

## CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

### 1.1 OVERVIEW AND U.S. EXPOSURES

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

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

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

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

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

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

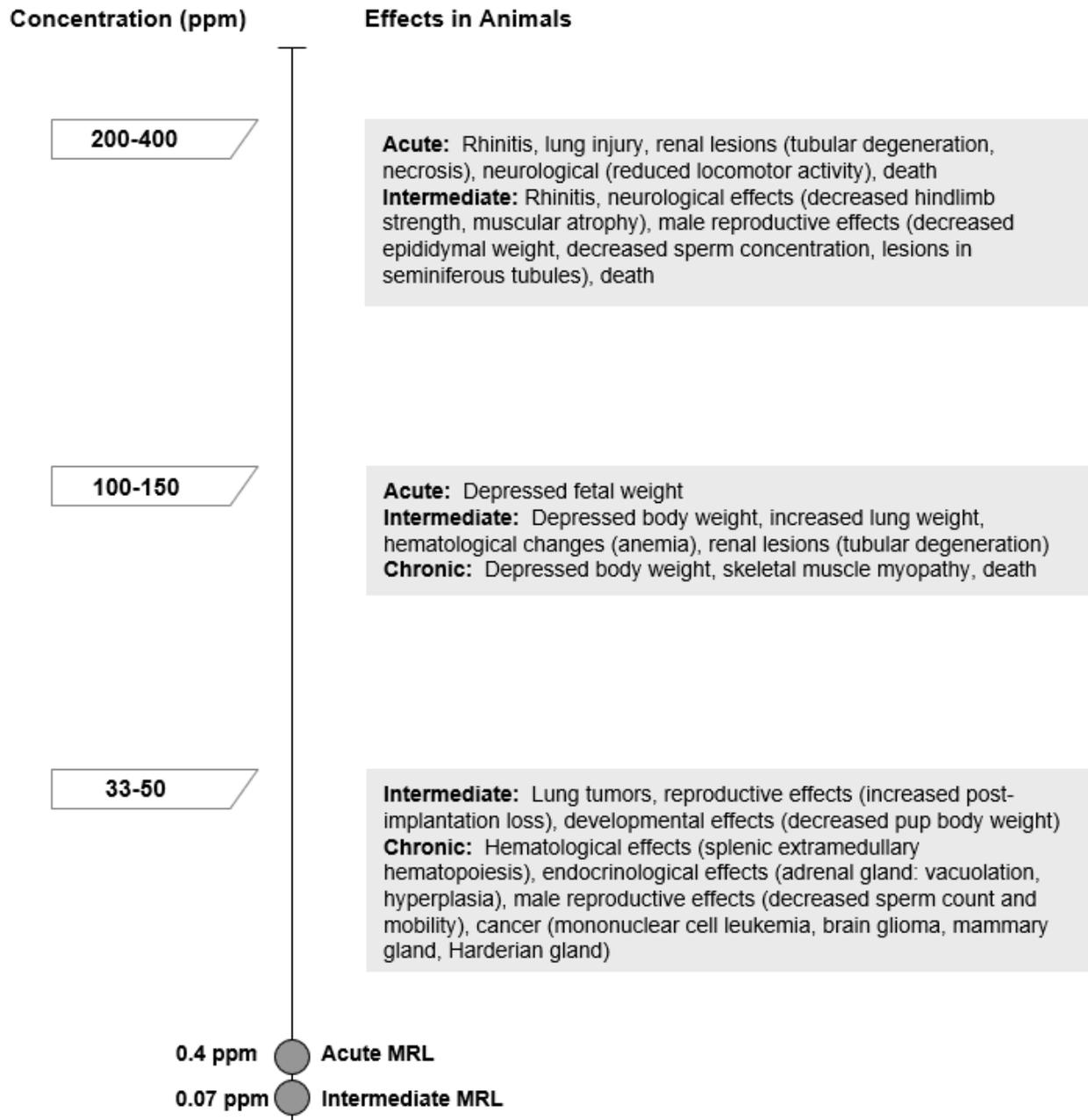
## 1.2 SUMMARY OF HEALTH EFFECTS

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

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

