	
Outcome: Reproductive effects							
Cohort							
Gresie-Brusin et al. 2007	+	–	+	na	–	+	Second
Hemminki et al. 1982	+	–	+	na	–	+	Second
Rowland et al. 1996	+	–	+	na	–	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Respiratory effects										
Inhalation acute exposure										
Hollingsworth et al. 1956 (rat, 841 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 357 ppm)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 4-hour)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 2-week)	+	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig, 113 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rabbit, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 406 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 102 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (dog, 292 ppm)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, GDs 1–16)	+	+	+	+	+	+	+	+	+	First

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit, GDs 1–19)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 14-week)	+	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	- -	+	+	Second
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First
Outcome: Hematological effects										
Inhalation intermediate exposure										
Fujishiro et al. 1990 (rat, 500 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 102 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (dog, 292 ppm)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1984a (mouse, 11-week)	++	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984a (monkey, 2-year)	+	+	+	+	+	+	+	+	+	First
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	- -	+	+	Second
Outcome: Endocrine effects										
Inhalation acute exposure										
Hollingsworth et al. 1956 (rat, 841 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig 841 ppm)	+	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	- -	+	+	Second
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Neurological effects										
Inhalation acute exposure										
EPA 2005a	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 4-hour)	+	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
EPA 2005b	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rabbit, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 357 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rat, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (mouse, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (rabbit, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (monkey, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Hollingsworth et al. 1956 (guinea pig, 204 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 406 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (rat, 102 ppm)	+	+	+	+	+	+	+	+	+	First
Jacobson et al. 1956 (dog, 292 ppm)	+	+	+	+	+	+	+	+	+	First
Kaido et al. 1992 (rat, 500 ppm)	++	+	+	+	+	+	+	+	+	First
Matsuoka et al. 1990 (rat, 500 ppm)	+	+	+	+	+	+	+	+	+	First
Ohnishi et al. 1985 (rat, 13-week)	+	+	+	+	+	+	+	+	+	First

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Ohnishi et al. 1986 (rat, 9-month)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1984a (mouse, 11-week)	++	+	+	+	+	+	-	+	+	Second
Inhalation chronic exposure										
Lynch et al. 1984a (monkey, 2-year)	+	+	+	+	+	+	+	+	+	First
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First
Outcome: Reproductive effects										
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
Kaido et al. 1992 (rat, 13-week)	++	+	+	+	+	+	+	+	+	First
Mori et al. 1991a (rat, 13-week)	+	+	+	+	+	+	+	+	+	First
Mori et al. 1991b (rat, 6-week)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit, GDs 1–19)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1982b (rat, 12-week)	++	+	+	+	+	+	+	+	+	First
Snellings et al. 1984a (mouse, 11-week)	++	+	+	+	+	+	+	+	+	First
Inhalation chronic exposure										
Lynch et al. 1984a (monkey, 2-year)	+	+	+	+	+	+	+	+	+	First
Lynch et al. 1984b (rat, 2-year)	+	+	+	+	+	+	+	+	+	First
NTP 1987 (mouse, 102-week)	+	+	+	+	+	+	+	+	+	First

Table C-8. Summary of Risk of Bias Assessment for Ethylene Oxide—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	**Confidence in the outcome assessment?***	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Developmental effects										
Inhalation acute exposure										
Neeper-Bradley and Kubena 1993 (rat)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit)	+	+	+	+	+	+	+	+	+	First
Rutledge and Generoso 1989 (mouse)	+	+	+	+	+	+	+	+	+	First
Saillenfait et al. 1996 (rat, 400–1,200 ppm)	+	+	+	+	+	+	+	+	+	First
Saillenfait et al. 1996 (rat, 200 or 400 ppm)	+	+	+	+	+	+	+	+	+	First
Saillenfait et al. 1996 (rat, 800 or 1,200 ppm)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1982a (rat, 10–100 ppm)	++	+	+	+	+	+	+	+	+	First
Inhalation intermediate exposure										
EPA 1994 (rat)	++	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	+	+	+	+	+	+	+	+	+	First
NIOSH 1982 (rabbit, GD 1–19)	+	+	+	+	+	+	+	+	+	First
Snellings et al. 1982b (rat, 12-week)	++	+	+	+	+	+	+	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to ethylene oxide and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to ethylene oxide and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies and experimental animal studies are presented in Tables C-9 and C-10, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-9. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-10. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining body weight effects, respiratory effects, reproductive effects, and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-11 and C-12, respectively.

