Ethyl chloride; CASRN 75-00-3

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Ethyl chloride

File First On-Line 04/01/1991

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<td>yes</td>
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<td>not evaluated</td>
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I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Ethyl chloride
CASRN — 75-00-3
Primary Synonym — Chloroethane

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)
Substance Name — Ethyl chloride  
CASRN — 75-00-3  
Primary Synonym — Chloroethane  
Last Revised — 04/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

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<th>Critical Effect</th>
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| Delayed fetal ossification            | NOAEL: 4000 mg/cu.m (1504 ppm)  
NOAEL(ADJ): 4000 mg/cu.m  
NOAEL(HEC): 4000 mg/cu.m         | 300| 1  | 1E+1 mg/cu.m |
| Mouse Development Inhalation study    | LOAEL: 13,000 mg/cu.m (4946 ppm)  
LOAEL(ADJ): 13,000 mg/cu.m  
LOAEL(HEC): 13,000 mg/cu.m       |    |    |              |
| Scortichini et al., 1986              |                                                 |    |    |              |

*Conversion Factors: MW = 64.5. Assuming 25°C and 760 mm Hg, NOAEL (mg/cu.m) = 1504 ppm x MW/24.45 = 4000 mg/cu.m. For developmental effects this concentration is not adjusted; therefore NOAEL(ADJ) = NOAEL. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. b:a lambda(a) is unknown, b:a lambda(h) = 2.69,
(Gargas et al., 1989). Since \( b/a \) \( \lambda(a) \) is unknown, a default value of 1.0 is used for this ratio. \( \text{NOAEL(HEC)} = \text{NOAEL(ADJ)} \times 1 = 4000 \text{ mg/cu.m.} \)

I.B.2. Principal and Supporting Studies (Inhalation RfC)


In a developmental study conducted in groups of 30 CF-1 mice, Scortichini et al. (1986) exposed animals to mean time-weighted averages of 0 (air), 491 +/-37 ppm (1.3 g/cu.m), 1504 +/- 84 ppm (4000 mg/cu.m), and 4946 +/- 159 ppm (13,000 mg/cu.m.) 99.9% ethyl chloride for 6 hours/day on days 6 through 15 of gestation. The animals were sacrificed on the 18th day of gestation. In accordance with current EPA practice these values are not duration adjusted. No maternal toxicity was recorded in this study (clinical signs, body weight, liver weight, and food and water consumption were monitored), although an earlier pilot study with non-pregnant female mice at these same concentrations showed an exposure-related decrease in body weight gain (data not presented). In the present study, no exposure-related changes were noted in resorption rate, litter size, sex ratios, or fetal body weights. No exposure-related fetal visceral malformations were observed. In the fetuses of the dams exposed to 4946 ppm, there was a statistically significant increased incidence \( (p < 0.05) \) of foramina of the skull bones, a small area of delayed ossification. At this concentration, 5 fetuses were affected in a total of 5 litters vs. 1 fetus in 1 litter in the controls and in each lower exposure group (the skull bones were examined in 22 to 25 litters in the controls and at each exposure level). The authors cite that the historical incidence of foramina of the skull bones in their facility with this strain of mice is 0.2% of the fetuses with a range of 0 to 1.2% The effect in this study at 4946 ppm ethyl chloride represented 4% of the fetuses. Additional information volunteered by one author (TRH) indicated that the foramina in question were small, pin-point lesions although apparently the openings were not measured. This skull effect was accompanied by an increasing incidence of cervical ribs (a supernumerary rib considered to be a malformation). The incidence of fetuses having this malformation was 2/257 (1%) of the controls, and, in order of increasing exposure concentrations, 1/299 (0.3%), 6/311 (2%), and 4/242 (2%). The corresponding figures for the incidence in litters was 2/22 (9%) in controls and 1/25 (4%), 5/26 (19%), and 4/22 (18%) in the litters of exposed dams. This effect was not indicated as statistically significant and no historical incidence for this malformation is given in the text. This study shows that exposure to ethyl chloride results in fetotoxicity. The exposure concentration of 1504 ppm is the NOAEL of this study \( \text{NOAEL(HEC)} = 4000 \text{ mg/cu.m.} \) based on foramina of the skull bones. The highest concentration used in this study, 4946 ppm, is a LOAEL, \( (\text{HEC}) = 13,000 \text{ mg/cu.m.} \)

