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.

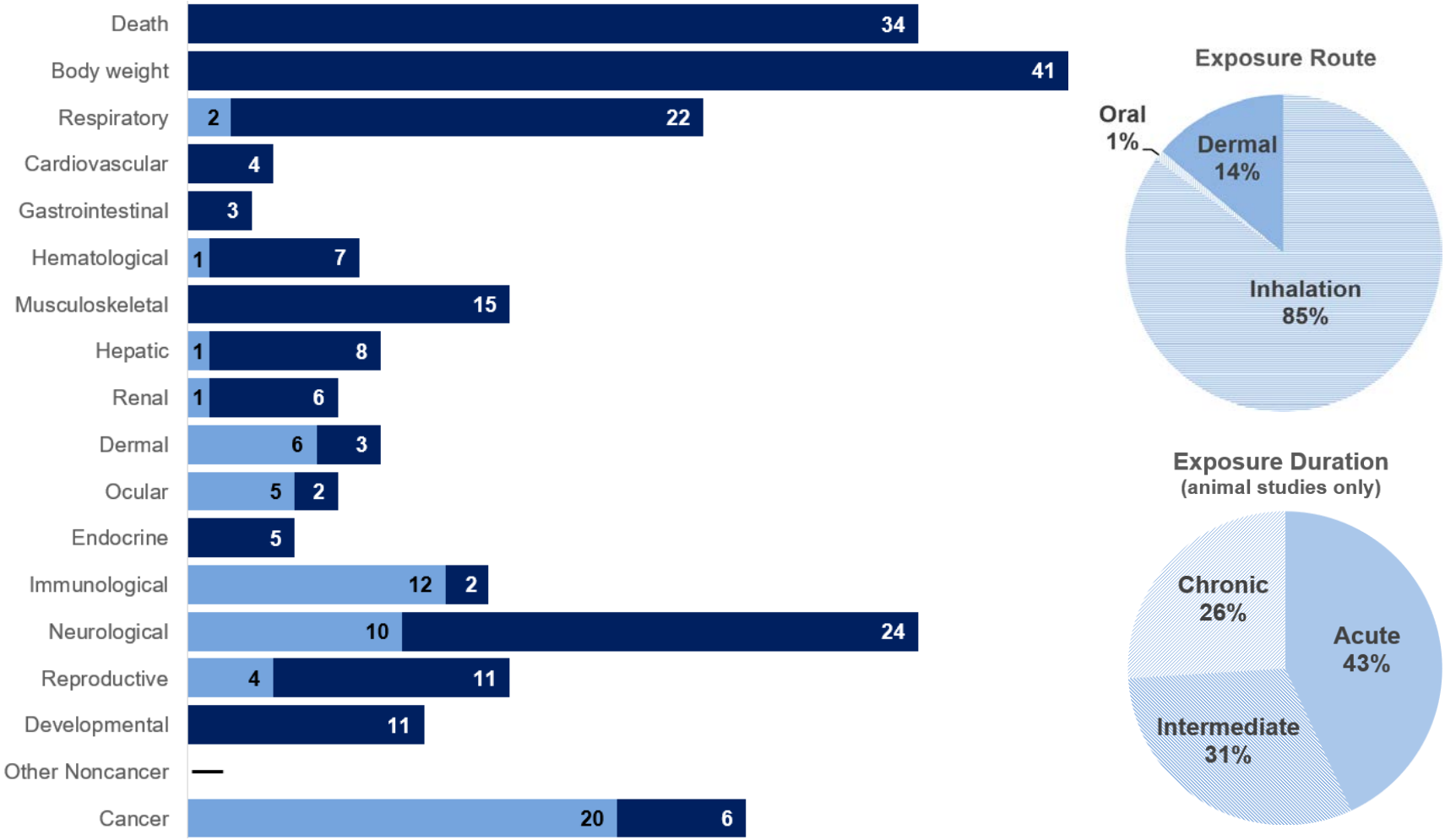
- **Reproductive Endpoints:** Male reproductive effects are a presumed health effect in humans based on a high level of evidence in animal studies. Animal studies provide convincing evidence of ethylene oxide-induced effects on the male reproductive system (e.g., decreases in male reproductive organ 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									

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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									

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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

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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									

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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									

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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									

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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									

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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)

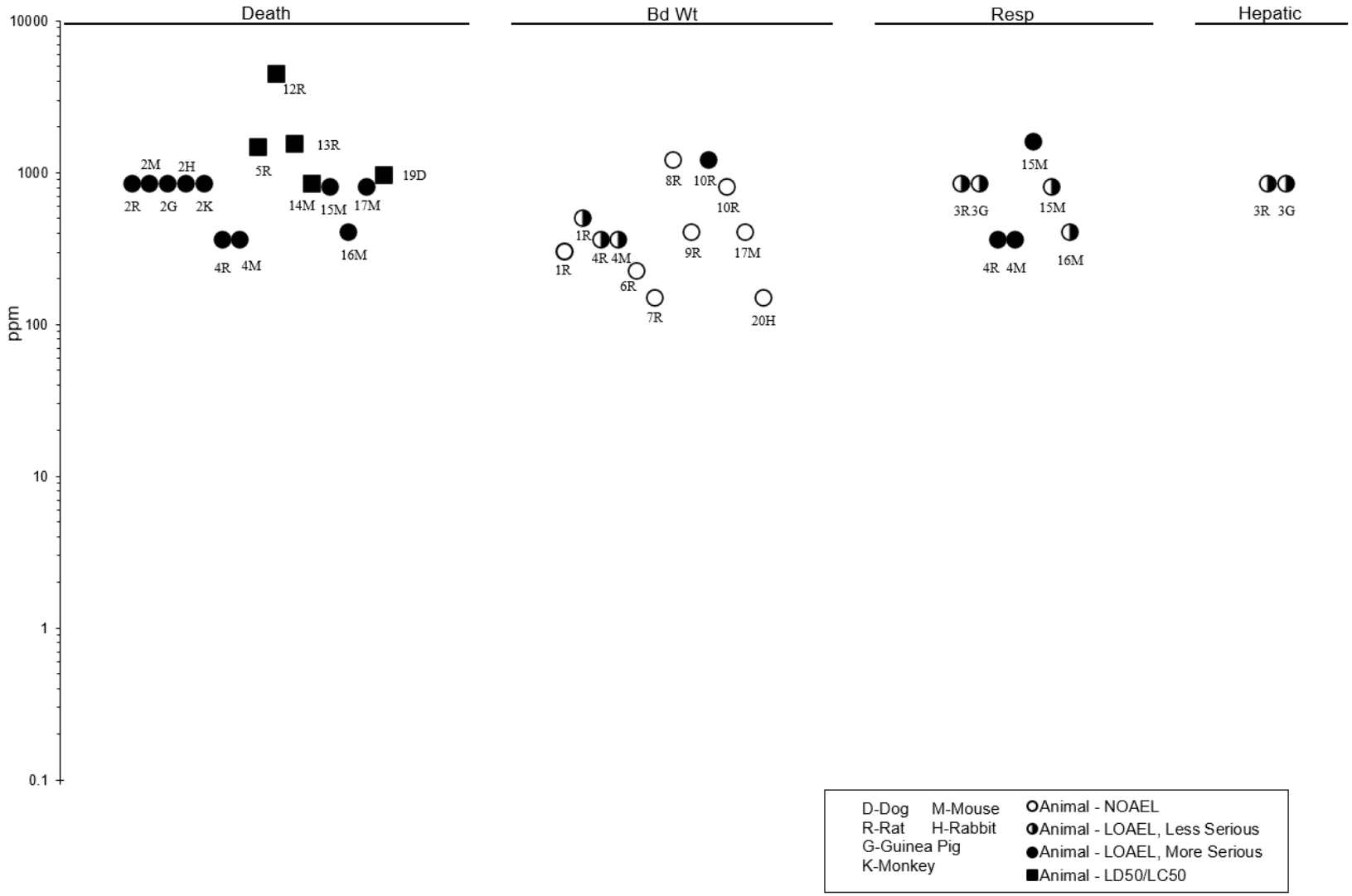


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Acute (≤14 days)