Table C-11. Presence of Key Features of Study Design for Ethylene Oxide—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects					
Case series					
Deschamps et al. 1992	No	No	Yes	Yes	Low
Thiess 1963	No	No	Yes	Yes	Low
Outcome: Neurological effects					
Case series					
Blackwood and Erskine 1938	No	No	Yes	No	Very low
Brashear et al. 1996	No	No	Yes	No	Very low
Crystal et al. 1988	No	No	Yes	No	Very low
Dretchen et al. 1992	No	No	Yes	No	Very low
Estrin et al. 1987	No	No	Yes	No	Very low
Finelli et al. 1983	No	No	Yes	No	Very low
Gross et al. 1979	No	No	Yes	No	Very low

Table C-11. Presence of Key Features of Study Design for Ethylene Oxide—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Kuzuhara et al. 1983	No	No	Yes	No	Very low
Salinas et al. 1981	No	No	Yes	No	Very low
Schröder et al. 1985	No	No	Yes	No	Very low
Sexton and Henson 1949	No	No	Yes	No	Very low
Von Oettingen 1939	No	No	Yes	No	Very low
Zampollo et al. 1984	No	No	Yes	No	Very low
Outcome: Reproductive effects					
Cohort					
Gresie-Brusin et al. 2007	No	Yes	Yes	Yes	Moderate
Hemminki et al. 1982	No	Yes	Yes	Yes	Moderate
Rowland et al. 1996	No	Yes	Yes	Yes	Moderate

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
Hollingsworth et al. 1956 (rat, 841 ppm)	Yes	Yes	No	No	Low
Hollingsworth et al. 1956 (rat, 357 ppm)	Yes	Yes	No	No	Low
NIOSH 1982 (rat)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit)	Yes	Yes	No	No	Low
NTP 1987 (mouse, 4-hour)	No	No	Yes	No	Very low
NTP 1987 (mouse, 2-week)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
EPA 1994 (rat)	Yes	Yes	Yes	No	Moderate
Hollingsworth et al. 1956 (4 species, 113 ppm)	Yes	No	No	No	Very low
Hollingsworth et al. 1956 (5 species, 204 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 406 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 102 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (dog, 292 ppm)	Yes	No	No	No	Very low
NIOSH 1982 (rat, GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit, GDs 1–19)	Yes	Yes	No	No	Low
NTP 1987 (mouse, 14-week)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High
Outcome: Hematological effects					
Inhalation intermediate exposure					
Fujishiro et al. 1990 (rat, 500 ppm)	Yes	Yes	Yes	No	Moderate
Jacobson et al. 1956 (rat, 102 ppm)	Yes	Yes	No	No	Low
Jacobson et al. 1956 (dog, 292 ppm)	Yes	No	No	No	Very low
Snellings et al. 1984a (mouse, 11-week)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
Lynch et al. 1984a (monkey, 2-year)	Yes	Yes	Yes	No	Moderate
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
Outcome: Endocrine effects					
Inhalation acute exposure					
Hollingsworth et al. 1956 (2 species, 841 ppm)	Yes	Yes	No	No	Low
Inhalation chronic exposure					
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High
Outcome: Neurological effects					
Inhalation acute exposure					
EPA 2005a	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 4-hour)	No	No	Yes	No	Very low

