MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY
WATER BUREAU

TOXICOLOGICAL ASSESSMENT FOR CHLOROETHANE (CASRN 75-00-3) HUMAN CANCER VALUE (HCV)

Literature Review Date: May 12, 2008

Shannon Briggs

A review of the available literature on chloroethane (a.k.a., ethyl chloride) indicates only one study which adequately investigates carcinogenic potential. In this study, NTP (1989) administered chloroethane to groups of 50 B6C3F1 mice and F344/N rats of each sex for two years by inhalation. Clear evidence of carcinogenic activity was found for female mice, as indicated by an increased incidence of uterine carcinomas of endometrial origin. This tumor induction was high (43/50 versus 0/49 in controls) and the malignancy rate was high with invasion of the myometrium and metastasis to a wide variety of organs. The exposed groups of male and female rats had equivocal evidence of carcinogenic activity. The highly significant appearance of cancer in female mice at a site distant from the site of inhalation administration indicates that chloroethane is a systemic carcinogen with probable carcinogenic activity by oral exposure. A subsequent review of the results of the NTP (1989) study by Picut et al. (2003) supports the original findings of the NTP (1989) study. The quantitative oral cancer risk assessment of chloroethane utilizes the female mouse data and an estimation of systemic dose from the inhalation exposure. The Global 82 linear multistage model was used to derive a slope factor of 0.00200006 $(mg/kg/d)^{-1}$.

Reference:

NTP. 1989. Toxicology and Carcinogenesis Studies of Chloroethane in F344/N Rats and B6C3F1 Mice. U.S. DHHS. NTP T.R. #346.

Picut, C.A., H. Aoyama, J.W. Holder, L.S. Gold, R.R. Maronpot, and D. Dixon. 2003. Bromoethane, Chloroethane, and Ethylene Oxide Induced Uterine Neoplasms in B6C3F1 Mice from 2-year NTP Inhalation Bioassays: Pathology and Incidences Data Revisited. Exp. Toxicol. Pathol.55(1):1-9.

HUMAN CANCER VALUE WORKSHEET

Chemical Name: chloroethane CAS No. 75-00-3
Developed By: S. Briggs
Reviewed By: D. Bush Verification Date: 10/24/08

Key Study: NTP (1989) Toxicology and Carcinogenesis Studies of Chloroethane in F344/N Rats and B6C3F1 Mice. This study found a significant increase in carcinomas of the uterus (endometrial origin) in female mice exposed to 15,048 ppm (inhalation) for two years at 6 hours/day, 5 days per week. The study average dose is 9,650 mg/kg/d (see below).

$$\frac{15{,}048 \text{ ppm} \times (2.66 \text{ mg/m}^3\text{/ppm}) \times (0.054 \text{ m}^3\text{/d})^{*} \times (5/7 \text{ days}) \times 0.8^{**} \times (6/24 \text{ hrs})}{0.032 \text{ kg}} = 9{,}650 \text{ mg/kg/d}$$

* 0.054 m^3/d = daily ventilation rate derived from a weight-specific estimated ventilation from USEPA (1998-PB-179874)
** 0.8 = default absorption coefficient

Animal Weight	Adj. Ave. Dose	Tumors	Animals at Risk
0.032 kg	0	0	46
	9,650	43	49

Species scaling factor = $(70 \text{ kg}/ \text{ animal weight kg})^{1/4}$

Global 82
q = 95% upper confidence / MLE dose
q = 0.0000134386 / 0.04595127972
q = 0.000292453

q* = (q)(species scaling factor)
q* = $(0.000292453)(70\text{kg}/0.032 \text{ kg})^{1/4}$
q* = .00200006039 $(\text{mg/kg/d})^{-1}$

$$\text{RAD} = \frac{0.00001}{.00200006039} = 0.00499985 \text{ mg/kg/d}$$

$$\text{HCV}_{dw} = \frac{(0.00499985 \text{ mg/kg/d})\ (70 \text{ kg})}{2.0 \text{ l/d} + [(.0036 \text{ kg/d} \times 1.5 \text{ l/kg}) + (.0114 \text{ kg/d} \times 1.9 \text{ l/kg})]} = 0.173 \text{ mg/l}$$