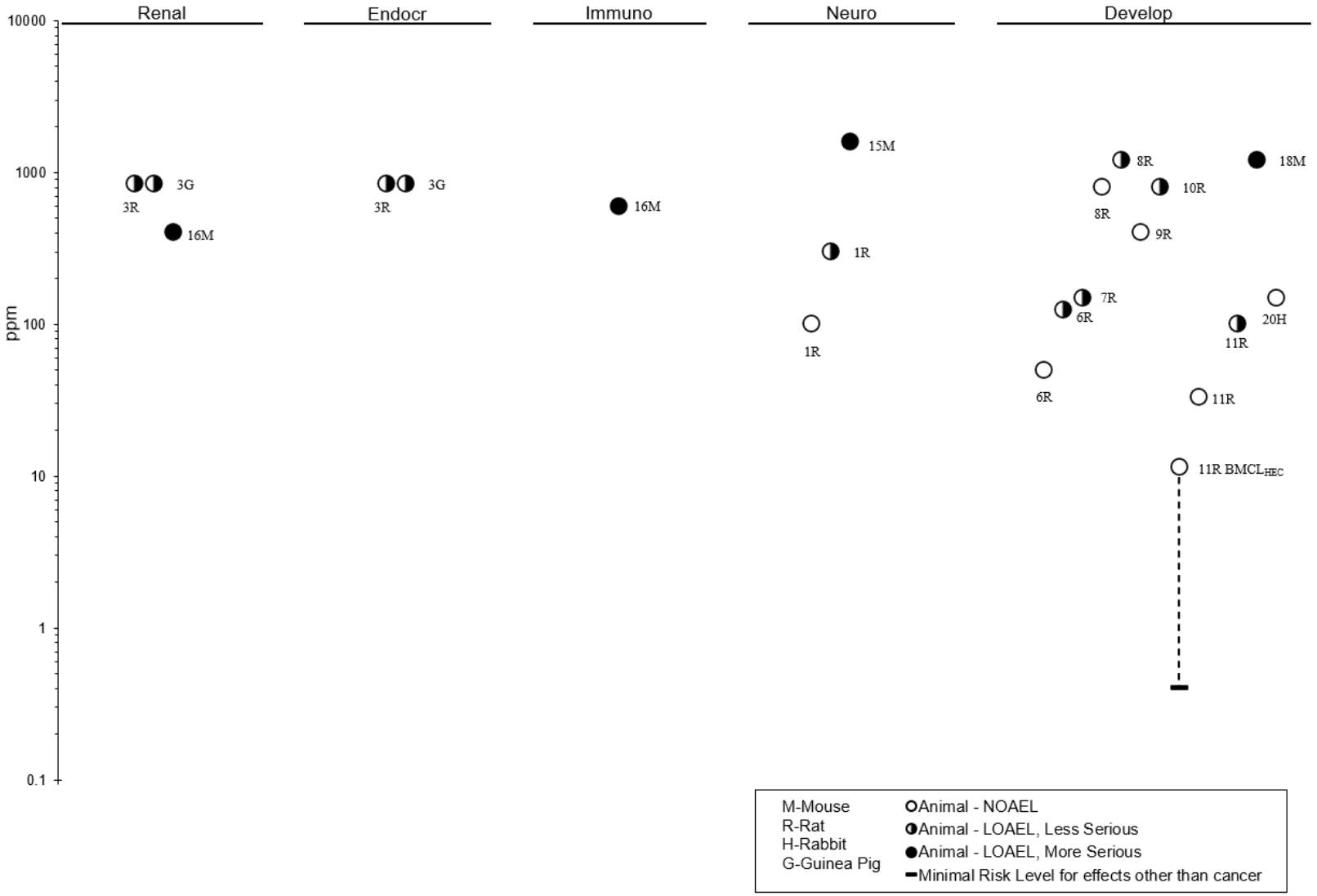


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Intermediate (15-364 days)

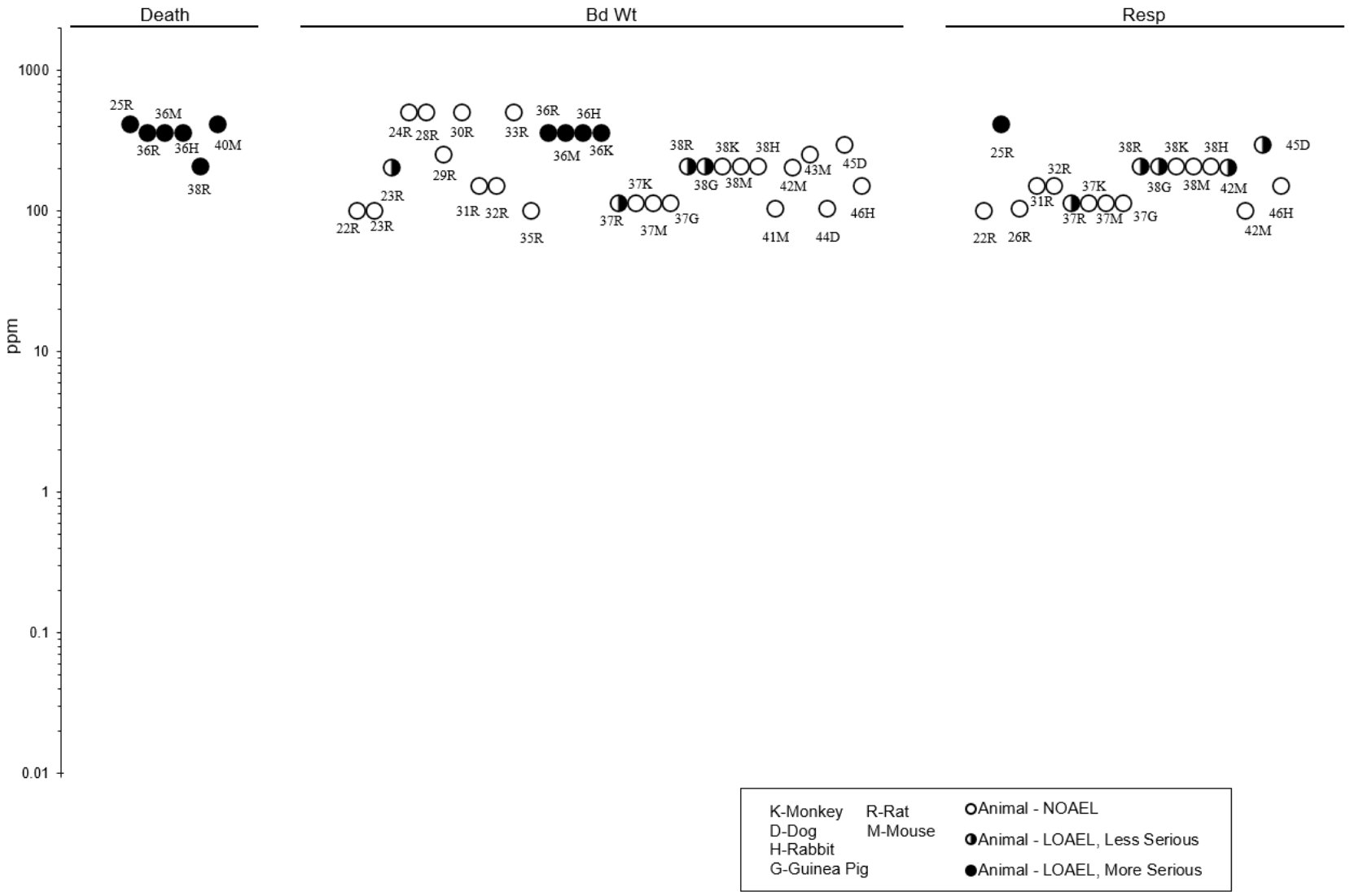


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

Intermediate (15-364 days)

