Air Guidance Values
Site Assessment and Consultation Unit
Environmental Health Division
651-201-4897

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Air Toxicological Summary for: Ethylene Oxide (EtO)

CAS: 75-21-8

Air Exposure Durations:
$Acute_{1h}$ = 1 hour
$Acute_{24h}$ = 24 hours
Intermediate = greater than 24 hours to 1 year
Chronic = greater than 1 year to a lifetime
Cancer = 0 to 70 years (lifetime)

$Acute_{1hr}$ Non-Cancer Health Based Value ($HBV_{Acute1hr}$) = Not Derived (insufficient data)

$Acute_{24hr}$ Non-Cancer Health Based Value ($HBV_{Acute24hr}$) = 50 µg/m³

$$= \frac{(POD_{HEC}\ mg/m^3)}{(UF)}$$

$$= \frac{(4.5\ mg/m^3)}{(100)}$$

$$= 0.045\ mg/m^3 \text{ rounded to } 50\ \mu g/m^3$$

Reference Concentration:	POD_{HEC}/Total UF = 0.045 mg/m³
Source of toxicity value:	MDH 2024; based on EPA 1994 aci ATSDR 2022 (animal study)
Point of Departure (POD) and Critical Effect:	NOAEL = 10 ppm; post implantation loss in F0, decreased PND 21 body weight in F1 males
Human Equivalent Concentration (HEC):	2.5 ppm (4.5 mg/m3); [10 ppm x 6h/24h]; DAF = 1
Total uncertainty factor (UF):	100
UF allocation:	An uncertainty factor of 3 was used for interspecies extrapolation to account for dosimetric differences from animal (rodent) to human. An uncertainty factor of 10 was

used for intraspecies extrapolation to account sensitive subpopulation among humans. An UF of 3 is used to account for database deficiencies in developmental neurotox studies.

Intermediate Non-Cancer Health Based Value (HBV_{Inter}) = 30 µg/m³

$$= \frac{(POD_{HEC}\ mg/m^3)}{(UF)}$$

$$= \frac{(3.22\ mg/m^3)}{(100)}$$

$$= 0.032\ mg/m^3 = 30\ \mu g/m^3$$

Reference Concentration:	POD_{HEC}/Total UF = 0.032 mg/m³
Source of toxicity value:	MDH 2024; Snellings et al. 1984 (animal study)
POD and Critical Effect:	NOAEL = 10 ppm; Impaired neurological function, decrease in absolute testes weights
HEC:	1.79 ppm (3.22 mg/m³); [10 ppm x 6h/24h x 5d/7d]; DAF = 1
Total UF:	100
UF allocation:	An uncertainty factor of 3 was used for interspecies extrapolation to account for dosimetric differences from animal (rodent) to human. An uncertainty factor of 10 was used for intraspecies extrapolation to account sensitive subpopulation among humans. An UF of 3 is used to account for database deficiencies in developmental neurotox studies.

Chronic Non-Cancer Health Based Value ($HBV_{Chronic}$) = 10 µg/m³

$$= \frac{(POD_{HEC}\ mg/m^3)}{(UF)}$$

$$= \frac{(3.22\ mg/m^3)}{(300)}$$

$$= 0.011\ mg/m^3 = 10\ \mu g/m^3$$

Reference Concentration:	POD_{HEC}/Total UF = 0.011 mg/m^3
Source of toxicity value:	MDH 2024; Snellings et al. 1984 (animal study)
POD and Critical Effect:	NOAEL = 10 ppm; Impaired neurological function, decrease in absolute testes weights
HEC:	1.79 ppm (3.22 mg/m^3); [10 ppm x 6h/24h x 5d/7d]; DAF = 1
Total UF:	300
UF allocation:	An uncertainty factor of 3 was used for interspecies extrapolation to account for dosimetric differences from animal (rodent) to human. An uncertainty factor of 10 was used for intraspecies extrapolation to account sensitive subpopulation among humans. An UF of 3 is used to account for database deficiencies in developmental neurotox studies. An uncertainty factor of 3 is used for subchronic to chronic extrapolation.