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
EPA 1994 (rat)	Yes	Yes	No	No	Low
EPA 2005b	Yes	Yes	Yes	Yes	High
Hollingsworth et al. 1956 (monkey, 357 ppm)	Yes	No	No	No	Very low
Hollingsworth et al. 1956 (4 species, 357 ppm)	Yes	No	No	No	Very low
Hollingsworth et al. 1956 (5 species 204 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 406 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (rat, 102 ppm)	Yes	No	No	No	Very low
Jacobson et al. 1956 (dog, 292 ppm)	Yes	No	No	No	Very low
Kaido et al. 1992 (rat, 500 ppm)	Yes	No	Yes	No	Low
Matsuoka et al. 1990 (rat, 500 ppm)	Yes	Yes	No	No	Low
Ohnishi et al. 1985 (rat, 13-week)	Yes	No	Yes	Yes	Moderate
Ohnishi et al. 1986 (rat, 9-month)	Yes	No	Yes	Yes	Moderate
Snellings et al. 1984a (mouse, 11-week)	Yes	Yes	No	No	Low
Inhalation chronic exposure					
Lynch et al. 1984a (monkey, 2-year)	Yes	Yes	Yes	No	Moderate
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High
Outcome: Reproductive effects					
Inhalation intermediate exposure					
EPA 1994 (rat)	Yes	Yes	Yes	No	Moderate
Kaido et al. 1992 (rat, 13-week)	Yes	No	Yes	No	Low
Mori et al. 1991a (rat, 13-week)	Yes	No	Yes	Yes	Moderate
Mori et al. 1991b (rat, 6-week)	Yes	Yes	Yes	Yes	High
NIOSH 1982 (rat, GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit, GDs 1–19)	Yes	Yes	No	No	Low
Snellings et al. 1982b (rat, 1-generation)	Yes	Yes	Yes	No	Moderate
Snellings et al. 1984a (mouse, 11-week)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
Lynch et al. 1984a (monkey, 2-year)	Yes	Yes	Yes	No	Moderate
Lynch et al. 1984b (rat, 2-year)	Yes	Yes	Yes	No	Moderate
NTP 1987 (mouse, 102-week)	Yes	Yes	Yes	Yes	High

Table C-12. Presence of Key Features of Study Design for Ethylene Oxide—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Developmental effects					
Inhalation acute exposure					
Neeper-Bradley and Kubena 1993 (rat)	Yes	Yes	Yes	Yes	High
NIOSH 1982 (rat)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit)	Yes	Yes	No	No	Low
Rutledge and Generoso 1989 (mouse)	Yes	Yes	Yes	No	Moderate
Saillenfait et al. 1996 (rat, 400–1,200 ppm)	Yes	Yes	Yes	Yes	High
Saillenfait et al. 1996 (rat, 200 or 400 ppm)	Yes	Yes	Yes	Yes	High
Saillenfait et al. 1996 (rat, 800 or 1,200 ppm)	Yes	Yes	Yes	Yes	High
Snellings et al. 1982a (rat, 10–100 ppm)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
EPA 1994 (rat)	Yes	Yes	Yes	No	Moderate
NIOSH 1982 (rat, GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Yes	Yes	No	No	Low
NIOSH 1982 (rabbit, GDs 1–19)	Yes	Yes	No	No	Low
Snellings et al. 1982b (rat, 1-generation)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-13. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-13.

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation acute exposure		
Animal studies		
Hollingsworth et al. 1956 (rat, 841 ppm)	Low	Moderate
Hollingsworth et al. 1956 (rat, 357 ppm)	Low	
NIOSH 1982 (rat)	Low	
NIOSH 1982 (rabbit)	Low	

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1987 (mouse, 4-hour)	Very low	
NTP 1987 (mouse, 2-week)	Moderate	
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Moderate	High
Hollingsworth et al. 1956 (4 species, 113 ppm)	Very low	
Hollingsworth et al. 1956 (5 species, 204 ppm)	Very low	
Jacobson et al. 1956 (rat, 406 ppm)	Very low	
Jacobson et al. 1956 (rat, 102 ppm)	Very low	
Jacobson et al. 1956 (dog, 292 ppm)	Very low	
NIOSH 1982 (rat, GDs 1–16)	Low	
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Low	
NIOSH 1982 (rabbit, GDs 1–19)	Low	
NTP 1987 (mouse, 14-week)	High	
Inhalation chronic exposure		
Human studies (case series)		
Deschamps et al. 1992	Very low	Low
Thiess 1963	Low	
Animal studies		
Lynch et al. 1984b (rat, 2-year)	Moderate	High
NTP 1987 (mouse, 102-week)	High	
Outcome: Hematological effects		
Inhalation intermediate exposure		
Animal studies		
Fujishiro et al. 1990 (rat, 500 ppm)	Moderate	Moderate
Jacobson et al. 1956 (rat, 102 ppm)	Low	
Jacobson et al. 1956 (dog, 292 ppm)	Very low	
Snellings et al. 1984a (mouse, 11-week)	Moderate	
Inhalation chronic exposure		
Animal studies		
Lynch et al. 1984a (monkey, 2-year)	Moderate	Moderate
Lynch et al. 1984b (rat, 2-year)	Moderate	
Outcome: Endocrine effects		
Inhalation acute exposure		
Animal studies		
Hollingsworth et al. 1956 (2 species, 841 ppm)	Low	Low
Inhalation chronic exposure		
Animal studies		
Lynch et al. 1984b (rat, 2-year)	Moderate	High
NTP 1987 (mouse, 102-week)	High	
Outcome: Neurological effects		
Inhalation acute exposure		
Animal studies		
EPA 2005a	High	High

