Tri-o-cresyl Phosphate (CAS# 78-30-8) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared by:

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GreenScreen® Executive Summary for Tri-o-cresyl Phosphate (CAS #78-30-8)

Tri-o-cresyl phosphate is a chemical that functions as a plasticizer, flame retardant, lubricant, water-proofing agent, solvent, chemical intermediate and gasoline additive.

Tri-o-cresyl phosphate was assigned a GreenScreen® Benchmark Score of 1 ("Avoid – Chemical of High Concern") as it has high Group I Human Toxicity (Reproductive Toxicity (R)). This corresponds to GreenScreen® benchmark classification 1e in CPA 2011. A data gap (DG) exists for respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), tri-o-cresyl phosphate meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if tri-o-cresyl phosphate were assigned a High score for the data gap SnR*, it would be still categorized as a Benchmark **1** Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 1 ("Avoid: Chemical of high concern") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Tri-o-cresyl Phosphate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**M**	**H**	**L**	*M*	**vH**	**vH**	*H*	**vH**	**H**	**M**	DG	*L*	*L*	*vH*	*vH*	**vL**	*M*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms

GreenScreen® Assessment for Tri-o-cresyl Phosphate (CAS #78-30-8)

GreenScreen® Version 1.2 Draft Assessment
Note: Verification Has Not Been Performed on this GreenScreen® Assessment

Tri-o-cresyl Phosphate: Tri-o-cresyl Phosphate

CAS Number: 78-30-8

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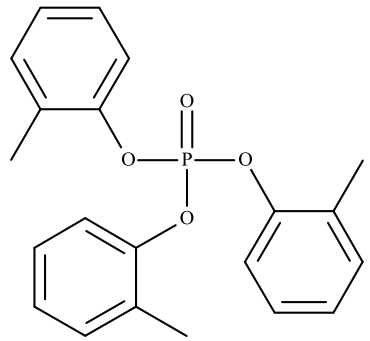
Organization: ToxServices LLC
Date: April 24, 2014

Confirm application of the *de minimus* rule[1]: N/A

Chemical Structure(s):



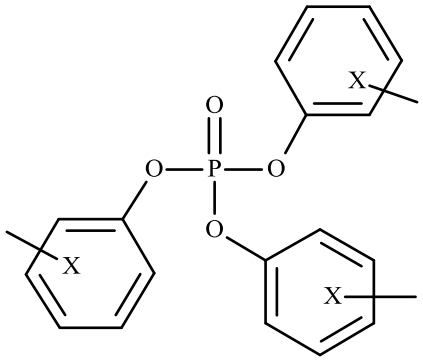
Also called: o-Tolyl phosphate; TOCP; Tris(o-cresyl)-phosphate; o-Trikresylphosphate; TOTP; Tris(o-methylphenyl)phosphate; Phosphoric acid, tri-o-tolyl ester; Phosphoric acid, tris(2-methylphenyl) ester; Tri-o-tolyl phosphate; Phosphoric acid, tris(2-methylphenyl) ester; Tri-ortho-cresylphosphate; Tricresyl phosphate; triorthocresyl phosphate (ChemIDplus 2014)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:

Tricresyl phosphate is a trimester of cresol and phosphoric acid. Cresol has three isomeric configurations: ortho-, meta- and para-, leading to 10 possible isomers of tricresyl phosphate. Therefore, commercially available tricresyl phosphate is a mixture of these isomers (NTP 1994). Tri-o-cresyl phosphate is largely removed from commercial tricresyl phosphate, primarily due to its neurotoxicity, which was initially believed to the most toxic isomer of all tricresyl phosphate

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

isomers. However, further studies indicated that isomers with mono-o-cresyl groups (omm, omp, opp) and those with to di-o-cresyl groups (oom, oop) are actually 10 and 5 times more neurotoxic than tri-o-cresyl phosphate, respectively (van der Veen and de Boer 2012). Based on structural similarity of tri-o-cresyl phosphate and other isomers in tricresyl phosphate, the toxicological profile of the commercial tricresyl phosphate is expected to be reasonably similar to that of tri-o-cresyl phosphate. Therefore, data on commercial tricresyl phosphate are cautiously used to fill the data gaps for tri-o-cresyl phosphate.



Tricresyl phosphate
(CAS # 1330-78-5)

Identify Applications/Functional Uses:
1. Plasticizer in lacquers and varnishes
2. Flame retardant
3. Synthetic lubricant
4. Water-proofing agent
5. Extraction solvent, and solvent for nitrocellulose
6. Chemical intermediate in synthesis of pharmaceuticals
7. Lead scavenger in gasoline (HSDB 2013)

GreenScreen® Summary Rating for Tri-o-cresyl Phosphate[2]: Tri-o-cresyl phosphate was assigned a GreenScreen® Benchmark Score of 1 ("Avoid – Chemical of High Concern") as it has high Group I Human Toxicity (Reproductive Toxicity (R)). This corresponds to GreenScreen® benchmark classification 1e in CPA 2011. A data gap (DG) exists for respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), tri-o-cresyl phosphate meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if tri-o-cresyl phosphate were assigned a High score for the data gap SnR*, it would be still categorized as a Benchmark 1 Chemical.