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)
UF — A factor of 10 is used to account for sensitive populations. An uncertainty factor of 3 (rather than 10) is used for interspecies extrapolation due to dosimetric adjustment of the inhaled concentration. As no multigeneration reproductive study and no definitive developmental toxicity studies were available, a full factor of 10 is proposed for database deficiencies.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Although used as a surgical anesthetic, ethyl chloride has a narrow margin of safety for this purpose as anesthesia occurs at 20 to 30 mg% and respiratory failure at 40 mg% (Dobkin and Byles, 1971). Ethyl chloride is explosive at 4% (40,000 ppm, 106 g/cu.m) in air, overlapping the concentrations required to produce anesthesia (3 to 4.5%). Neurological symptoms have been observed in human case-studies in instances of ethyl chloride abuse. Hes et al. (1979) noted cerebellar-related symptoms including ataxia, tremors, dysarthria (speech difficulties), slowed reflexes, nystagmus (involuntary movement of the eyeball), and hallucinations in a 28-year old female who sniffed 200 to 300 mL of ethyl chloride off her coat sleeve daily for 4 months. Examination revealed that her liver was enlarged (3 cm) and slightly tender and was accompanied by a mild and transient disturbance (not clinically described) of liver function. All symptoms were resolved by the end of 4 weeks. Similar neurological symptoms were noted in a 52-year old male who had a 30-year history of intermittent ethyl chloride (as well as alcohol and barbiturate) abuse (Nordin et al., 1988). Questioning upon hospitalization revealed that he had been inhaling at least 100 mL of ethyl chloride daily for the previous 4 months. No liver effects were reported and the patient fully recovered from the neurological symptoms by 6 weeks after admission. Ethyl chloride has been demonstrated to be a cardiac sensitizer (Balazs, et al., 1986) in dogs at or near concentrations producing anesthesia, i.e., 30,000 to 45,000 ppm (du Pont, 1971). In this condition, cardiac tissue is hypersensitized to the effects of stimulatory endogenous catecholamines which can result in arrhythmias and cardiac arrest.

Rowe et al. (1939) exposed groups of rabbits (4/group) and rats (12/group; strain unspecified) to 26.4 g/cu.m ethyl chloride 7.5-8 hours/day, 5 days/week for 6.5 months. No effects on weight gain, liver weights, histopathology (including lungs), or clinical signs were noted.

Landry et al. (1989) exposed groups of 14 (7/sex) B6C3F1 mice to 0 (air), 250 ppm (0.66 g/cu.m), 1247 ppm (3.3 g/cu.m), or 4843 ppm (12.8 g/cu.m) 99.9% EC, 23 hours/day for 11 consecutive days. The duration-adjusted values for these exposures in increasing concentrations are 0, 0.63, 3.2, and 12.2 g/cu.m. The actual duration of exposure in this study (253 hours) was comparable to that obtained in a 4 hour/day, 5-day exposure week (260 hours). A blind neurobehavioral observation battery was conducted on the 12th day followed by collection of samples for clinical chemistry and hematology. Body and organ weights were taken and
histopathology was performed. The only exposure-related effect observed in this study was a slight increase in the mean liver weights of both male and female mice exposed to 4843 ppm. (The increase in liver weight was approximately 6 g/100g vs. 5.3 g/100 g in controls; p=0.05.) Histopathologic examination revealed a minimal increase in the degree of hepatocellular vacuolization in 4 of 7 animals of both sexes at this exposure. These alterations were minimal and not accompanied by any increase in serum enzymes. This study defines a free-standing NOAEL of 4843 ppm, the NOAEL(HEC) for this extrarespiratory effect = 12.2 g/cu.m.

Landry et al. (1982) exposed groups of 8-10 week old F344 rats (6/sex/group) to 0 (air), 1600 ppm (4.2 g/cu.m), 4000 ppm (10.6 g/cu.m), or 10000 ppm (26.4 g/cu.m) of 99.7% ethyl chloride 6 hours/day, 5 days/week for 2 weeks. The duration-adjusted values are 0, 0.8, 1.9, or 4.7 g/cu.m, respectively. Clinical observations and chemistry, hematology, urinalysis, and complete histopathology (including the entire respiratory tract) were performed. The only exposure-related effect observed was a statistically significant increase in liver to body weight ratios in male rats exposed to 4000 ppm (3.64 g/100g) and 10,000 ppm (3.73 g/100g) as compared with controls (3.47 g/100 g) ethyl chloride. As this alteration was not accompanied by any histopathology or increases in serum enzymes it is considered an adaptive response, not an adverse effect. Therefore this study identifies the highest level of exposure in this study (10,000 ppm) as a free-standing NOEL, NOEL(HEC) for extrarespiratory effects = 4.7 g/cu.m.