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
NTP 1987 (mouse, 4-hour)	Very low	
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Low	High
EPA 2005b	High	
Hollingsworth et al. 1956 (monkey, 357 ppm)	Very low	
Hollingsworth et al. 1956 (4 species, 357 ppm)	Very low	
Hollingsworth et al. 1956 (5 species 204 ppm)	Very low	
Jacobson et al. 1956 (rat, 406 ppm)	Very low	
Jacobson et al. 1956 (rat, 102 ppm)	Very low	
Jacobson et al. 1956 (dog, 292 ppm)	Very low	
Kaido et al. 1992 (rat, 500 ppm)	Low	
Matsuoka et al. 1990 (rat, 500 ppm)	Low	
Ohnishi et al. 1985 (rat, 13-week)	Moderate	
Ohnishi et al. 1986 (rat, 9-month)	Moderate	
Snellings et al. 1984a (mouse, 11-week)	Low	
Inhalation chronic exposure		
Human studies		
Blackwood and Erskine 1938	Very low	Very low
Brashear et al. 1996	Very low	
Crystal et al. 1988	Very low	
Dretchen et al. 1992	Very low	
Estrin et al. 1987	Very low	
Finelli et al. 1983	Very low	
Gross et al. 1979	Very low	
Kuzuhara et al. 1983	Very low	
Salinas et al. 1981	Very low	
Schröder et al. 1985	Very low	
Sexton and Henson 1949	Very low	
Von Oettingen 1939	Very low	
Zampollo et al. 1984	Very low	
Animal studies		
Lynch et al. 1984a (monkey, 2-year)	Moderate	High
Lynch et al. 1984b (rat, 2-year)	Moderate	
NTP 1987 (mouse, 102-week)	High	
Outcome: Reproductive effects		
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Moderate	High
Kaido et al. 1992 (rat, 13-week)	Low	
Mori et al. 1991a (rat, 13-week)	Moderate	
Mori et al. 1991b (rat, 6-week)	High	
NIOSH 1982 (rat, GDs 1–16)	Low	
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Low	

Table C-13. Initial Confidence Rating for Ethylene Oxide Health Effects Studies

	Initial study confidence	Initial confidence rating
NIOSH 1982 (rabbit, GDs 1–19)	Low	
NTP 1987 (mouse, 14-week)	High	
Snellings et al. 1982b (rat, 1-generation)	Moderate	
Snellings et al. 1984a (mouse, 11-week)	Moderate	
Inhalation chronic exposure		
Human studies		
Gresie-Brusin et al. 2007	Moderate	
Hemminki et al. 1982	Moderate	Moderate
Rowland et al. 1996	Moderate	
Animal studies		
Lynch et al. 1984a (monkey, 2-year)	Moderate	
Lynch et al. 1984b (rat, 2-year)	Moderate	High
NTP 1987 (mouse, 102-week)	High	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Neeper-Bradley and Kubena 1993 (rat)	High	
NIOSH 1982 (rat)	Low	
NIOSH 1982 (rabbit)	Low	
Rutledge and Generoso 1989 (mouse)	Moderate	High
Saillenfait et al. 1996 (rat, 400–1,200 ppm)	High	
Saillenfait et al. 1996 (rat, 200 or 400 ppm)	High	
Saillenfait et al. 1996 (rat, 800 or 1,200 ppm)	High	
Snellings et al. 1982a (rat, 10–100 ppm)	High	
Inhalation intermediate exposure		
Animal studies		
EPA 1994 (rat)	Moderate	
NIOSH 1982 (rat, GDs 1–16)	Low	Moderate
NIOSH 1982 (rat, 3 weeks premating and GDs 1–16)	Low	
NIOSH 1982 (rabbit, GDs 1–19)	Low	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, hematological, endocrine, neurological, reproductive, and developmental effects are presented in Table C-14. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with ethylene oxide exposure is presented in Table C-15.