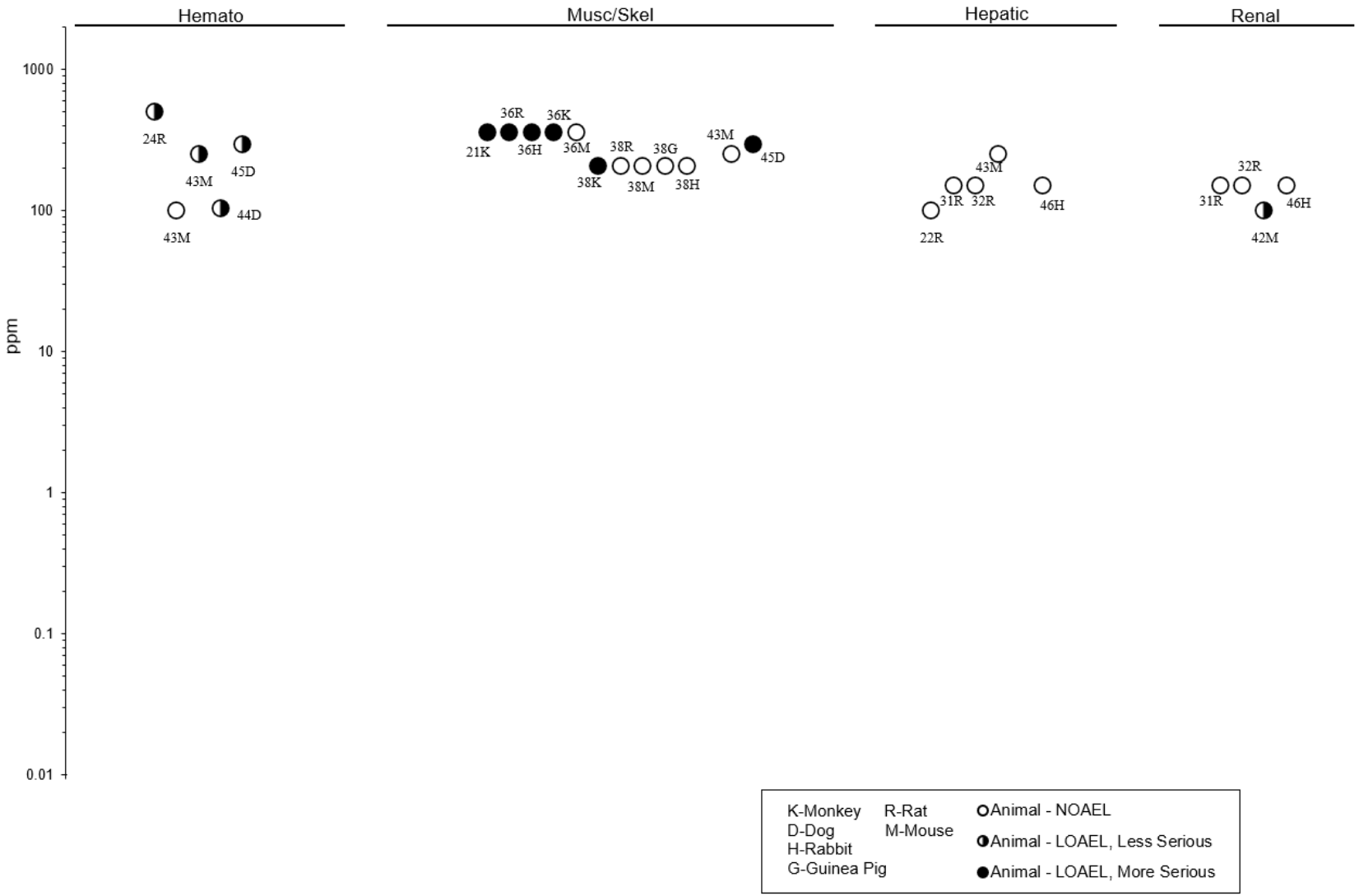
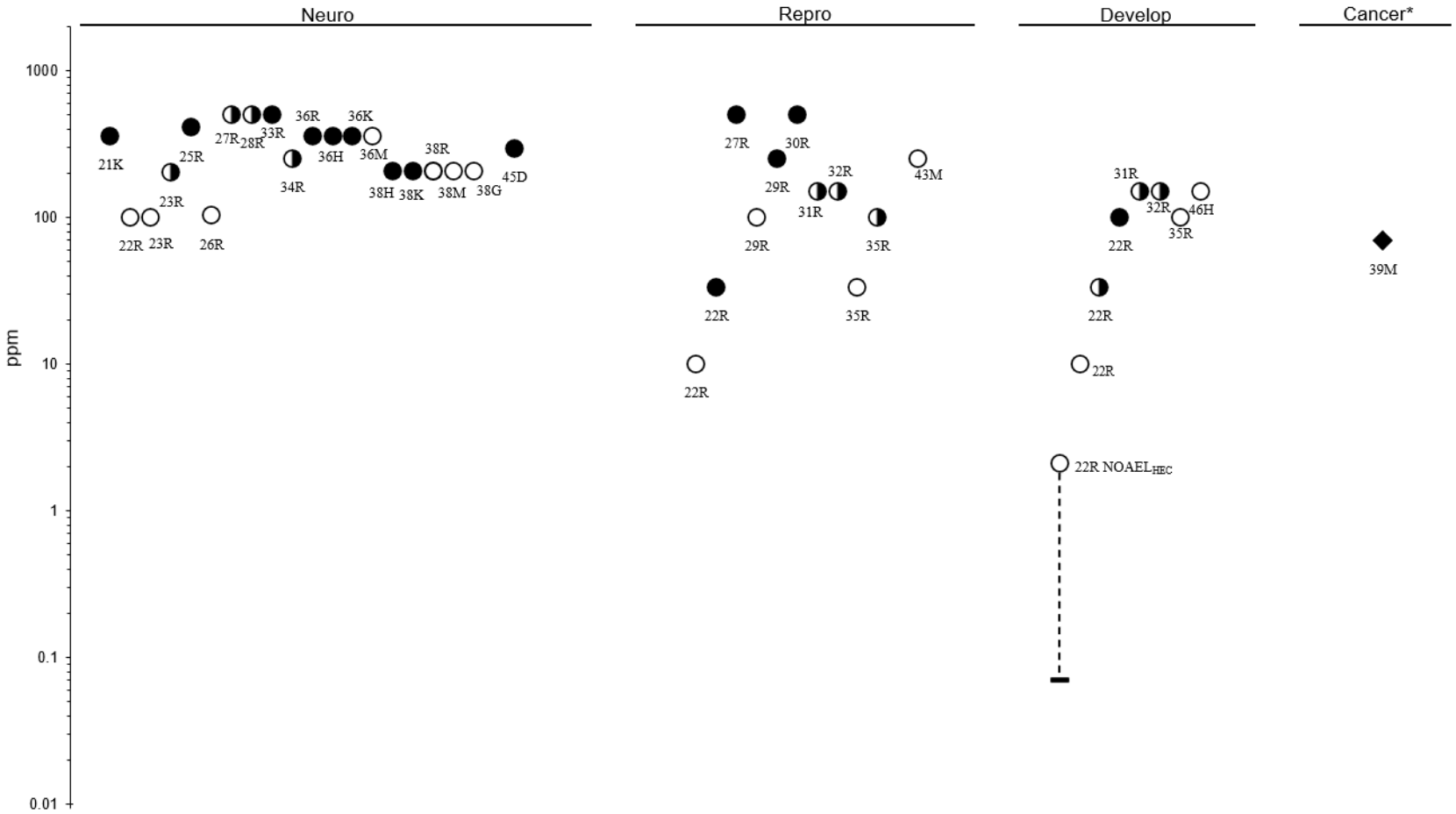


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

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)