170 ug/l

$$\text{HCV}_{non\text{-}dw} = \frac{(0.00499985 \text{ mg/kg/d})\ (70 \text{ kg})}{0.01 \text{ l/d} + [(.0036 \text{ kg/d} \times 1.5 \text{ l/kg}) + (.0114 \text{ kg/d} \times 1.9 \text{ l/kg})]} = 9.4438 \text{ mg/l}$$

9,400 ug/l

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TOXICOLOGICAL ASSESSMENT FOR CHLOROETHANE (CASRN 75-00-3) HUMAN NONCANCER VALUE (HNV)

Literature Review Date: May 12, 2008
Shannon Briggs

A review of the literature failed to reveal human or repeated-dose oral laboratory animal data which could be used for criteria derivation. The best available study was a chronic inhalation study in rats and mice conducted by NTP (1989). In this study, groups of F344/N rats and B6C3F1 mice (50 animals/sex/species) were exposed to 0 (chamber controls) or 15,000 ppm (nominal concentration) chloroethane. Actual mean concentrations were 15,051 ppm (rats) and 15,048 ppm (mice). Exposures were for 6 hrs/d, 5d/wk for 102 weeks (rats) or 100 weeks (mice).

NOAELs were not identified in this study. Treated rats of both sexes demonstrated significant depression of mean body weight. Their time-weighted-average (TWA) doses are estimated to be 5,400 and 5,800 mg/kg/d for males and females, respectively. The magnitude of the body weight suppression was in the range of 5-10% during weeks 45-102. A slight reduction in survival probability was also apparent in female rats during the last 20 weeks of the study.

The TWA doses to male and female mice are estimated to be 9,700 and 9,650 mg/kg/d, respectively. Treated female mice were observed to be hyperactive during exposures. Survival was reduced in exposed mice of both sexes, with the effect in female mice possibly related to tumor development. The incidence of nephropathy was marginally increased in exposed female mice and was characterized by scattered foci of tubular regeneration and minimal glomerulosclerosis. An increase in karyomegaly (mild) of renal tubular cells was noted in exposed male and female mice. Exposed male mice were also more prone to the development of non-neoplastic urogenital lesions.

In a short-term study, Landry et al. (1982) found that an increase in liver weight was the most sensitive endpoint following exposure to chloroethane. Longer term studies also found effects on the liver. For instance, NTP (1989) conducted a 13-week inhalation studies on rats and mice exposed to 2,500, 5,000, 10,000, and 19,000 ppm for 6 hrs/d, 5 d/wk. The 10,000 ppm level was a NOAEL in both species. This exposure level is estimated to be equivalent to a TWA dose of 4,000 mg/kg/d (rats) and 6,300 mg/kg/d (mice). The 19,000 ppm level (estimated TWA doses of 7,400 mg/kg/d for rats and 12,000 mg/kg/d for mice) resulted in significantly increased relative liver weights in male rats and female mice, and decreased body weights in male rats. In another study, Landry et al. (1989) exposed groups of 7 mice/sex to 250, 1,250, or 5,000 ppm chloroethane for 23 hrs/d, for 11 consecutive days. Mild liver effects (increase in the mean relative liver weight in both sexes and minimal hepatocellular vacuolization) were reported at the 5,000 ppm level (estimated TWA dose of 9,600 mg/kg/d).

A developmental study was conducted on mice by Scortichini et. al. (1986). In this study, groups of 50 CF-1 pregnant mice were exposed for 6 hrs/d to chloroethane during days 6 through 15 of gestation to TWA concentrations of 0 (air), 491±37 ppm (1.3 g/m^3), 1,504±84 ppm (4,000 mg/m^3), and 4,946±159 ppm (13,000 mg/m^3). Animals were sacrificed on the 18th day of gestation. Results showed no exposure-related changes in resorption rate, litter size, sex ratios, fetal body weights, or malformations of fetal viscera. Fetuses of dams exposed to 4,946 ppm had significant increases in the incidence of foramina of skull bones (small area of delayed ossification). At this concentration, 5 fetuses were affected in a total of 5 litters (4% incidence) vs. 1 fetus in 1 litter in controls and each lower exposure group. The historical incidence of foramina of skull bones in CF-1 mice in this laboratory is 0.2% (0 to 1.2%). EPA (1998) concluded that the concentration of 4,000 mg/m^3 (1,504 ppm) was a NOAEL. The concentration of 13,000 mg/m^3 (4,946 ppm) was considered a LOAEL based on foramina of the skull bones. EPA used the NOAEL of 4,000 mg/m^3 with an uncertainty factor of 300 (10x for each intraspecies and interspecies extrapolation) to derive an RfC for chloroethane.