Table C-14. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Human studies	Low	-1 for risk of bias	Very low
Animal studies	High	No adjustments	High
Outcome: Hematological effects			
Animal studies	Moderate	No adjustments	Moderate
Outcome: Endocrine effects			
Animal studies	Moderate	No adjustments	Moderate
Outcome: Neurological effects			
Human studies	Very low	-2 for risk of bias	Very low
Animal studies	High	No adjustments	High
Outcome: Reproductive effects			
Human studies	Moderate	-1 for risk of bias	Low
Animal studies	High	No adjustments	High
Outcome: Developmental effects			
Animal studies	High	No adjustments	High

Table C-15. Confidence in the Body of Evidence for Ethylene Oxide

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	Very low	High
Hematological effects	No data	Moderate
Endocrine effects	No data	Moderate
Neurological effects	Very low	High
Reproductive effects	Low	High
Developmental effects	No data	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-7 and C-8). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below

are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:

- No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
- Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
- Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., ORs) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.

  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for ethylene oxide, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for ethylene oxide is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for Ethylene Oxide

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects	Very low	Health effect	Very low
Neurological effects	Very low	Health effect	Very low
Reproductive effects	Low	Health effect	Low
Animal studies			
Respiratory effects	High	Health effect	High
Hematological effects	Moderate	Health effect	Moderate
Endocrine effects	Moderate	Health effect	Moderate
Neurological effects	High	Health effect	High
Reproductive effects	High	Health effect	High
Developmental effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

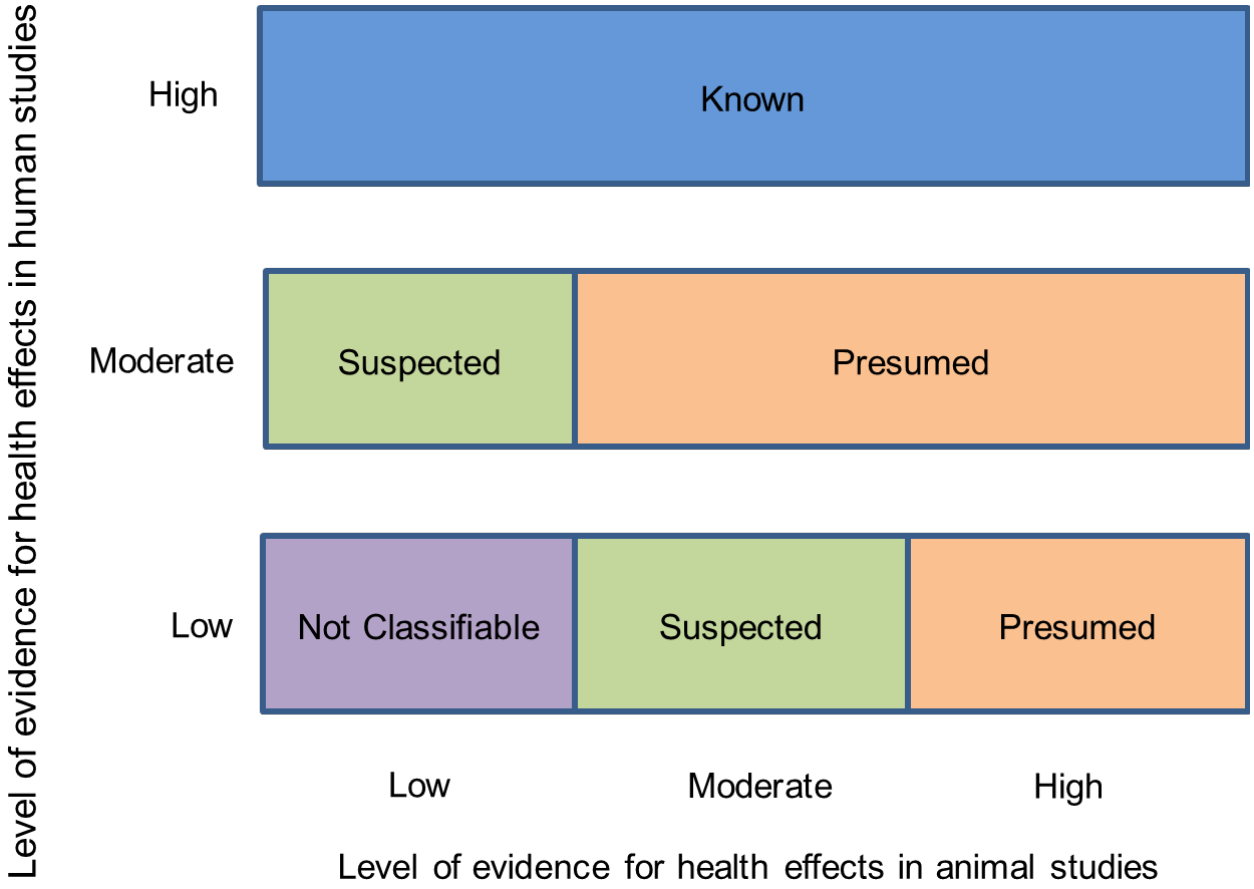
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies

- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for ethylene oxide are listed below and summarized in Table C-17. Ethylene oxide is a presumed hazard to humans for respiratory effects, neurological effects, reproductive effects, and developmental effects. Ethylene oxide is a suspected hazard to humans for hematological effects and endocrine effects.

Presumed

- Respiratory effects
  - Occupational exposures, presumably to relatively high concentrations in workplace air, have resulted in compromised respiratory function (Deschamps et al. 1992; Thiess 1963).
  - Inhalation exposures of laboratory animals to ethylene oxide vapor concentrations ≥100 ppm have resulted in adverse respiratory effects (Hollingsworth et al. 1956; Jacobson et al. 1956; NTP 1987).

- Neurological effects
  - Clinical signs and symptoms of neurological effects have been reported in occupational exposure scenarios that included estimated ethylene oxide levels as low as 3 ppm, although most reports indicated exposures at much higher levels (Blackwood and Erskine 1938; Brashear et al. 1996; Crystal et al. 1988; Dretchen et al. 1992; Estrin et al. 1987; Finelli et al. 1983; Gross et al. 1979; Kuzuhara et al. 1983; Salinas et al. 1981; Schröder et al. 1985; Sexton and Henson 1949; von Oettingen 1939; Zampollo et al. 1984).
  - Impaired neurological function and histopathologic lesions have been reported in laboratory animals exposed to ethylene oxide by inhalation at concentrations ≥100 ppm (EPA 2005b; Hollingsworth et al. 1956; Jacobson et al. 1956; Kaido et al. 1992; Lynch et al. 1984b; Matsuoka et al. 1990; NTP 1987; Ohnishi et al. 1985, 1986; Snellings et al. 1984a)

- Reproductive effects
  - Limited human data indicate potential for ethylene oxide-induced reproductive effects among occupationally-exposed persons (Gresie-Brusin et al. 2007; Hemminki et al. 1982).
  - Adverse male reproductive effects have been reported in laboratory animals exposed to ethylene oxide by inhalation at concentrations ≥33 ppm (EPA 1994; Kaido et al. 1992; Lynch et al. 1984b; Mori et al. 1991a, 1991b). Decreased numbers of viable pups have been reported in rats repeatedly exposed to ethylene oxide vapor at 100 ppm prior to mating and throughout gestation and lactation periods (Snellings et al. 1982b).

- Developmental effects
  - No human data are available on the potential for developmental effects of ethylene oxide.
  - Developmental effects such as depressed fetal weight, delayed ossification, dilatation in fetal renal pelvis and ureter, and fetal fluid retention and ocular defects have been associated with inhalation exposure to ethylene oxide by parental laboratory animals at exposure levels ≥33 ppm (EPA 1994; Neeper-Bradley and Kubena 1993; NIOSH 1982; Rutledge and Generoso 1989; Saillenfait et al. 1996; Snellings et al. 1982a).

Suspected

- Hematological effects
  - No human studies have associated ethylene oxide exposure with hematological effects.
  - Inhalation exposure of laboratory animals to ethylene oxide vapor concentrations as low as 50 ppm resulted in splenic histopathology (Lynch et al. 1984a, 1984b); higher

exposure concentrations were associated with changes in selected hematology parameters (Fujishiro et al. 1990; Jacobson et al. 1956; Snellings et al. 1984a).

- Endocrine effects
  - No human data are available regarding ethylene oxide exposure and endocrine effects.
  - Inhalation exposure of laboratory animals to ethylene oxide vapor concentrations as low as 50 ppm resulted in histopathologic lesions in adrenal glands (Lynch et al. 1984a, 1984b).