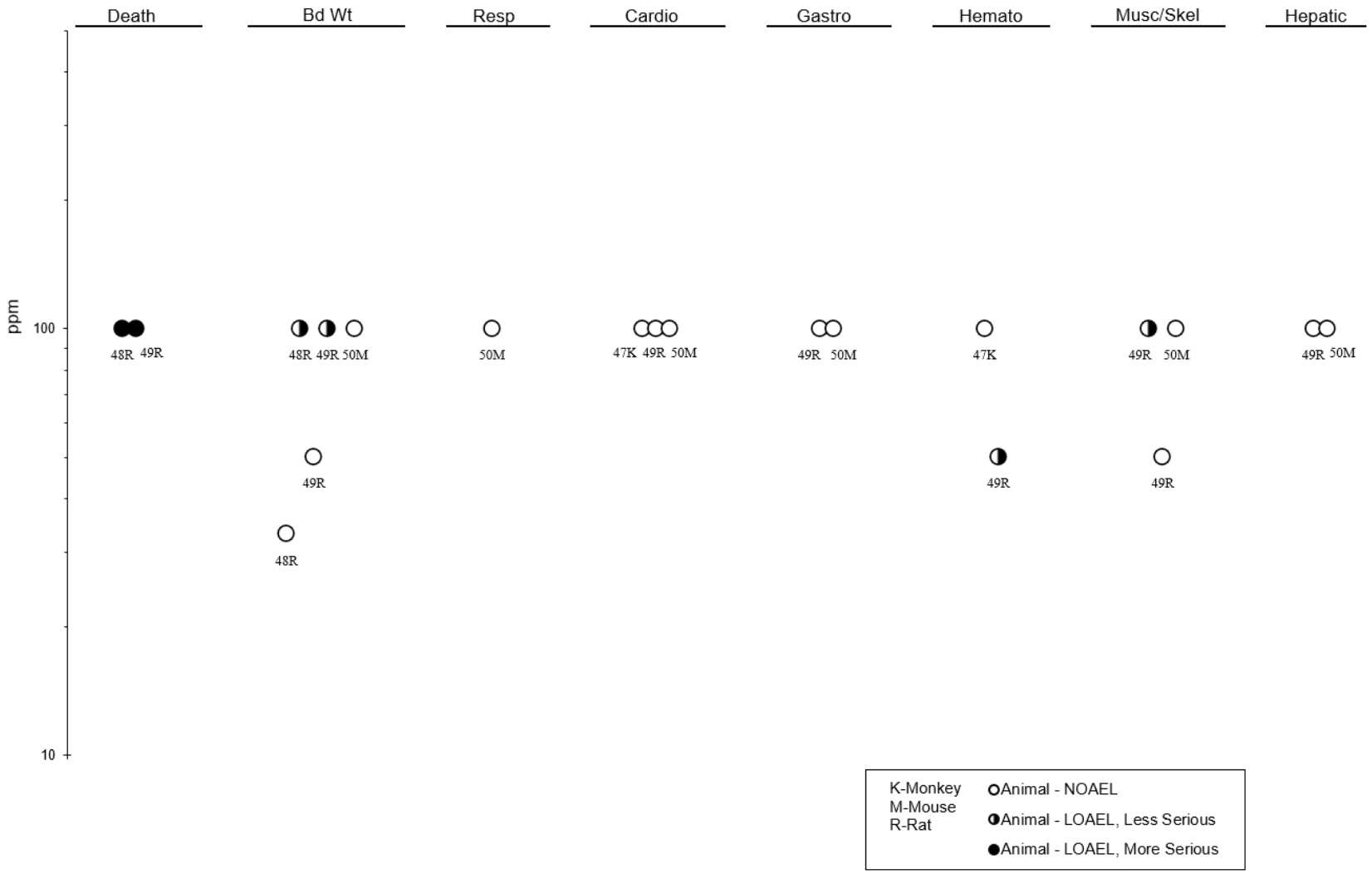
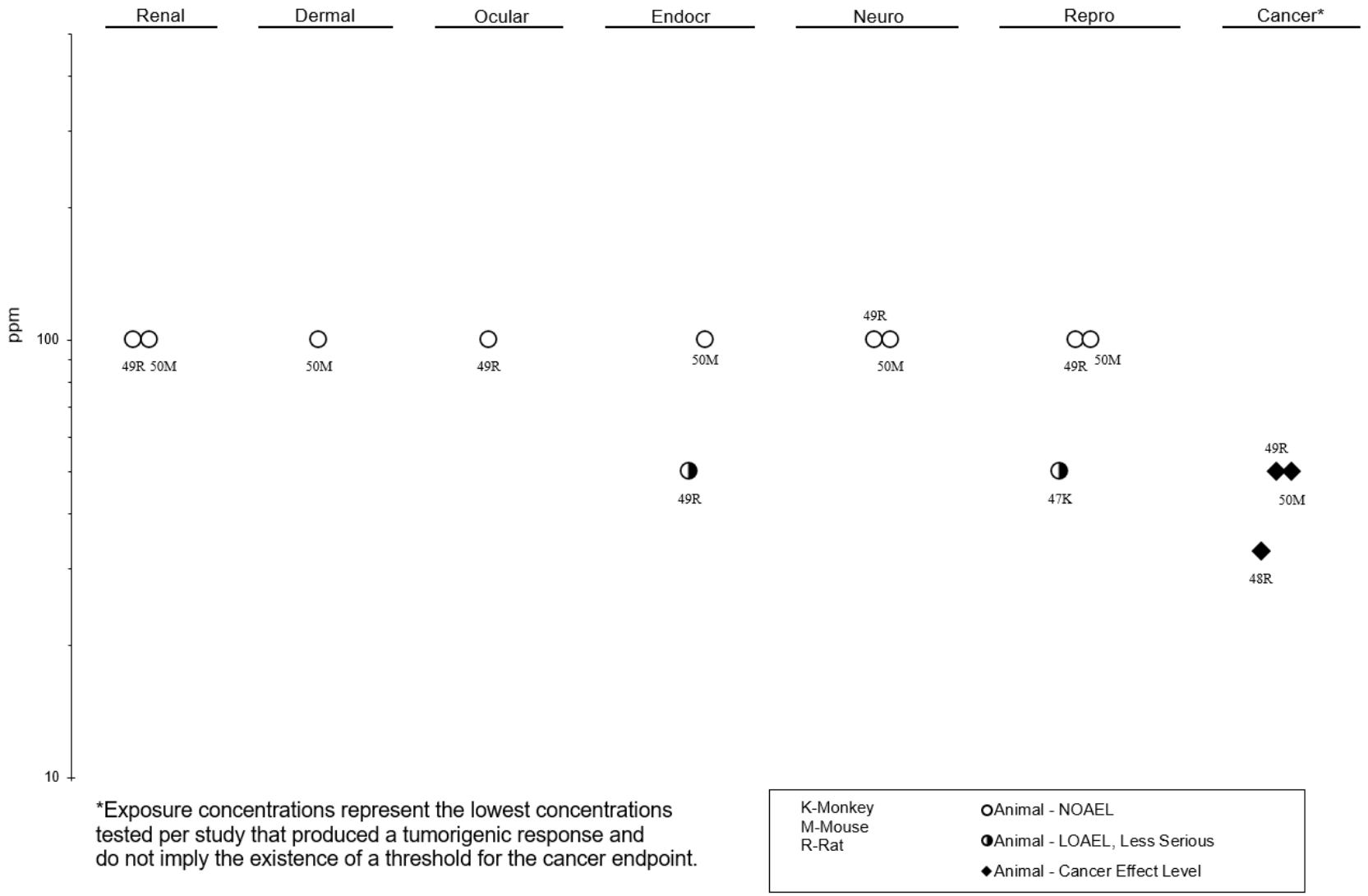


Figure 2-2. Levels of Significant Exposure to Ethylene Oxide – Inhalation

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)

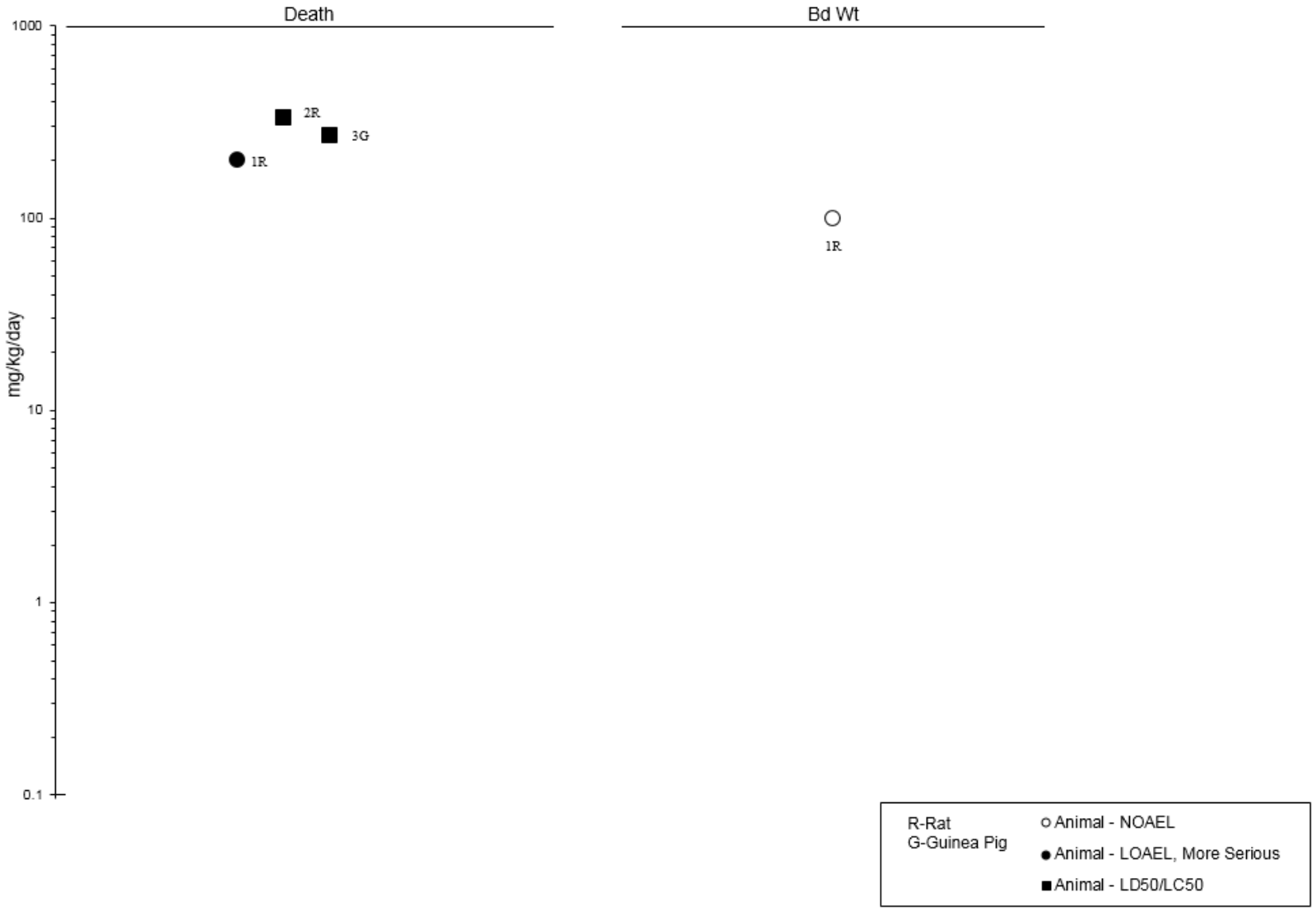


Figure 2-3. Levels of Significant Exposure to Ethylene Oxide – Oral

Intermediate (15-364 days)