Groups of F344 rats and B6C3F1 mice (50/group/sex) were exposed to either 0 (air) or 15,000 ppm of 99.5% ethyl chloride (39.6 g/cu.m) 5 days/week, 6 hours/day for 102 weeks (rats) or 100 weeks (mice) in an NTP (1989) study. The duration-adjusted concentration becomes 7.1 g/cu.m. The exposure level was set at this limit because of safety considerations for explosions. A single level of exposure was chosen as no exposure-related changes were seen in the 90-day study (see below) at a slightly higher concentration (19,000 ppm). Monitoring for toxicological effects was by twice daily observation, body weights, and a complete necropsy and histologic examination including tissues of the entire respiratory tract (3 levels of the nasal epithelium, personal communication with study director) and brain. Survival of female mice after week 82 was significantly lower than controls apparently due to an increase in deaths from carcinomas of the uterus; there were no other statistically significant differences in survival between control and treated animals of either species. The incidences and severity of microscopic pathologies noted in tissues (including uterine tissue) were not different between the treated and control animals of either species. Hyperactivity was observed but only in female mice (no incidences given) and only during exposure. Mean body weights were decreased in both male and female rats. In females, the maximum difference in body weights between exposed and control animals was 13% and occurred at 59 weeks of exposure when 49 of 50 test animals were still alive. Although some fluctuations towards normalcy were observed from this time forward, terminal body weights of 23 surviving treated animals were still 10% less than their corresponding controls. In male rats, mean body weights were also decreased when compared with controls, although the
decrease achieved a maximum differential of only 8%. The mean body weights of mice were not affected by exposure. Based on the mild decrease in mean body weight gain, 15,000 ppm is judged as a free-standing NOAEL. The NOAEL(HEC) = 7.1 g/cu.m.

Groups of F344 rats and B6C3F1 mice (10/group) were exposed to either 0 (air), 2500 ppm (6.6 g/cu.m), 5000 ppm (13.2 g/cu.m), 10,000 ppm (26.4 g/cu.m), or 19,000 ppm (50.1 g/cu.m) of 99.5% ethyl chloride 5 days/week, 6 hours/day for 13 weeks (NTP, 1989). The duration-adjusted concentrations are 0, 1.2, 2.4, 4.7, or 9.0 g/cu.m, respectively. Monitoring for toxicological effects was by daily observation, body weights, and a complete necropsy and histologic examination including tissues of the entire respiratory tract and brain. No exposure-related clinical signs or gross or histopathological effects were observed in either species. Relative liver weights were slightly increased in the male rats (14%) and female mice (18%) exposed to 19,000 ppm. Slight decreases in mean body weights were noted in the rats (8% in the males, 4% in the females) exposed to 19,000 ppm; no dose-related tendency could be discerned from the data. As no toxicity was apparent, 19,000 ppm is considered as a free-standing NOAEL in this study. The NOAEL(HEC) = 9.0 g/cu.m.

The results obtained in the two studies of Troshina (1964 & 1966) discussed below do not concur with those found by NTP (1989), Landry et al. (1982, 1989), or Rowe et al. (1939). All of the latter are carefully conducted studies with appropriate controls and relatively complete presentation and description of the data obtained. As presented, the studies of Troshina may be described as ambiguously conducted with deficient use of controls and no or little presentation of data. These deficiencies preclude consideration of these studies as a reliable source of information about the toxic effects of this chemical.

In the study published in 1964, Troshina exposed 12 rats (sex or strain not specified) for 2 hours/day for 60 days (assumed consecutive) 14 g/cu.m ethyl chloride, the duration-adjusted value being 1.2 g/cu.m. There is mention of but no description of controls used in this study. Body weight, hematology, some histopathology, and the "functional state of the nervous system and the liver" were assessed for adverse effects. Body weights were unaffected. Using a functional test of liver metabolic capacity (conversion of gastrically administered sodium benzoate to hippuric acid as measured by urinary excretion), a decrease in hippuric acid excretion was noted after the exposure, from 90.3% in controls to 33.6% in the exposed animals. Lung pathology was described as bronchitis, hyperemia, and (apparently) intraalveolar thickening. The author claims these effects are exposure-related indications of irritant action, although no mention is made of histology from control lungs. Description of liver pathology included nodule formation originating from the reticuloendothelial cells while "very slight" adiposity was also noted. Belying this description of substantial pathology, the author states that these changes were "weakly pronounced." After noting a increased tendency of exposed animals to form cutaneous abscesses (4 of 12), the authors examined other animals (apparently exposed
under identical conditions for 2 weeks, n = at least 3) for decrements in phagocytic activity. Their data showed a decrease in phagocyte number, index (not described), and percent of active cells at the end of the 2-week period, although evaluation past this early time point was apparently not done. No scientific conclusions could be reliably drawn from this study, although effects would suggest the exposure level of 1.2 g/cu.m to be a frank-effect level (FEL). For extrarespiratory effects, FEL(HEC) = 1.2 g/cu.m. The FEL(HEC) was also calculated for a gas:respiratory effect in the thoracic region. MVa = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(TH) = 3461.6 sq.cm., Sh(TH) = 640581 sq.cm. RGDR = (MVa/Sa) / (MVh/Sh) = 1.3. FEL(HEC) = FEL(ADJ) x RGDR = 1.6 g/cu.m.

