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

Adopted as Rule: November 2023

Toxicological Summary for: Tris - (1,3 - dicholorisopropyl) phosphate

CAS: **13674-87-8**

Synonyms: Tris(1,3-dichloro-2-propyl)phosphate; Tri[2-chloro-1-(chloromethyl)ethyl] phosphate; Fyrol FR 2; TDCPP; TDCP

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 20 µg/L

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

$$= \frac{\text{(0.0067 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 18 rounded to **20 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0067 mg/kg-d (mice)
Source of toxicity value:	MDH, 2013
Point of Departure:	15 mg/kg-d (NOAEL from 3 month dietary study by Kamata et al 1989)
Human Equivalent Dose (MDH, 2011):	15 x 0.13 = 2.0 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects)
Critical effect(s):	Increased liver and kidney weights
Co-critical effect(s):	None

Additivity endpoint(s): Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = 8 µg/L

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

$$= \frac{\text{(0.0019 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 8.4 rounded to **8 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0019 mg/kg-d (rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	1.94 mg/kg-d ($BMDL_{10\%}$ calculated by ATSDR 2012 based on renal tubule epithelial hyperplasia reported in Bio/dynamics 1981)
Human Equivalent Dose (MDH, 2011):	1.94 x 0.29 = 0.56 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects)
Critical effect(s):	Renal tubule epithelial hyperplasia and seminal vesicle atrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system; Male reproductive system

Cancer Health Risk Limit (cHRL) = 0.8 µg/L

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

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.13 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (0.13 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (0.13 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= 0.764 rounded to **0.8 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Cancer classification:	Has not been classified by US EPA Probable human carcinogen (Consumer Product Safety Commission 2006) Identified under Proposition 65 as a chemical known to cause cancer (CalEPA 2012)
Slope factor:	0.13 per mg/kg-d (2 year dietary study in rats, Freudenthal and Henrich 2000)
Source of slope factor:	CalEPA 2012
Tumor site(s):	Liver, kidney and testes

Volatile: **No**

Summary of Guidance Value History:

Guidance values for TDCPP were developed in 2013. In 2021 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a change in the chronic duration water guidance value from 9 µg/L to 8 µg/L. In November 2023, the guidance values were adopted into Minnesota Rules, 4717.7860, as Health Risk Limits (HRLs).

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	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] A recent epidemiological study reported significant associations between serum prolactin and free T4 levels and TDCPP levels in household dust. However, study limitations preclude drawing conclusions from these observations. Oral toxicity studies in laboratory animals have mainly been limited to organ weights and histological assessments. Chronic exposure resulted in effects on male reproductive organs and increased thyroid weights at higher doses (> 2,600-fold higher than the chronic RfD). Hormonal measurements, however, were not taken. Studies conducted *in vitro* and in zebrafish demonstrate that TDCPP affects steroidogenesis, acts as an estrogen receptor antagonist and alters thyroid hormone concentrations. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding endocrine activity.

[2] Oral studies of immunological effects have been limited to measurements of thymus and spleen organ weights which do not appear to be sensitive endpoints. However, a 4 day subcutaneous injection study reported changes in immune function. In addition immune effects have been observed following exposure to other triphosphate flame retardants. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate oral toxicity dataset regarding immunological assessment.

[3] Oral mammalian developmental studies are limited. No multigeneration studies have been conducted. Two developmental studies reported increased incidence of fetal death as dose levels resulting in maternal toxicity. These dose levels were more than 3000-fold higher than the subchronic and chronic RfDs.

[4] Male reproductive organ effects were observed at the lowest dose tested in a 2 year dietary study in rats. These effects, in part, form the basis of the chronic RfD. Oral studies regarding functional reproductive effects are limited. No multigeneration studies have been conducted. Female reproductive effects have not been adequately assessed. Effects on male reproductive ability were not observed in a 12 week study in rabbits. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding reproductive toxicity.

[5] Oral studies regarding neurotoxicity are limited. A 2 year dietary study did not report clinical signs or morphological changes in the brain. Changes in red blood cell cholinesterase were measured but were inconsistent throughout the study. No developmental neurobehavioral effects were reported following *in utero* exposure but data reporting in that particular study were limited. Studies on other structurally related chemicals suggest the need for additional studies. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding neurological assessment.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). (2012). Toxicological Profile for Phosphate Ester Flame Retardants. from http://www.atsdr.cdc.gov/ToxProfiles/tp202.pdf

Australian Government Department of Health and Aging: National Industrial Chemicals Notification and Assessment Scheme (NICNAS). (2001). Triphosphates: Priority Existing Chemical (PEC) Assessment Report No. 17.

Australian Guidelines- Natural Resource Management Ministerial Council; Environmental Protection and Heritage Council; and National Health and Medical Research Council. (2008). Augmentation of Drinking Water Supplies. from http://nepc.gov.au/system/files/resources/5fe5174a-bdec-a194-79ad-86586fd19601/files/wq-agwr-gl-adws-corrected-final-200809_1.pdf

California Environmental Protection Agency (CalEPA) - Office of Environmental Health Hazard Assessment (OEHHA). (2011). Evidence on the Carcinogenicity of Tris(1,3-dichloro-2-propyl)phosphate. from http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf

California Environmental Protection Agency (CalEPA) - Office of Environmental Health Hazard Assessment (OEHHA). (2012). Proposition 65. Initial Statement of Reasons. Proposed Amendment to Specific Regulatory Levels Posing No Significant Risk. Tris (1,3-Dichloro-2-Propyl) Phosphate. from https://oehha.ca.gov/media/060112TDCPPISOR.pdf

Consumer Product Safety Commission. (2006). Staff Preliminary Risk Assessment of Flame Retardant (FR) Chemicals in Upholstered Furniture Foam., from https://www.cpsc.gov/content/CPSC-Staff-Preliminary-Risk-Assessment-of-Flame-Retardant-FR-Chemicals-in-Upholstered-Furniture-Foam-December-2006

Dishaw LV, CM Powers, IT Ryde, SC Roberts, FJ Seidler, TA Slotkin, et al. (2011). Is the PentaBDE replacement, tris (1,3-dichloropropyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. *Toxicology and Applied Pharmacology, 256*, 281-289.