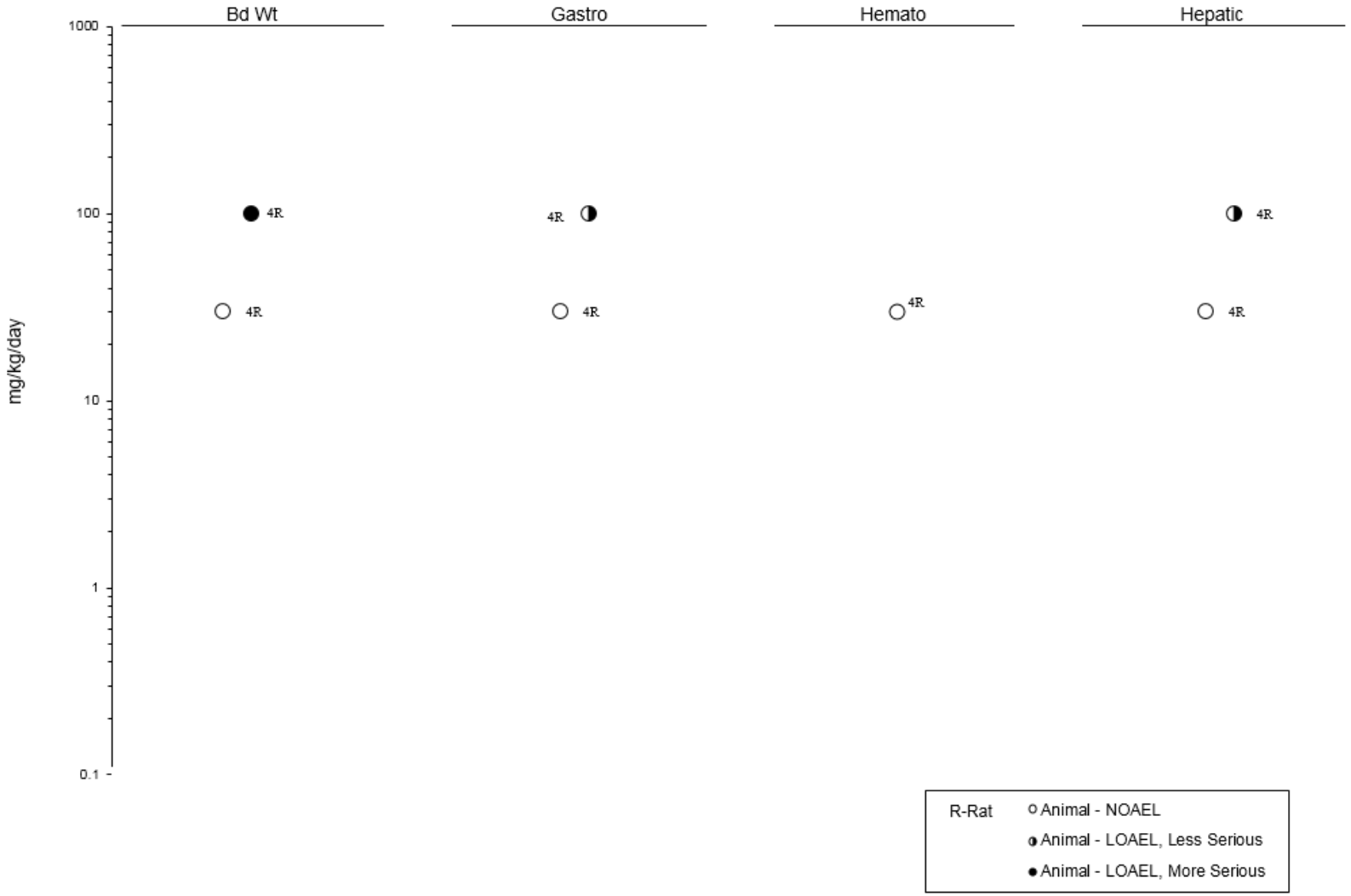
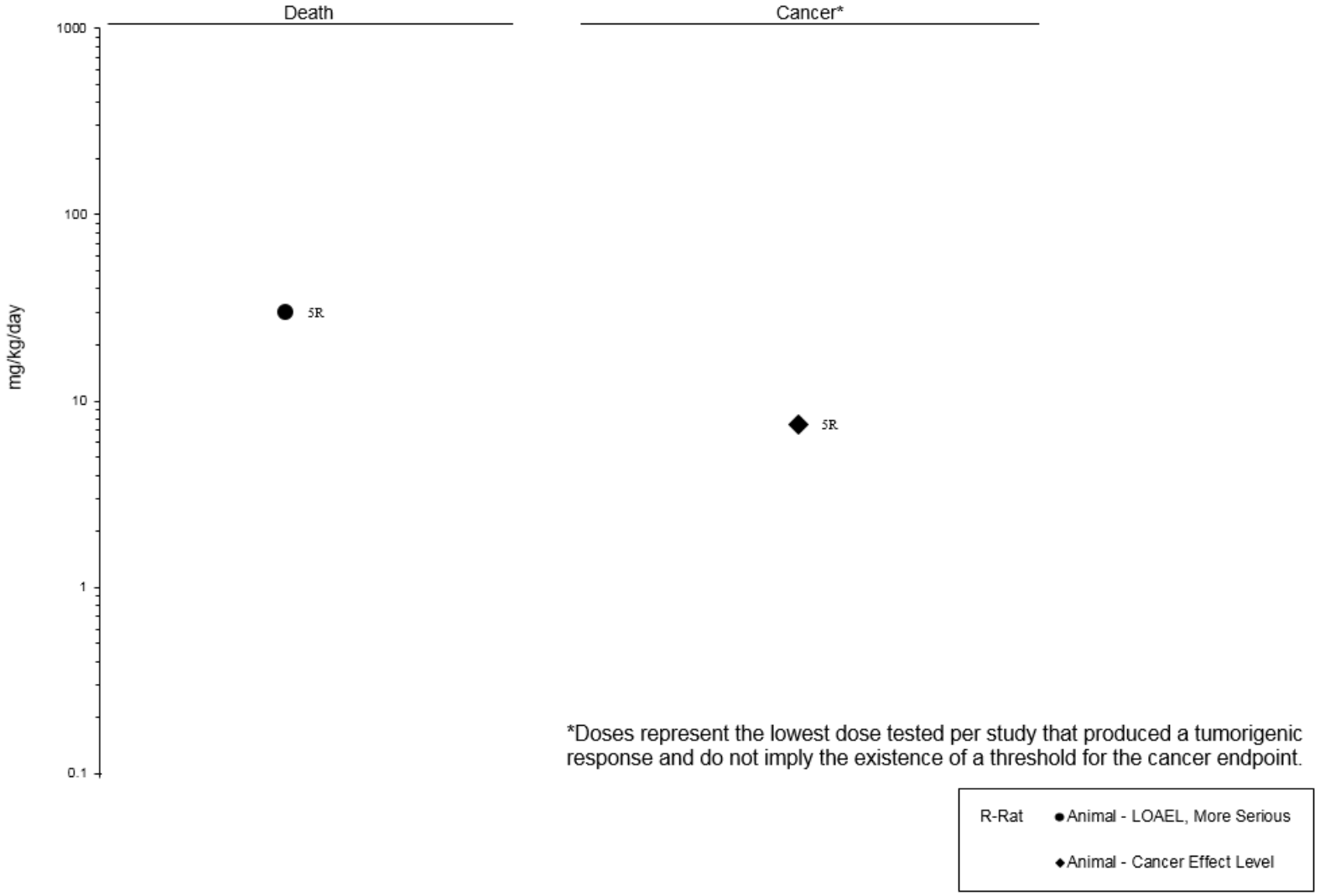