In the 1966 study by the Troshina, exposures were lowered substantially from the 1964 experiments (presumably due to the frank effects) and are reported as 0, 0.06, or 0.57 g/cu.m in exposures to 12 rats which lasted for 6 months at 4 hours/day, 6 days/week. The duration-adjusted values would be 0, 0.0085, or 0.0811 g/cu.m. Using the same indicators of toxicity as in the 1964 study, the author reported decreases in phagocytic activity although these indices "fluctuated within considerable limits." Although no data are presented, the author also describes several exposure-related effects including disturbed liver function, lowered blood pressure, fatty liver, and what is interpreted as intraalveolar thickening in the lungs. No scientific conclusions could be reliably drawn from this study, although effects claimed would suggest the exposure level of 0.0085 g/cu.m = 8.5 mg/cu.m = NOAEL(HEC) based on extrarespiratory effects. The NOAEL(HEC) was also calculated for a gas:respiratory effect in the pulmonary region. MVa = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(PU) = 3424 sq.cm., Sh(TH) = 635545 sq.cm. RGDR = (MVa/Sa) / (MVh/Sh) = 1.3. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 11.1 mg/cu.m.

Experiments conducted by Breslin et al. (1988) suggest that exposure to ethyl chloride may disrupt the estrus cycle of mice. Two groups (10/group) of female B6C3F1 mice were acclimated in exposure chambers over a 2-week period or until the estrus cycles of most mice was a 4-6 day interval (as judged by a vaginal lavage technique). Males were included in each chamber to synchronize and promote regular estrus cyclicity. Following acclimatization one group was exposed to 15,000 ppm (39.6 g/cu.m) ethyl chloride 6 hours/day for a minimum of 14 consecutive days (through 3 estrus cycles). No effects on behavior, gross or histopathology were observed in the group undergoing exposure although the mean body weights in the exposed group was significantly increased rather than decreased. The mean length of the estrus cycle in exposed mice was 5.6 days, significantly longer in duration than the pre-exposure duration for the same group (5.0 days) and for the corresponding controls (4.5 days). The protraction of the period could not be attributed to an increase in any particular phase of the estrus cycle and is therefore suggestive of a general stress response. A direct exposure-related effect of ethyl chloride on neuroendocrine function cannot be excluded. As this effect is regarded as a systemic effect, the exposure is duration adjusted to establish a free-standing LOAEL of 6.6 g/cu.m. The LOAEL(HEC) = 6.6 g/cu.m.
I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Although the principal study is well-conducted, it does not establish a firm concentration-response relationship with an adverse effect and was not performed at levels eliciting maternal toxicity. There are no multigenerational reproductive studies for this compound, and without a developmental study in a second species, the overall confidence in the data base is medium. Medium confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.


Verification Date — 12/20/1990

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Ethyl chloride
CASRN — 75-00-3
Primary Synonym — Chloroethane

Not available at this time.
VI. Bibliography

Substance Name — Ethyl chloride
CASRN — 75-00-3
Primary Synonym — Chloroethane

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References


VI.C. Carcinogenicity Assessment References

None
VII. Revision History

Substance Name — Ethyl chloride  
CASRN — 75-00-3  
Primary Synonym — Chloroethane

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VIII. Synonyms

Substance Name — Ethyl chloride  
CASRN — 75-00-3  
Primary Synonym — Chloroethane  
Last Revised — 07/01/1995

- 75-00-3
- Ethane, chloro-
- Aethylchlorid [German]
- Aethylis
- AETHYLIS CHLORIDUM
- Anodynou
- Chelen
- Chloorethaan [Dutch]
- Chlorene
- Chlorethyl
- Chloridum
- Chloroaethan [German]
- Chloroethane
- Chlorure d'ethyle [French]
- Chloryl
- CHLORYL ANESTHETIC
- Cloretilo
- Cloroetano [Italian]
- Cloruro de etilo [Spanish]
- CLORURO DI ETILE [Italian]
• Dublofix
• ETHANE, CHLORO-
• ETHER CHLORATUS
• ETHER HYDROCHLORIC
• ETHER MURIATIC
• Ethyl Chloride
• ETYLU CHLOREK [Polish]
• HSDB 533
• Hydrochloric ether
• Kelene
• Monochlorethane
• Monochloroethane
• Muriatic ether
• Narcotile
• NCI-CO6224
• UN 1037