European Commission. (2008). European Union Risk Assessment Report: Tris[2-Chloro-1-(Chloromethyl)ethyl]phosphate (TDCP). CAS No: 13674-87-8. from https://echa.europa.eu/documents/10162/13630/trd_rar_ireland_tccp_en.pdf/315063b0-593d-4703-9519-562c258506e6

Freudenthal RI and RT Henrich. (2000). Chronic Toxicity and Carcinogenic Potential of Tris-(1,3-

Dichloro-2-propyl) Phosphate in Sprague-Dawley Rat. *International Journal of Toxicology, 19*, 119-125.

Kamata E, K Naito, Y Nakaji, Y Ogawa, S Suzuki, T Kaneko, et al. (1989). Acute and subacute toxicity studies of Tris (1,3-dichloro-2-propyl) Phosphate on Mice. *Bull Natl Inst Hyg Sci, 107*, 36-43.

Kawashima K, S Tanaka, S Nakaura, S Nagao, T Endo, K Onoda, et al. (1983). Effect of phosphoric acid tri-esters flame retardants on the prenatal and postnatal developments of the rats. *The Japanese Society of Toxicology, 8*(1), 339.

Liu X, K Ji, & K Choi. (2012). Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and zebrafish. *Aquatic Toxicology, 114-115*, 173-181.

Luster MI, JH Dean, GA Boorman, DL Archer, L Lauer, LD Lawson, et al. (1981). The Effects of Orthophenylphenol, Tris(2,3-dichloropropyl) Phosphate, and Cyclophosphamide on the Immune System and Host Susceptibility of Mice following Subchronic Exposure. *Tox Appl Tox, 58*, 252-261.

McGee SP, EM Cooper, HM Stapleton, & DC Volz. (2012). Early Zebrafish Embryogenesis Is Susceptible to Developmental TDCPP Exposure. . *Environmental Health Perspectives, 120*, 1585-1591.

Meeker JD and HM Stapleton. (2010). House Dust Concentrations of Organophosphate Flame Retardants in Relation to Hormone Levels and Semen Quality Parameters. *Environmental Health Perspectives, 118*, 318-323.

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. Support document relating to Health Risk Limits for Groundwater Rules. Retrieved from https://www.leg.state.mn.us/archive/sonar/SONAR-03733.pdf#page=2

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses. from https://www.health.state.mn.us/communities/environment/risk/docs/guidance/hedrefguide.pdf

National Research Council (NRC): Subcommittee on Flame-Retardant Chemicals. (2000). Toxicological Risks of Selected Flame-Retardants. Chapter 16. Tris (1,3-dichloropropyl-2) Phosphate., from http://www.nap.edu/catalog.php?record_id=9841

Organization for Economic Co-operation and Development (OECD). (2009). Screening Information Dataset (SIDs) Initial Assessment Profile., from http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?Key=aedbd212-ac9a-4436-8ce6-cf29eabd7cbe&idx=0

Tanaka S, S Nakaura, K Kawashima, S Nagao, T Endo, K Onoda, et al. (1981). Effect of oral administration of tris(1,3-dichloroisopropyl)phosphate to pregnant rats on prenatal and postnatal developments. *Eisei Shikenjo Hokoku, 99*, 50-55.

U.S. Environmental Protection Agency - Office of Research and Development. (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. from https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. Environmental Protection Agency - Regional Screening Tables. Mid-Atlantic Risk Assessment -

Regional Screening Table. from https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables

US Environmental Protection Agency - Office of Water. (2012). 2012 Edition of the Drinking Water Standards and Health Advisories. from http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf

US Environmental Protection Agency (EPA) Design for the Environment (DfE) Program. (2005a). Flame Retardant Alternatives: Tris(1,3-dichloro-2-propyl) Phosphate Hazard Review.

US Environmental Protection Agency (EPA) Design for the Environment (DfE) Program. (2005b). Volume 1. Furniture Flame Retardancy Partnership: Environmental Profiles of Chemical Flame Retardant Alternatives for Low-Density Polyurethane Foam. from https://www.epa.gov/sites/default/files/2013-12/documents/ffr_foam_alternatives_vol1.pdf

US Environmental Protection Agency. (2019). *Exposure Factors Handbook Chapter 3 Update 2019*. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-3.

van der Veen I and J de Boer. (2012). Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis. *Chemosphere, 88*, 1119-1153.

Wang Q, K Liang, J Liu, L Yang, Y Guo, C Liu, et al. (2013). Exposure of zebrafish embryos/larvae to TDCPP alters concentrations of thyroid hormones and transcriptions of genes involved in the hypothalamic-pituitary-thryoid axis. *Aquatic Toxicology, 126*, 207-213.

World Health Organization (WHO). (1998 incorporating corrigenda published November 2004). Environmental Health Criteria 209. Flame Retardants: Tris(chloropropyl) phospate and Tris(2-chloroethyl) phosphate. from http://apps.who.int/iris/bitstream/10665/42148/1/WHO_EHC_209.pdf