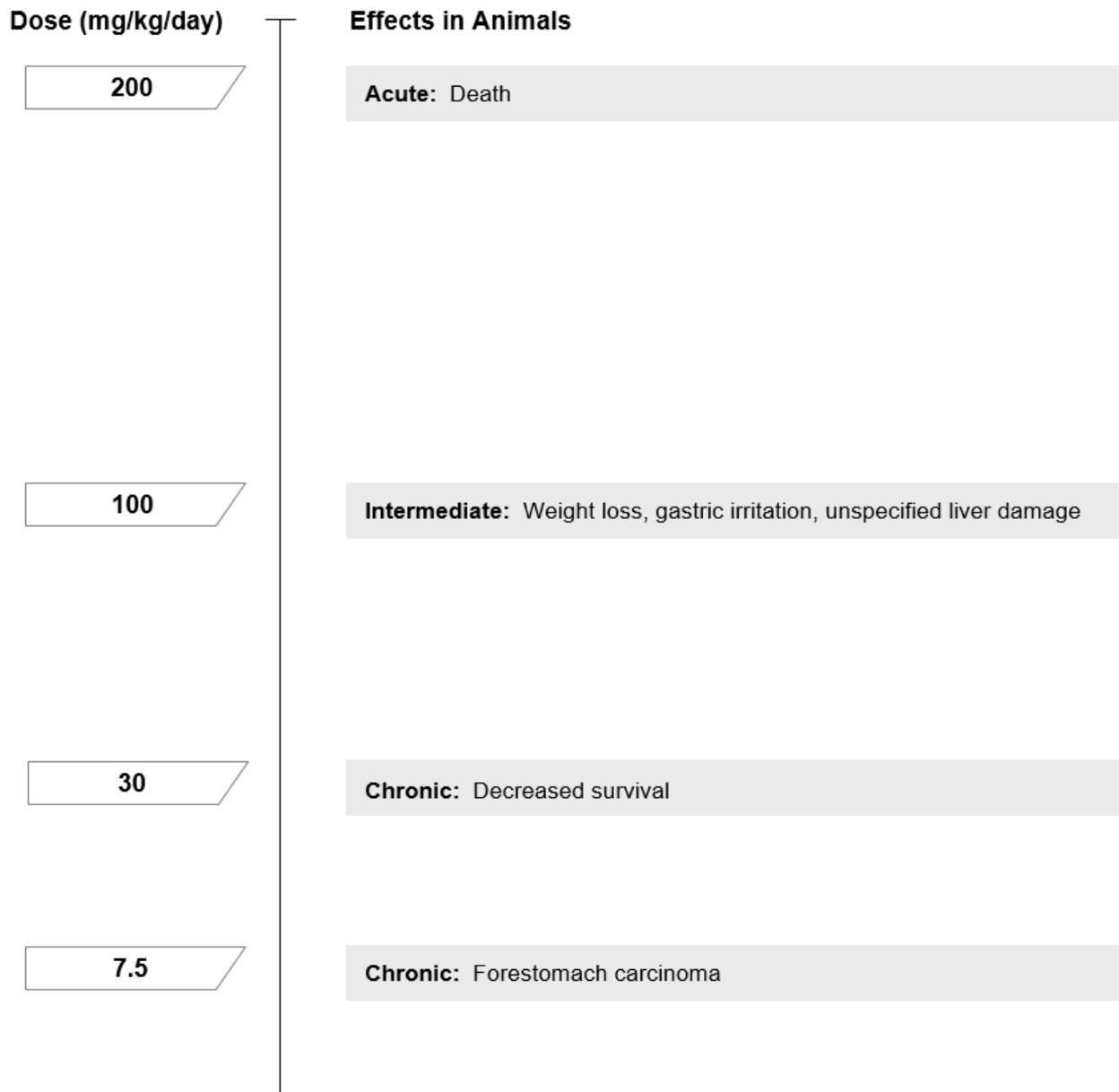
- Respiratory effects represent a presumed health effect endpoint for humans
- Hematological effects represent a suspected health effect endpoint for humans
- The endocrine system is a suspected health effect endpoint for humans
- Neurotoxicity is a presumed health effect for humans
- Reproductive toxicity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

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

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

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

\*No oral MRLs were developed for ethylene oxide.

