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Toxicological Summary for: Trichloroethylene (TCE)

CAS: 79-01-6

Synonyms: TCE, Trichloroethene, 1,1,2-Trichloroethene, 1,1-Dichloro-2-Chloroethylene, 1-Chloro-2,2-Dichloroethylene

Acute Non-Cancer Health Based Value (nHBV_{Acute}) = Not derived. Acute exposures have produced toxicity at very high exposures, but those studies were not used to derive an nHBV_{Acute} (see EPA IRIS 2011 for further study detail). The Johnson et al. 2003 study was not used to calculate an nHBV_{Acute} due to multiple TCE exposures over a 22-day period. Based on the available information, there is confidence that short-term and chronic HBVs are protective of potential acute effects from exposure to TCE; however data is not currently available to derive a 1-hour benchmark value.

Short-term Non-Cancer Health Based Value (nHBV_{Short-term}) = 2 µg/m³

The short-term value is protective for a 24-hour to 30-day exposure durations.

$$= \frac{\text{(Point of Departure (POD), mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(0.021 mg/m}^3\text{)}}{\text{(10)}}$$

$$0.0021 \text{ mg/m}^3 = 2.1 \text{ µg/m}^3$$

Reference Concentration: $\text{POD/Total UF} = 0.021 \text{ mg/m}^3 / 10 = 0.0021 \text{ mg/m}^3 = 2.1 \text{ µg/m}^3$ (Sprague-Dawley rats)

Source of toxicity value: EPA IRIS 2011 calculated from Johnson et al., 2003

Point of Departure: HEC_{99,BMDL01} (99th percentile for human equivalent concentration, benchmark dose level 1% extra risk) = 0.021 mg/m³. The HEC_{99,BMDL01} is the physiologically-based pharmacokinetic (PBPK) model-derived route-to-route extrapolated 99th percentile HEC to the rat internal lower bound benchmark dose BMDL₀₁ of 0.0142 mg TCE metabolized by oxidation/kg^{3/4}/day, based on fetal heart malformations.

Dose Adjustment Factor (DAF): Route-to-route extrapolation using PBPK model; (EPA IRIS 2011)

Human Equivalent Concentration: HEC₉₉ = 0.021 mg/m³ EPA derived (EPA IRIS 2011)

Total uncertainty factor: 10
 Uncertainty factor allocation: 3 for interspecies variability (to address toxicodynamic concerns)
 3 for intraspecies variability (to address toxicodynamic concerns)
 Critical effect(s): fetal cardiac malformations

The short-term TCE HBV is protective of sensitive receptors (people) that are affected by shorter than chronic health risks from TCE. Women of childbearing age who may become pregnant and women in the first eight weeks of pregnancy are likely the most sensitive group based on TCE's potential to cause toxicity in short-term exposures.

Subchronic Non-Cancer Health Based Value (nHBV_{Subchronic}) = nHBV_{Short-term} = 2 µg/m³

Subchronic studies were not used to calculate an nHBV_{Subchronic}, as these studies were found to be unacceptable or produced values greater than the nHBV_{Short-term}. Therefore, as short-term exposures occur within the subchronic duration, the nHBV_{Subchronic} is set equal to the nHBV_{Short-term}.

Chronic Non-Cancer Health Based Value (nHBV_{chronic}) = 2 µg/m³

$$= \frac{(\text{POD}, \text{mg}/\text{m}^3)}{(\text{UF})}$$

$$= \frac{(0.19 \text{ mg}/\text{m}^3)}{(100)}$$

$$= 0.0019 \text{ mg}/\text{m}^3 = 1.9 \text{ µg}/\text{m}^3$$

Reference Dose/Concentration: 0.19 mg/m³/100 = 0.0019 mg/m³ = 1.9 µg/m³ (female B6C3F1 mice)

Source of toxicity value: Keil et al. 2009; EPA IRIS 2011

Point of Departure: HEC_{99,LOAEL} (lowest observed adverse effect level) of 0.19 mg/m³. The HEC_{99,LOAEL} is the route-to-route extrapolated 99th percentile HEC to the mouse LOAEL of 0.35 mg/kg/day, using the internal dose metric of TCE metabolized/kg^{3/4}/day. BMD modeling could not be used due to inadequate model fit caused by supralinear dose-response shape.