No oral studies suitable for criteria development were found in the literature. The LOAEL of 15,051 ppm (5,400 mg/kg/d) found for male rats in the NTP (1989) study, instead of the NOAEL found in the Scortichini et al. (1986) study, was used to derive the HNV because the NTP (1989) study was longer in duration and it examined more endpoints. This approach would be expected to protect for the developmental effects found in the Scortichini et al. (1986) study because the LOAELs from the two studies are comparable. Uncertainty factors of 10x were used for each interspecies and intraspecies extrapolation. An additional 3x was used to extrapolate from a LOAEL with minimal effects (5 to 10% weight gain depression) to a NOAEL.

References:

Landry, T.D., et al. 1982. Ethyl chloride: a two-week inhalation toxicity study and effects on liver non-protein sulfhydryl concentrations. Fund. Appl. Tox. 2:230-234.

Landry, T.D., et al. 1989. Ethyl chloride: 11-day continuous exposure inhalation toxicity study in B6C3F1 mice. Fund. Appl. Tox. 13:516-522.

NTP. 1989. Toxicology and Carcinogenesis Studies of Chloroethane (Ethyl Chloride) In F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP TR No. 346.

Scortichini, B.H., et. al. 1986. Ethyl chloride: Inhalation Teratology Study in CF-1 Mice. Dow Chemical Co. EPA Document #86-870002248.

U.S. EPA. 2008. Integrated Risk Information System (IRIS database) Substance File on Ethyl Chloride (75-00-3), last revised on 4/1/1991 for inhalation assessment and 1/1/1995 for carcinogenicity assessment.

HUMAN NONCANCER VALUE WORKSHEET

Chemical Name: chloroethane CAS No. 75-00-3
Developed By: S. Briggs
Reviewed By: D. Bush Verification Date: 10/24/08

Key Study: NTP (1989) reported a chronic rat inhalation LOAEL of 15,051 ppm based on decreased body weight; an estimated dose for male rats is equal to 5,400 mg/kg/d (see below).

$$\frac{15{,}051 \text{ ppm} \times (2.66 \text{ mg/m}^3\text{/ppm}) \times (0.4 \text{ m}^3\text{/d})^{*} \times (5/7 \text{ days}) \times 0.8^{**} \times (6/24 \text{ hrs})}{0.425 \text{ kg}} = 5{,}400 \text{ mg/kg/d}$$

* 0.4 m^3/d = inhalation rate per USEPA (1998-PB-179874)
** 0.8 = default absorption coefficient

UF = 10x for each interspecies, intraspecies and 3x for LOAEL to NOAEL extrapolation based on a 5 to 10% decrease in weight gain in male rats.

ADE = 18 mg/kg/d $\quad$ ADE = $\frac{5400 \text{ mg/kg/d}}{300}$

drinking water

$$\text{HNV} = \frac{(18 \text{ mg/kg/d}) \quad (70 \text{ kg}) \quad (0.8)}{(2 \text{ L/d}) + (0.0036 \text{ kg/d} * 1.5 \text{ L/kg}) + (0.0114 \text{ kg/d} * 1.9 \text{ L/kg})} = 497.272 \text{ mg/L}$$

Human Noncancer Value for drinking water = 500 mg/L

non-drinking water

$$\text{HNV} = \frac{(18 \text{ mg/kg/d}) \quad (70 \text{ kg}) \quad (0.8)}{(0.01 \text{ L/d}) + (0.0036 \text{ kg/d} * 1.5 \text{ L/kg}) + (0.0114 \text{ kg/d} * 1.9 \text{ L/kg})} = 27{,}199 \text{ mg/L}$$

Human Noncancer Value for non-drinking water = 27,000 mg/L