Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: November 2015

Toxicological Summary for: Trichloroethylene (TCE)

CAS: **79-01-6**

Synonyms: 1,1,2-Trichloroethene, 1,1-Dichloro-2-Chloroethylene, 1-Chloro-2,2-Dichloroethylene, Acetylene Trichloride, TCE, Trethylene, Triclene, Tri, Trimar, Trilene

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived

The study design of the key study evaluated for the acute duration was insufficient for derivation of an RfD. Based on the available information, there is confidence that short-term and subchronic HRLs are protective of acute developmental effects from exposure to TCE.

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 0.4 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.00052 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 0.36 rounded to **0.4 µg/L**

Reference Dose/Concentration:	0.00052 mg/kg-d (laboratory animals)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	0.37 mg/kg-d (LOAEL, Peden-Adams et al. 2006)
Human Equivalent Dose (MDH 2011):	0.37 x 0.14 = 0.052 mg/kg-d (MDH 2011)
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics), 10 for intraspecies variability, 3 for use of a minimal LOAEL instead of a NOAEL
Critical effect(s):	Immune effects (impacts on humoral function and splenic T-cells observed in a developmental immune study)
Co-critical effect(s):	Fetal heart malformation
Additivity endpoint(s):	Developmental, Immune system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 0.4 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.00017 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 0.44 rounded to **0.4 µg/L**

Reference Dose/Concentration:	0.00017 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	0.37 mg/kg-d (LOAEL, Peden-Adams et al. 2006)
Human Equivalent Dose (MDH 2011):	0.37 x 0.14 = 0.052 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics), 10 for intraspecies variability, 10 for use of a LOAEL instead of a NOAEL
Critical effect(s):	Immune effects (impacts on thymic T-cells, suppression of PFC response, delayed hypersensitivity response observed in a developmental immune study)
Co-critical effect(s):	Fetal heart malformations
Additivity endpoint(s):	Developmental; Immune system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = Subchronic $nHRL_{Subchronic}$ = 0.4 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.00017 mg/kg/d)}^{**} \text{ x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 0.79 rounded to **0.8 µg/L**

**See the subchronic information above for more details about the reference dose

The Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the acute, short-term, and subchronic periods and therefore, the Chronic nHRL is set equal to the Short-term and Subchronic nHRL of 0.4 µg/L. The Additivity Endpoints are: Developmental, Immune system.

Cancer Health Risk Limit (cHRL) = 2 µg/L

$$= \frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.05 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.05 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.05 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= **2 µg/L**

Cancer Classification:	Carcinogenic to humans by all routes of exposure based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer and some human evidence of TCE carcinogenicity in the liver and lymphoid tissues. This conclusion is further supported by rodent bioassay data indicating carcinogenicity of TCE in

rats and mice at tumor sites that include those identified in human epidemiologic studies."

Slope factor: 0.05 (human) (Charbotel et al. 2006)

Source of slope factor: EPA 2011

Tumor site(s): Kidney, Liver, Non-Hodgkin's Lymphoma

Volatile: Yes (high)

Summary of Guidance Value History:

Updated Health-Based Values (HBVs) were calculated in 2013. The 2013 HBVs were adopted into rule as HRLs in 2015. The 2015 short-term, subchronic, and chronic HRLs (0.4 µg/L) are approximately 12 times lower than Maximum Contaminant Level (MCL)-based HRL of 5 µg/L as the result of: 1) use of more recent intake rates which incorporate higher intake rates during early life, 2) a 20 to 70-fold decrease in the RfD value, and 3) rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes – Secondary Observations	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1] Studies explicitly evaluating endocrine effects of TCE have not been conducted. Secondary observations in studies designed to evaluate reproductive parameters provide limited evidence of endocrine effects. A limited number of epidemiological studies have reported effects such as decreased levels of testosterone and abnormal menstrual cycles.

Decreased testosterone and abnormal menstrual cycles have been evaluated in animals studies, and these effects, like those above reported in humans, occur at levels >1000-fold higher than the short-term, subchronic and chronic RfDs. Therefore, it is likely that the Short-term, Subchronic and Chronic HBVs are protective of these effects.

[2] Human and animal studies provide strong evidence that TCE plays a role in autoimmune disease and hypersensitivity. There is also some evidence that TCE may play a role in immunosuppressive effects although the evidence for these effects is weaker. Immune-related effects observed in human and animals studies are not limited to diseases but also involve organs and tissues within the immune system. Immune effects provide the basis of the RfDs (0.00017 – 0.00052 mg/kg-d) for the short-term, subchronic, and chronic durations.

[3] A number of developmental outcomes have been observed in animal and human studies following inhalation and oral exposure to TCE. Some of the adverse developmental effects that have been

observed in these studies included: spontaneous abortion, perinatal death, pre- or post-implantation loss, increased resorptions, low birth weight and decreased postnatal growth, and congenital malformations and fetal cardiac defects in particular. Fetal cardiac malformations (Johnson et al. 2003) were identified as a sensitive effect in the recent EPA IRIS Toxicological Review (2011). The RfDs derived by MDH (0.00017 mg/kg-d – 0.00052 mg/kg-d) that are based on immune effects are 90-300 times lower than LOAEL reported in the Johnson et al. 2003 and are therefore considered to be protective of fetal cardiac malformations.

[4] There is consistent evidence in animal and human studies that exposure to TCE is associated with adverse reproductive effects in males and females. A limited number of epidemiological studies have reported effects such as decreased levels of testosterone and abnormal menstrual cycles at exposure levels >1000-fold higher than the short-term, subchronic and chronic RfDs. Reproductive studies in laboratory animals have evaluated effects on sperm, fertility, reproductive organs, and parturition. These effects, like those above reported in humans also occurred at levels >1000-fold higher than the short-term, subchronic and chronic RfDs.

[5] TCE is associated with a variety of neurological effects in both animal and human studies. Most neurological effects associated with TCE were observed in inhalation studies but some neurological effects have also been observed following oral exposure to the TCE. The strongest evidence of neurological effects in human resulting from exposure to TCE is for changes in trigeminal nerve function or morphology and impairment of vestibular functions (includes symptoms such as headaches, dizziness, and nausea). There is more limited evidence that TCE may cause delayed motor function, changes in auditory, visual, and cognitive function or performance. The lowest HED99 dose levels for neurological effects range from 3.5 mg/kg-d (developmental neurotoxicity in mice) to 7.3 mg/kg-d (trigeminal nerve effects in humans). The RfDs derived by MDH (0.00017 – 0.00052 mg/kg-d) are >6700-fold lower and are therefore protective of neurological effects observed in inhalation and oral animal and human studies.

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