Cancer Health Based Value = 0.002 µg/m^3

Cancer classification:	EPA IRIS 2016 – carcinogenic to humans IARC 2012 – carcinogenic to humans (Group 1)
Inhalation Unit Risk (IUR):	5 x 10^{-3} (µg/m^3)$^{-1}$; Per MDH policy (MDH 2020), age-dependent adjustment factors (ADAF) are applied to the IUR to protect against early-life sensitivity to EtO
Source of IUR:	EPA IRIS 2016 (occupational studies)
Tumor sites:	Reproductive, Immune
Tumor types:	Lymphoid cancer, breast cancer (female)

<u>Cancer ADAF and HBV Calculations:</u>

IUR_{adj} = IUR 3 x 10^{-3} (µg/m^3)$^{-1}$ x [(2 yrs x 10) + (14 yrs x 3) + (54 yrs x 1)] / 70 yrs

IUR_{adj} = 5 x 10^{-3} (µg/m^3)$^{-1}$

Cancer HBV = [additional lifetime cancer risk / IUR_{adj}]

Cancer HBV = [0.00001 / 5 x 10^{-3} (µg/m^3)$^{-1}$] = 0.002 µg/m^3

Volatile: Yes. Average Henry's Law = 1.48e^{-4} atm-m^3/mol; CompTox Chemicals Dashboard v2.5.3 accessed May 2025

Summary of Guidance Value History:

MDH had no previously published air guidance values for ethylene oxide.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]	Yes[6]

Comments on extent of testing or effects:

[1] Limited information is available for endocrine effects in animal studies and no studies were found regarding effects in humans. Per ATSDR 2022; 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 (1515 mg/m3) 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 (90 mg/m3) 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 (180 mg/m3) for up to 102 weeks (NTP 1987).

[2] Limited information regarding immunological effects in humans and animal studies are available following EtO inhalation exposure. Per ATSDR 2022; 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 (90 µg/m3) with occasional peaks of 8 ppm (14 µg/m3) 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). Thymic lymphocytic hypoplasia was reported for male and female mice intermittently exposed to ethylene oxide vapor at 400 ppm (729 mg/m3) for up to 2 weeks; at 600 ppm (1080 mg/m3), necrosis was observed in the thymus (males and females) and spleen (males) (NTP 1987).

[3] No information regarding developmental effects in humans were found, however; animal studies are available following EtO inhalation exposure. Per ATSDR 2022; 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 (270 mg/m3) (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 180 – 1441 mg/m3 during gestation. 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 (180 mg/m3) 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 (59 and 180 mg/m3) (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).

[4] Information regarding reproductive effects in humans and animal studies are available following EtO inhalation exposure. Per ATSDR 2022; 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 ($p<0.001$). 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 (180 – 900 µg/m3) with a highest measured concentration of 250 ppm (450 mg/m3). 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 (1856 µg/m3). 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 (180 mg/m3) 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 (450 – 900 mg/m3) (Kaido et al. 1992; Mori et al. 1991a, 1991b). Intermittent inhalation exposure of monkeys to ethylene oxide vapor at 50 ppm (90 mg/m3) (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 (180 mg/m3).

[5] Neurological effects have been associated with human and animal exposure ethylene oxide inhalation exposure at varying concentrations and durations. Occupational exposures to EtO report headache and nausea. Per ATSDR 2022; 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. 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. These effects were seen at estimated average exposure levels as low as 3 ppm (mg/m3); however, short-term exposures may have been as high as 700 ppm (1261 mg/m3) for some of these workers. Sural nerve biopsies revealed axonal degeneration and regeneration in two studies. 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. 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. 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 incidence of degeneration of myelinated fibers from the ethylene oxide-exposed rats than from controls.

[6] Per ATSDR 2022; 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. 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. Dyspnea was observed after 4 hours of exposure of mice to ethylene oxide vapor at a lethal exposure level of 1441 mg/m3 (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 (721 mg/m3) ethylene oxide for up to 2 weeks (NTP 1987). Intermediate-duration studies reported labored breathing and nasal discharge in rats exposed to 406 ppm (731 mg/m3) 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 (360 mg/m3) for up to 14 weeks (NTP 1987), and pulmonary congestion and alveolar collapse in dogs exposed to 292 ppm (526 mg/m3) for 6 weeks (Jacobson et al. 1956). Acute bronchopneumonia, chronic pneumonia, pulmonary edema, and suppurative rhinitis were observed in rats exposed at 50 ppm (90 mg/m3) 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 (180 mg/m3) 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).

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