Human Equivalent Concentration: HEC₉₉ = 0.19 mg/m³ EPA IRIS derived; (EPA IRIS 2011)

Total uncertainty factor: 100

Uncertainty factor allocation: 3 for interspecies variability; 3 for intraspecies variability; 10 for the use of a LOAEL POD.

Critical effect(s): decreased thymus weight (immune effects)

Cancer Health Based Value (cHBV) = 2 µg/m³

$$= \frac{\text{(Additional Lifetime Cancer Risk)}}{\text{(Inhalation Unit Risk* x } (\mu\text{g/m}^3)^{-1}\text{)}}$$

$$= \frac{(1\text{E}^{-5})}{6.78 \times 10^{-6} (\mu\text{g/m}^3)^{-1}}$$

$$1.5 \mu\text{g/m}^3 = 2 \mu\text{g/m}^3^{**}$$

*MDH derived an inhalation unit risk for each cancer site using age-adjustment factors for each kidney, non-Hodgkin lymphoma (NHL), and liver cancer and summed them for a total unit risk. These inhalation risk units assumes an individual is exposed to 1 µg/m³ in air from birth through age 70 years resulting in a lifetime unit risk of 6.78 x 10⁻⁶ per µg/m³.

**An MDH programmatic decision was made to establish the cHBV at 2 ug/m³.

Cancer classification: Carcinogenic to humans by all routes of exposure (EPA IRIS 2011); EPA has concluded that trichloroethylene is carcinogenic by a mutagenic mode of action. Application of ADAFs to the inhalation unit risk is recommended in combination with appropriate exposure data when assessing risk associated with early-life exposure.

Inhalation Unit Risk: Based on kidney cancer, liver cancer, non-Hodgkin lymphoma; human occupational study (Charbotel et al. 2006 and Raaschou-Nielsen et al. 2003)

Source of Inhalation Unit Risk: EPA IRIS 2011

Tumor site(s): Hematologic, Hepatic, Renal

Volatile: Yes (high)

Summary of Guidance Value History:

- Updated HBVs were calculated in 2018. The short-term, subchronic, and chronic durations, as well cancer guidance values, are all equal to 2 micrograms TCE per cubic meter of air (2 µg/m³). No HBV was derived for acute duration exposures. These values replace the previous MDH Risk Assessment Advice (RAA).
- In 2013, MDH released RAA for TCE in air at a level of 2 µg/m³.
- In 2002, an acute Health Risk Value (HRV) was promulgated for TCE based on developmental and reproductive effects. MDH no longer supports use of this HRV for the protection of public health.

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? | No ¹ | Yes | Yes | Yes | Yes | Yes |
| Effects observed? | Yes | Yes ² | Yes ³ | Yes ⁴ | Yes ⁵ | Yes ⁶ |

Comments on extent of testing or effects:

¹Studies directly investigating endocrine disrupting effects of TCE are not available; however, studies evaluating reproductive parameters provide some insight and evidence of endocrine effects resulting from TCE exposure (approximately 160,000 µg/m³) orders of magnitude greater than the 2018 HBV (2 µg/m³). EPA IRIS 2011 page 4-469, table 4-85 reports two occupational studies for altered endocrine function.

²Immune effects (decreased thymus weight in mice; Keil et al. 2009) were the chronic exposure endpoint for one of two critical studies for the developmental of the reference concentration (RfC). Several subchronic immune studies were evaluated for potential use in the RfC dose assessment. A developmental immunotoxicity study (Peden-Adams et al. 2006) resulted in decreased plaque-forming cell response and increased delayed-type hypersensitivity in mice and was used as a critical study for the deriving a TCE reference dose (EPA IRIS 2011) and MDH’s TCE water Health Risk Limit.