Table C-17. Hazard Identification Conclusions for Ethylene Oxide

Outcome	Hazard identification
Respiratory effects	Presumed
Hematological effects	Suspected
Endocrine effects	Suspected
Neurological effects	Presumed
Reproductive effects	Presumed
Developmental effects	Presumed

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

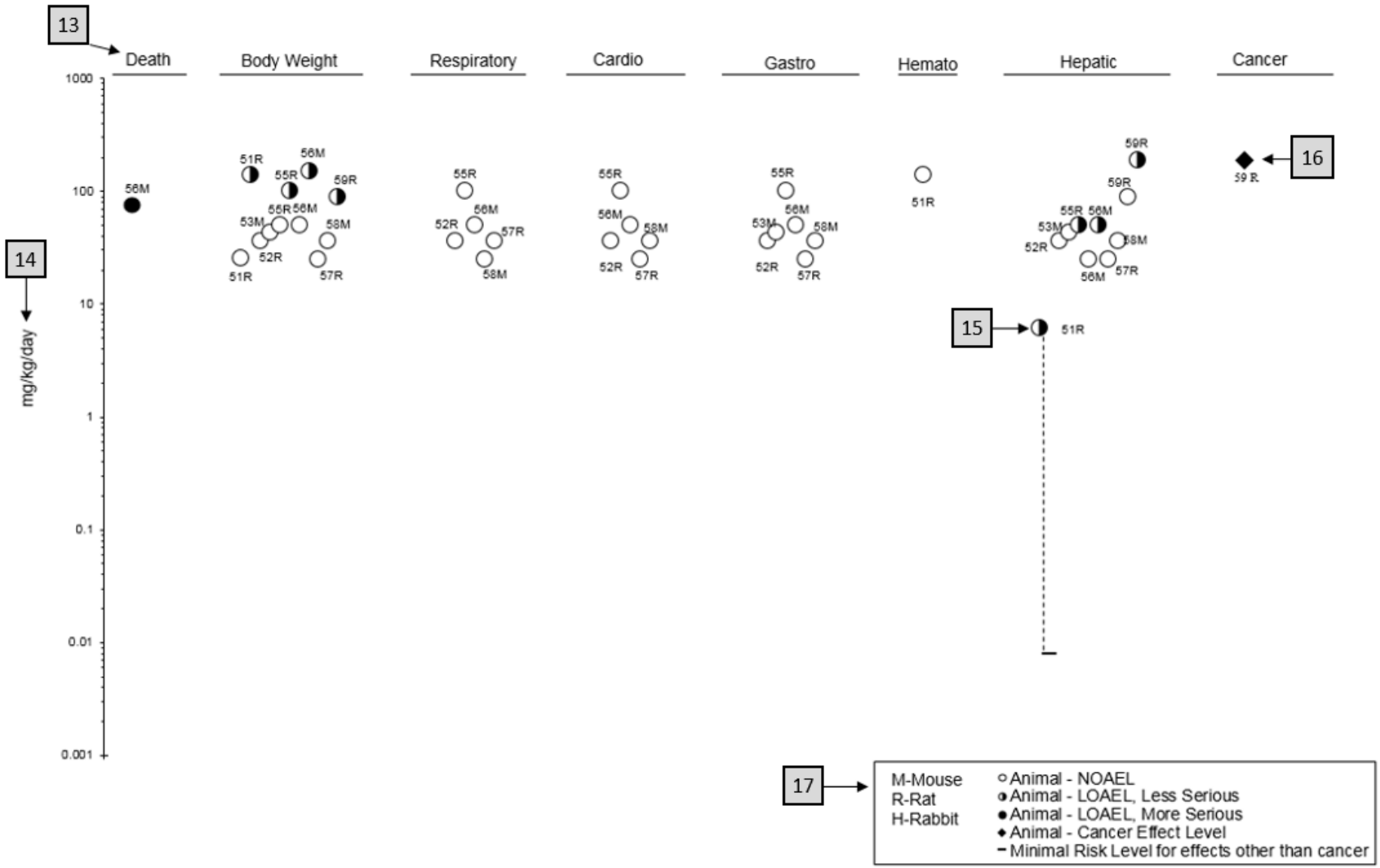
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result