Figure 2-3. Levels of Significant Exposure to Ethylene Oxide – Oral

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

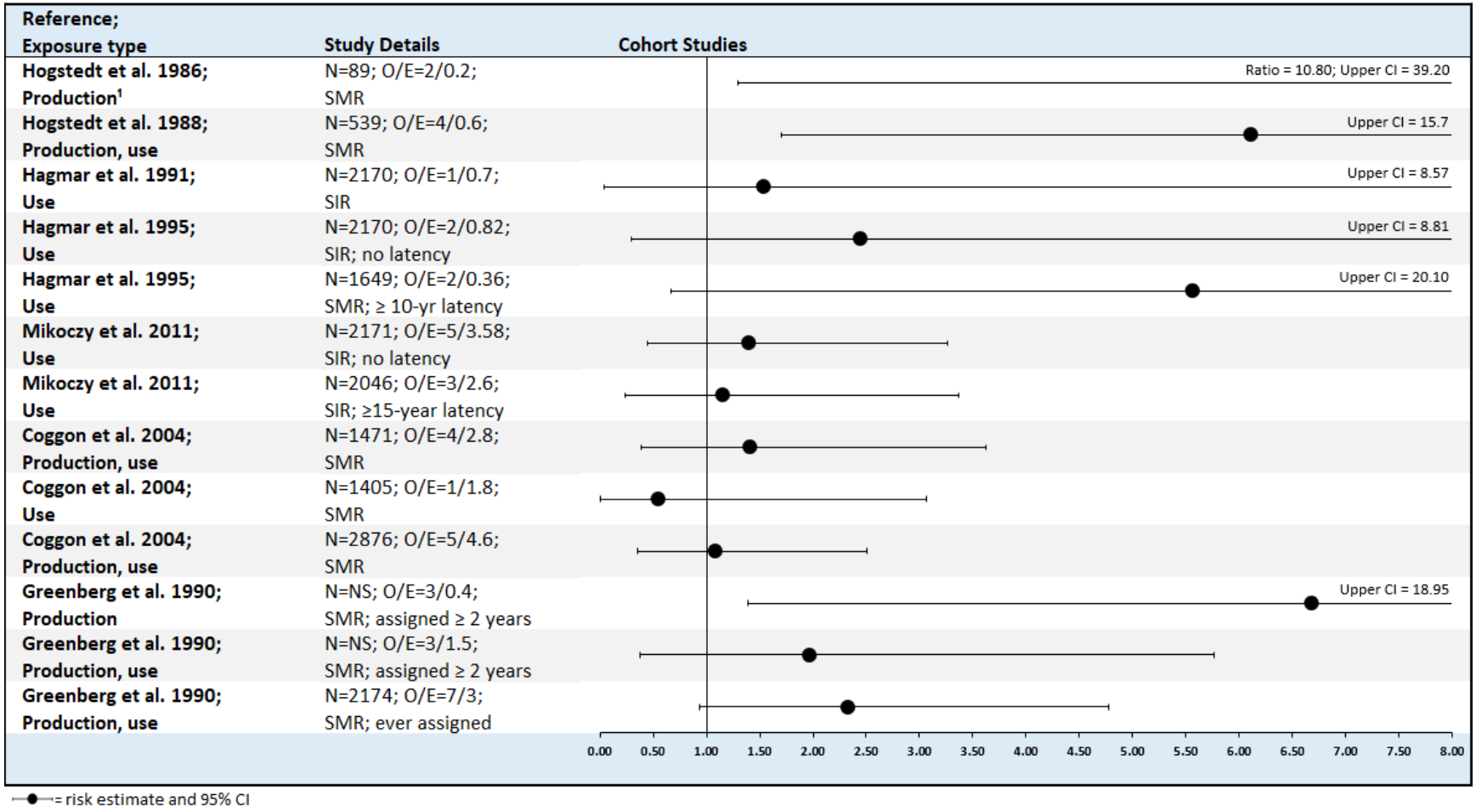
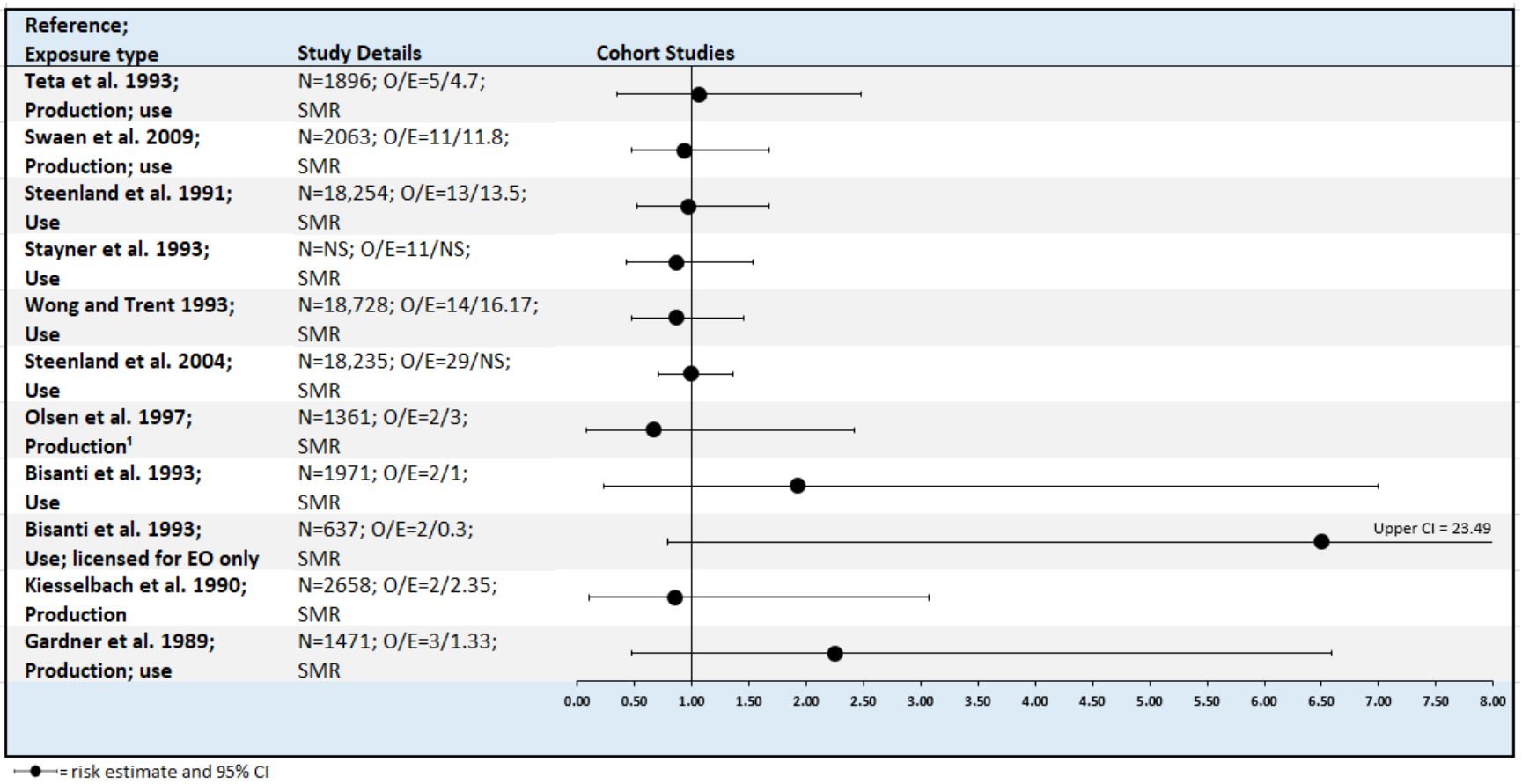
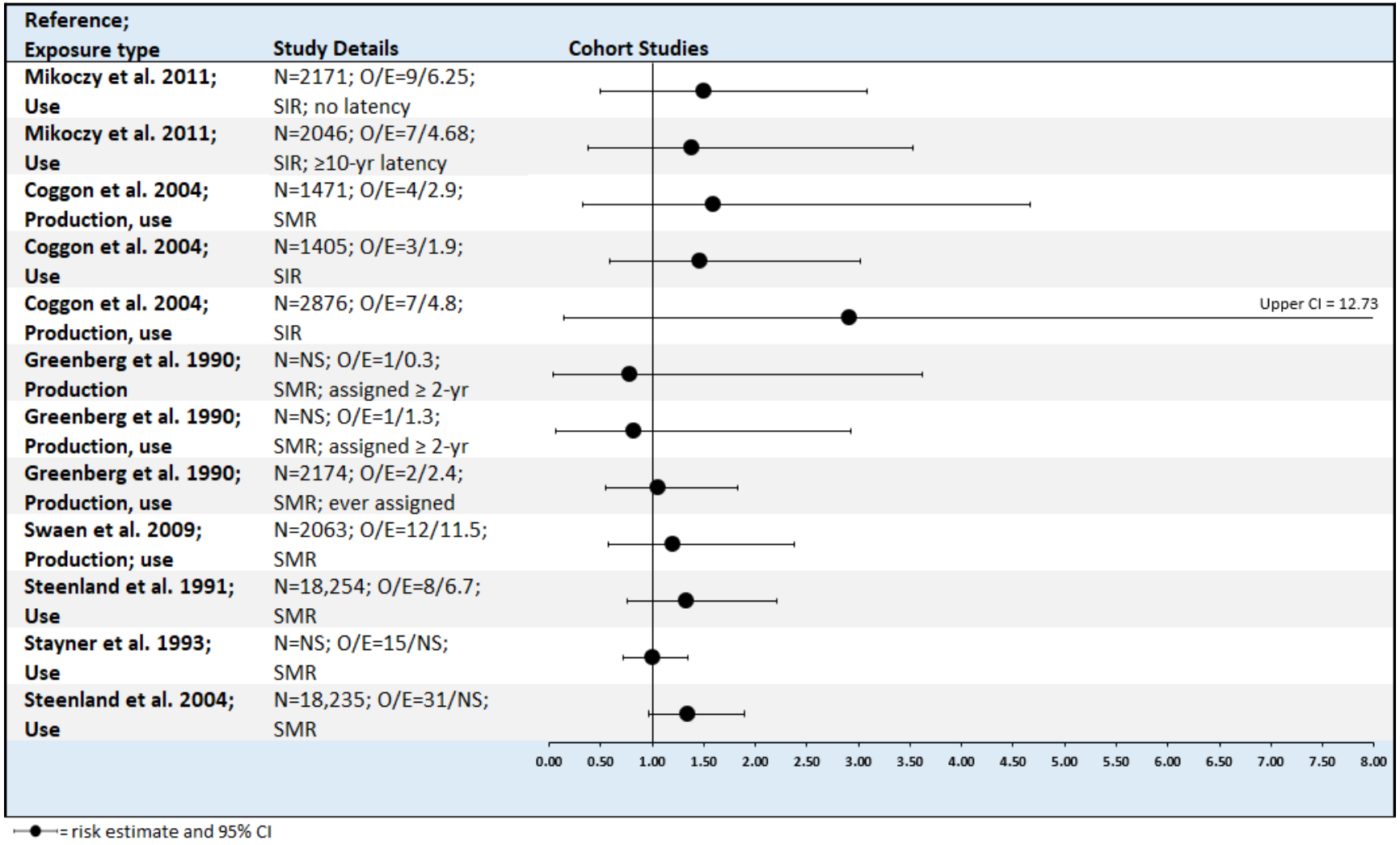