³The short-term reference concentration (Johnson et al. 2003) is based on developmental toxicity in rats (fetal cardiac malformation). The study author reported that significant increases in the percentage of abnormal hearts and the percentage of litters with abnormal hearts were observed in a generally dose-responsive manner. TCE developmental studies in humans examined the relationship between TCE exposure and prenatal developmental outcomes including spontaneous abortion and perinatal death; decreased birth weight, small for gestational age, and postnatal growth; congenital malformations; and other adverse birth outcomes (summarized in Table 4-95 EPA IRIS 2011).

⁴A number of human reproductive studies have been conducted that examined the effects of TCE on male and female reproduction following occupational and community exposures. These are briefly described here and summarized in Table 4-85 (EPA IRIS 2011). Epidemiological studies of female human reproduction examined infertility (reduced incidence of fecundability) and menstrual cycle disturbances (abnormal cycle, amenorrhea, lack of ovulation) related to TCE exposure orders of magnitude higher than the HBV. Occupational epidemiological studies of male reproductive effects reported decreased potency, sexual disturbances, gynaecomastia, impotence, altered sperm quality, and infertility at doses orders of magnitude greater than the HBV.

⁵The strongest neurological evidence of hazard in humans is for changes in trigeminal nerve function or morphology and impairment of vestibular function. Fewer and more limited evidence exists in humans on delayed motor function and changes in auditory, visual, and cognitive function or performance. Acute and subchronic animal studies show morphological changes in the trigeminal nerve, disruption of the peripheral auditory system leading to permanent function impairments and histopathology,

changes in visual evoked responses to patterns or flash stimulus, and neurochemical and molecular changes.

⁶TCE oxidative metabolism has been demonstrated to play a main role in TCE pulmonary toxicity in rodents. Clara cells are thought to be the cell type responsible for much of the CYP metabolism in the lung. Therefore, damage to this cell type would be expected to also affect metabolism. Laboratory studies in mice and rats have shown toxicity in the bronchial epithelium, primarily in Clara cells, following acute exposures to TCE by inhalation (see EPA IRIS 2011 Section 4.7.2.1.1). A few studies of longer duration have reported more generalized toxicity, such as pulmonary fibrosis in mice and pulmonary vasculitis in rats. Acute pulmonary toxicity appears to be dependent on oxidative metabolism, although the particular active moiety is not known. Two reports of a study of gun manufacturing workers reported asthma-related symptoms and lung function decrements associated with solvent exposure, but these studies are limited by multiple solvent exposures and the significant effect of smoking on pulmonary function.

Resources Consulted During Review:

Agency for Toxic Substances and Disease Registry. 2014. Draft Toxicological Profile for Trichloroethylene. <https://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

Minnesota Department of Health (MDH). 2010. Risk Assessment Advice for Incorporating Early-Life Sensitivity into Cancer Risk Assessments for Linear Carcinogens (July 2010). Retrieved from <http://www.health.state.mn.us/divs/eh/risk/guidance/adafrecmd.pdf>

US EPA. 2005. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. U.S. Environmental Protection Agency, Washington, DC, (EPA/630/R-03/003F) https://www3.epa.gov/airtoxics/childrens_supplement_final.pdf

US EPA Integrated Risk Information System (IRIS). 2011. Toxicological Review of Trichloroethylene (CAS No. 79-01-6). EPA/635/R-09/011F. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf

US EPA Integrated Risk Information System (IRIS). 2011. Trichloroethylene Chemical Assessment Summary. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0199_summary.pdf

US EPA Response to Halogenated Solvents Industry Alliance. March 2015. <https://www.epa.gov/sites/production/files/2015-10/documents/14001-response.pdf>

US EPA Response to Halogenated Solvents Industry Alliance. February 2016. https://www.epa.gov/sites/production/files/2016-03/documents/14001a-response_0.pdf