Toxicological Summary for Tris(2-chloroethyl)phosphate: CAS: 115-96-8

Synonyms: TCEP; Tris(chloroethyl)phosphate; 2-Chloroethanol phosphate; Phosphoric acid, tris(2-chloroethyl)ester; Tri(2-chloroethyl)phosphate; Trichloroethylene phosphate; Tris(2-chloroethyl)orthophosphate; Ethanol, 2-chloro-, phosphate (3:1)

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

Due to limited information, no acute guidance value is derived. Based on the available information, the short-term HRL for TCEP is also protective of potential developmental effects.

Short-Term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 300 µg/L

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

$$= \frac{\text{(0.15 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 259 rounded to **300 µg/L**

Reference Dose / Concentration:	0.15 mg/kg-d (rat, Fischer 344/N)
Source of toxicity value:	(MDH, 2011)
Point of Departure:	66 mg/kg-d (time-adjusted NOAEL - Matthews et al. 1990; NTP 1991a) with a time-adjusted LOAEL of 125 mg/kg-d.
Human Equivalent Dose Adjustment:	66 x 0.22 = 14.5 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address uncertainty regarding toxicodynamics (toxicokinetic portion addressed by HED), 10 intraspecies variability, 3 database insufficiencies (absence of adequate multigenerational developmental study)
Critical effect(s):	Increased absolute and relative kidney weights in male rats, decreased serum cholinesterase
Co-critical effect(s):	Decreased number of male pups per litter
Additivity endpoint(s):	Renal (kidney) system, Nervous system, Developmental

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = 200 µg/L

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

(Subchronic intake rate, L/kg/d)

$$= \frac{(0.068 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ µg/mg})}{(0.077 \text{ L/kg-d})}$$

= 177 rounded to **200 µg/L**

Reference Dose / Concentration:	0.068 mg/kg-d (rat, Fischer 344/N)
Source of toxicity value:	(MDH, 2011)
Point of Departure:	31 mg/kg-d (time-adjusted NOAEL; NTP 1991a, EPA PPRTV 2009)
Human Equivalent Dose Adjustment:	31 x 0.22 = 6.8 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address uncertainty regarding toxicodynamics (toxicokinetic portion addressed by HED), 10 intraspecies variability, 3 database insufficiencies (absence of adequate multigenerational developmental study)
Critical effect(s):	Increased kidney weights
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = Subchronic nHRL = 200 µg/L

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

$$= \frac{(0.067 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ µg/mg})}{(0.043 \text{ L/kg-d})}$$

= 311 rounded to 300 µg/L

Reference Dose / Concentration:	0.067 mg/kg-d (rat, Fischer 344/N)
Source of toxicity value:	(MDH, 2011)
Point of Departure:	25.8 mg/kg-d ($BMDL_{10}$adj; NTP 1991a and Matthews et al. 1993, BMD modeling by ATSDR 2009)
Human Equivalent Dose Adjustment:	25.8 x 0.26 = 6.7 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address uncertainty regarding toxicodynamics (toxicokinetic portion addressed by HED), 10 intraspecies variability; 3 database insufficiencies (absence of adequate multigenerational developmental study
Critical effect(s):	Renal tubule hyperplasia
Co-critical effect(s):	Regenerative renal cell proliferation including hyperplasia and hypertrophy of urinary tubule epithelium and nuclei enlargement.
Additivity endpoint(s):	Renal (kidney) system

The Chronic nHRL must be protective of shorter term exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Subchronic nHRL of 200 µg/L. Additivity endpoints: Renal (kidney) system

Cancer Health Risk Limit (cHRL) = **5 µg/L**

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

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.02 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.02 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.02 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 5.1 rounded to **5 µg/L**

Cancer classification:	Likely to be Carcinogenic to Humans (EPA PPRTV 2009) IARC Group 3 – not classifiable as to its carcinogenicity to humans (IARC 1999)
Slope factor:	0.02 $(mg/kg\text{-}d)^{-1}$(laboratory animal) (NTP 1991a)
Source of slope factor:	EPA PPRTV 2009
Tumor site(s):	Kidney

Volatile: No (low volatile)

Summary of changes since 1993/1994 HRL promulgation:
There was no 1993/1994 HRL promulgated for TCEP. Health-Based Values (HBVs) were derived in 2011. The HBVs were adopted into rule as HRLs in 2013.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	No	Yes	Yes	Yes
Effects?	No[1]	No[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. Endocrine parameters generally consisted of organ weights and gross and microscopic pathology of endocrine glands (thyroid, pituitary, adrenals). No alterations of these parameters were found in rats or mice for TCEP. No studies were available regarding effects on thyroid or sex hormones or endocrine function. In vitro studies were negative for estrogenic activity measured by reporter gene expression in yeast cells. TCEP also did not show estrogenic or anti-estrogenic activity in human endometrial cancer

cells. TCEP was shown to decrease sperm concentration and motility and increase numbers of abnormal sperm in rats. Reproductive effects that may be related to sperm effects occurred at dose levels > 600-fold higher than the short-term, subchronic, and chronic RfDs. TCEP had no effect on estrous cycle in rats.

2. TCEP has not been tested directly for immunotoxicity. Gross and microscopic evaluation of thymus, spleen and lymph nodes during toxicity studies did not reveal treatment-related alterations of immune system organs. TCEP was not a skin sensitizer in animal studies (EU 2009).

3. In general, exposure of rodents during gestation to TCEP did not result in adverse developmental effects to the fetuses or newborn animals; however, an adequate multigeneration study has not been performed. Malformations or behavioral effects in offspring were not found, even at overtly maternally-toxic doses. However, in a continuous breeding protocol reproductive study, there was a change in sex ratio in births occurring in the second generation of exposed mice and there was a reduction in the number of live pups per litter in the first generation. The effects on sex ratio occurred at dose levels >150-fold higher than the short-term, subchronic, and chronic RfDs.

4. Continuous exposure of two generations of mice to TCEP reduced fertility which was reported to be primarily related to alterations in sperm concentration, motility and abnormalities. There was a reduction in the number of litters, the number of live pups per litter and the number of pairs delivering a 5^{th} litter. Reproductive effects related to reduced fertility occurred at dose levels >200-fold higher than the short-term, subchronic, and chronic RfDs.

5. TCEP affected the nervous system in acute, intermediate and chronic exposure studies. In rats, TCEP has produced adverse neurological effects including morphological and behavioral effects. Brain lesions in rat studies included degenerative lesions including necrosis with hemorrhage, necrosis with loss of neurons in hippocampus, thalamic necrosis, and benign granular cell tumors. Very high oral doses of TCEP caused inhibition of serum cholinesterase in rats and plasma cholinesterase and brain neuropathy target esterase in hens, but did not produce delayed neurotoxicity. In rats, a high dose of TCEP caused ataxia, convulsions, hyperactivity, brain lesions and impaired performance in a water maze. The nervous system was identified as a critical endpoint for the short-term durations. Nervous system effects occurred at doses approximately >400-fold higher than the subchronic and chronic RfDs.

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