Figure 2-4. Summary of Studies Evaluating Leukemia in Workers Exposed to Inhaled Ethylene Oxide (continued)



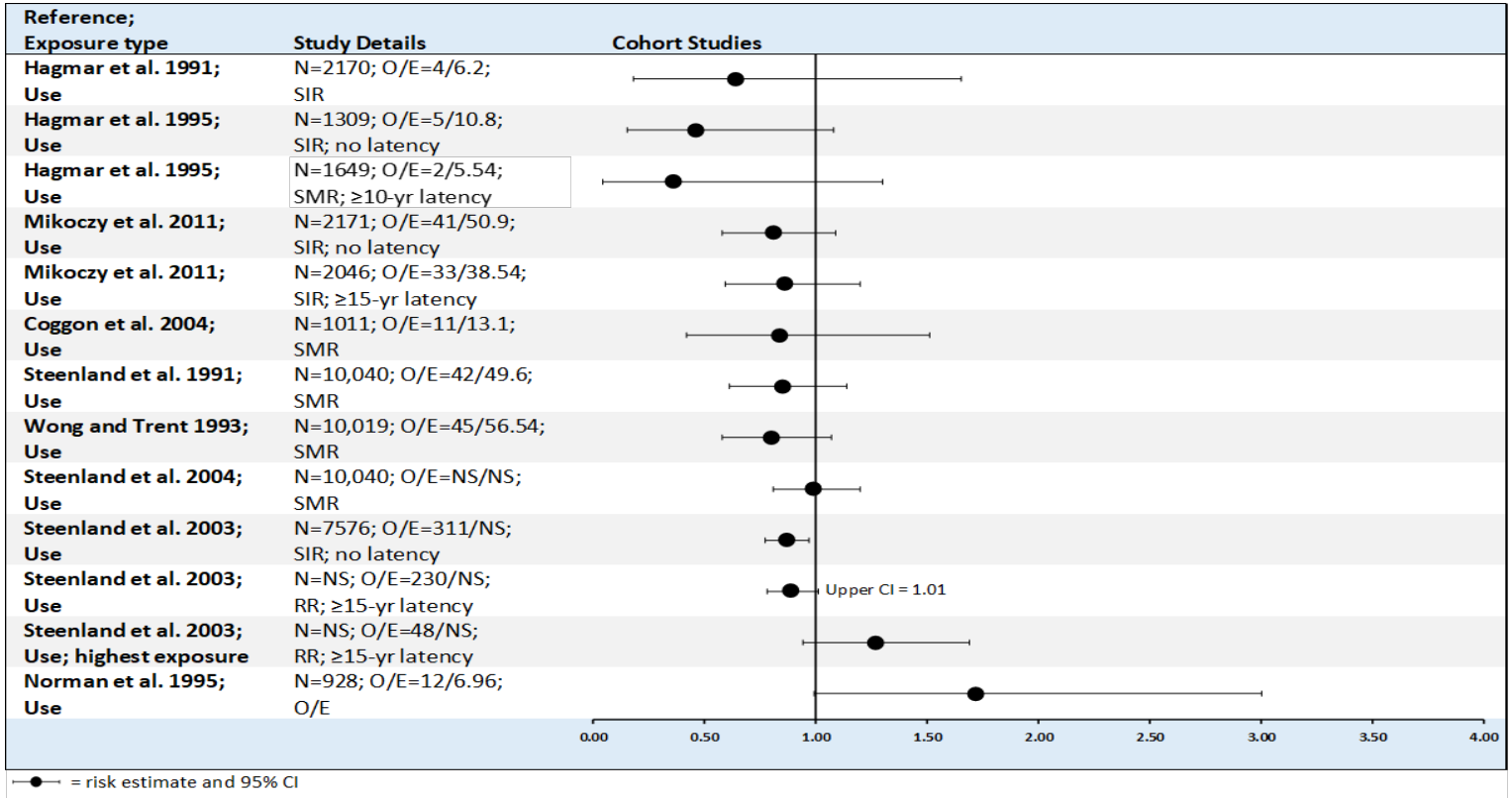
1 = production via chlorohydrin process; CI = confidence interval; EO = ethylene chloride; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene oxide production;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

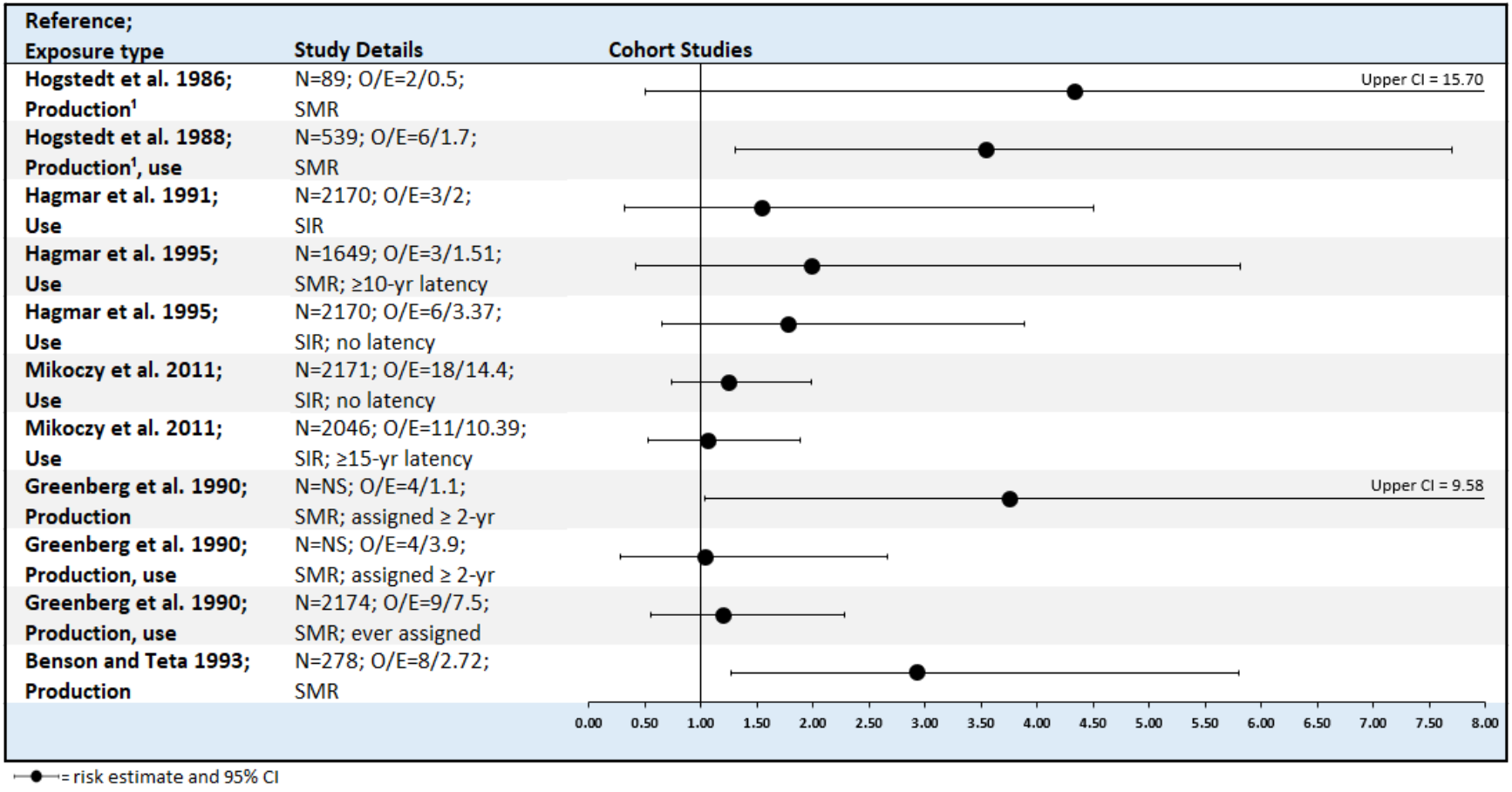
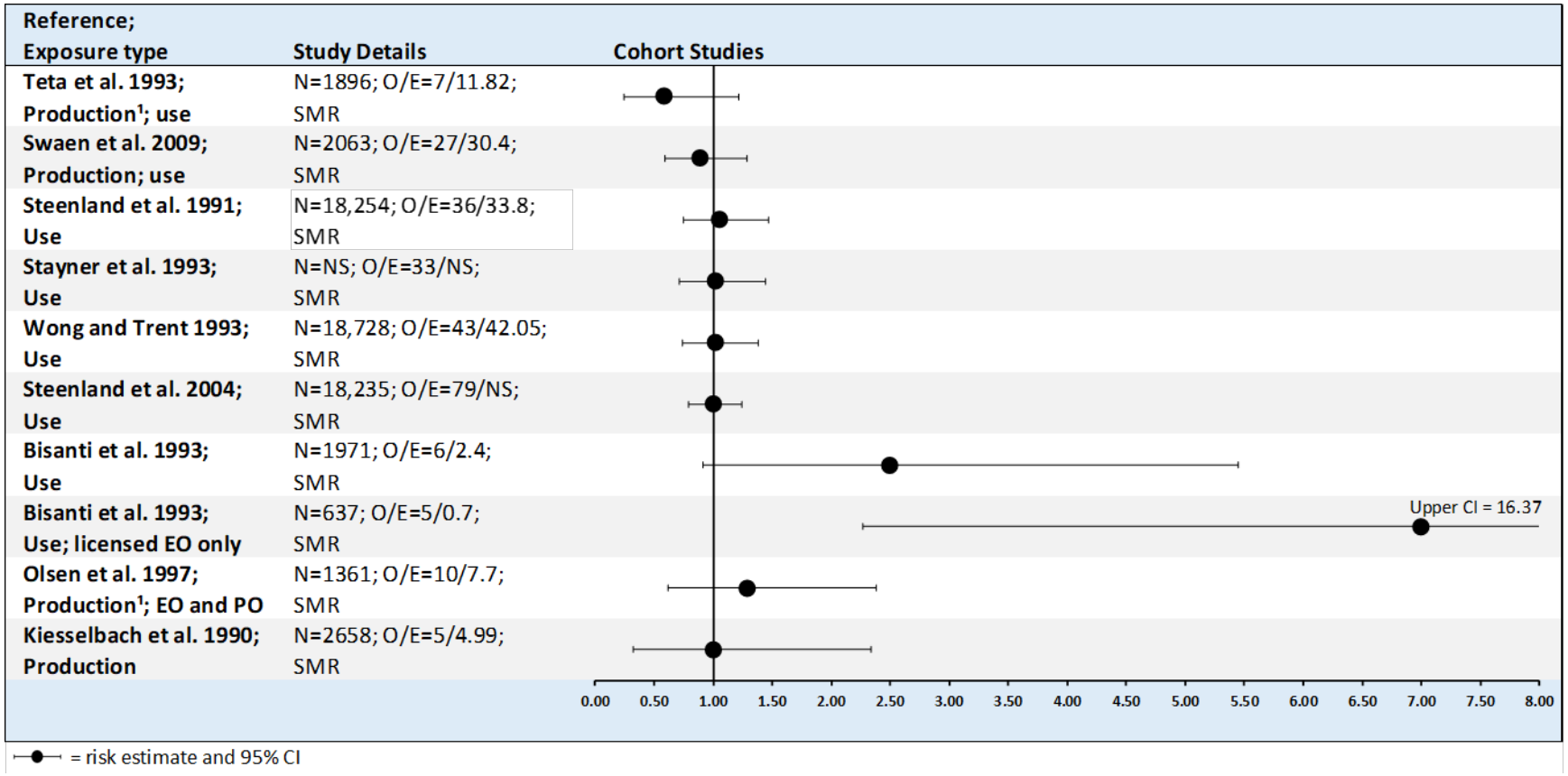