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

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

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

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

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

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

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

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

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

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

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

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

### 1.3 MINIMAL RISK LEVELS (MRLs)

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

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

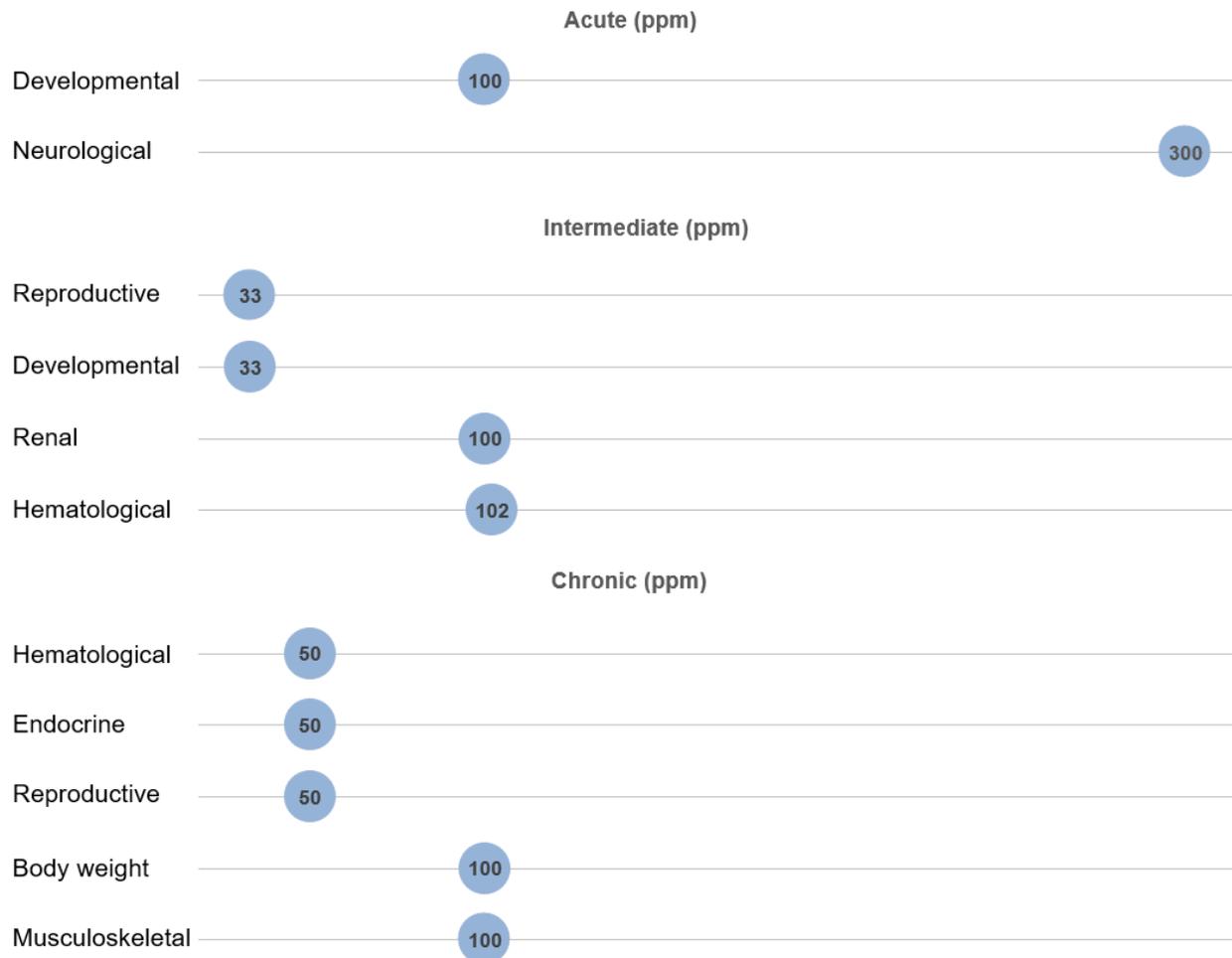
The MRL values for ethylene oxide are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

**Hematological, endocrine, reproductive, and developmental endpoints are the most sensitive noncancer targets of ethylene oxide inhalation exposure.**

Numbers in circles are the lowest LOAELs for all health effects in animals; no exposure-response human data were identified.



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**Table 1-1. Minimal Risk Levels (MRLs) for Ethylene Oxide<sup>a</sup>**

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

<sup>a</sup>See Appendix A for additional information.

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