Figure 2-7. Summary of Epidemiological Studies Evaluating Lympho-Hematopoietic Cancer in Workers Exposed to Ethylene Oxide* (continued)

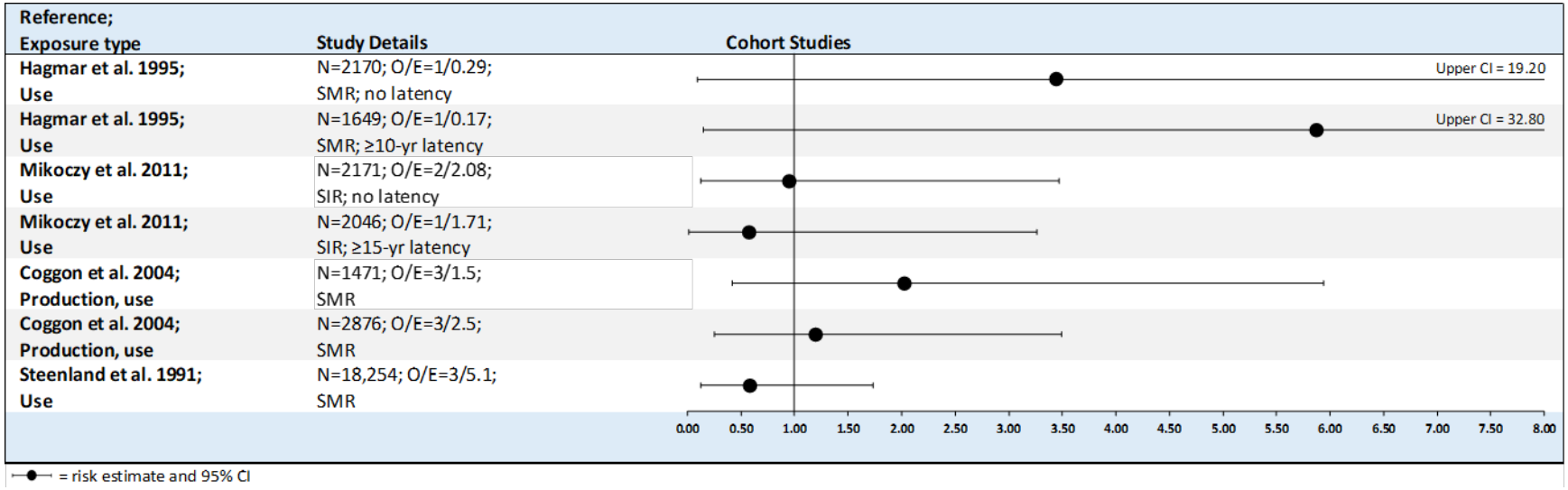


*SMRs/SIRs are presented in the figure for ease of comparison across multiple studies and datasets. Additional analyses noted below use internal comparisons, which may reduce potential confounding from the healthy worker effect.

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).

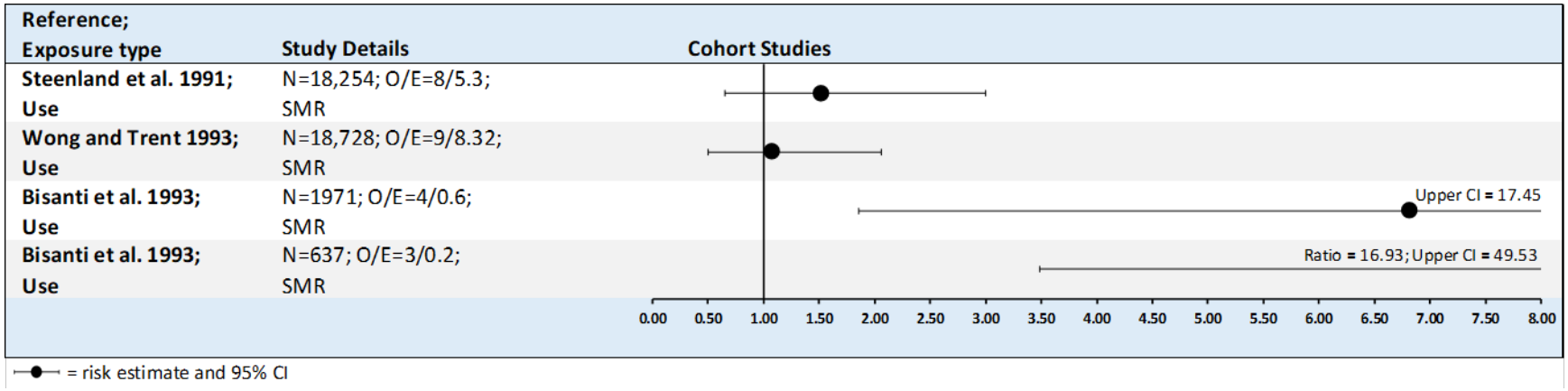
1 = production via chlorohydrin process; CI = confidence interval; EO = ethylene oxide; N = cohort size; NS = not specified; O/E = observed deaths (incidences)/expected; PO = propylene oxide; SIR = standardized incidence ratio; SMR = standardized mortality ratio; Production = workers involved in ethylene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