[2] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Figure 1: GreenScreen® Hazard Ratings for Tri-o-cresyl Phosphate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**M**	**H**	**L**	*M*	**vH**	**vH**	*H*	**vH**	**H**	**M**	DG	*L*	*L*	*vH*	*vH*	**vL**	*M*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[3]

Tri-o-cresyl phosphate is a stable compound on shelf. It decomposes on heating, giving out toxic fumes including phosphorus oxides (HSDB 2013).

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	List Translator Results[4,5]
N/A	Any	Decomposition	Phosphorus pentoxide	1314-56-3	LT-U
N/A	Any	Decomposition	Phosphorus trioxide	1314-24-5	Not in Pharos database

Introduction

Tri-o-cresyl phosphate is an organophosphorus compound and is one of the three major isomers of tricresyl phosphates, the other two being tri-p-cresyl phosphate (CAS #78-32-0) and tri-m-cresyl phosphate (CAS #563-40-2). These chemicals are mainly used as additives in lubricating oils and as plasticizers and flame retardants (NJ Health 2011). Tri-o-cresyl phosphate is prepared from cresol and phosphorus oxychloride, phosphoric acid, or phosphorus pentachloride. The commercial product is generally a mixture of isomers (CAS #1330-78-5) (HSDB 2011). However, tri-o-cresyl phosphate is largely removed from commercial tricresyl phosphate, primarily due to its neurotoxicity (van der Veen and de Boer 2012).

ToxServices assessed tri-o-cresyl phosphate against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen® Hazard Assessment) (ToxServices 2013).

[3] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.
[4] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2014) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[5] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2014) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for tri-o-cresyl phosphate can be found in Appendix C and a summary of the results can be found below:

Mammalian
- WHMIS: Class D1A – Very toxic material causing immediate and serious toxic effects
- GHS-Japan: Systemic toxicity (repeated exposure) – Category 1
- GHS-Japan: Systemic toxicity (single exposure) – Category 1
- EU R23: Toxic by inhalation
- EU R24: Toxic in contact with skin
- EU R25: Toxic if swallowed
- WHMIS: Class D2B – Toxic material causing other toxic effects

Organ toxicant
- EU R39: Danger of very serious irreversible effects
- EU H370: Causes damage to organs

Neurotoxicity
- G&L: Known to be neurotoxic in man

Acute aquatic toxicity
- R51: Toxic to aquatic organisms

Chronic aquatic toxicity
- EU H411: Aquatic chronic 2 – Toxic to aquatic life with long lasting effects
- EU R53: May cause long-term adverse effects in the aquatic environment

DOT: Tricresyl phosphate with > 3% ortho isomer: Class 6.1 group II – Poisonous/toxic materials

PhysioChemical Properties of Tri-o-cresyl Phosphate

Tri-o-cresyl phosphate is a colorless to pale yellow liquid at room temperature. Its vapor pressure indicates that it exists both in vapor and particulate phases. It is sparingly soluble in water (solubility not specified), and the estimated partition coefficient of 6.34 indicates that it's hydrophobic.

Table 1: Physical and Chemical Properties of Tri-o-cresyl Phosphate (CAS #78-30-8)

Property	Value	Reference
Molecular formula	$C_{21}H_{21}O_4P$	ChemIDplus 2014
SMILES Notation	P(Oc1c(cccc1)C)(Oc1c(cccc1)C)(Oc1c(cccc1)C)=O	ChemIDplus 2014
Molecular weight	368.367	ChemIDplus 2014
Physical state	Liquid	HSDB 2013
Appearance	Colorless or pale yellow	HSDB 2013
Melting point	11ºC	HSDB 2013
Vapor pressure	1.96×10^{-6}mmHg	HSDB 2013
Water solubility	Sparingly soluble	HSDB 2013
Dissociation constant	N/A	
Density/specific	1.1955 g/cm^3	HSDB 2013

Table 1: Physical and Chemical Properties of Tri-o-cresyl Phosphate (CAS #78-30-8)		
Property	**Value**	**Reference**
gravity		
Partition coefficient	6.34 (est), 5.11 (measured)	HSDB 2013, IPCS 1990

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Tri-o-cresyl phosphate was assigned a score of *L* for carcinogenicity based on negative data in structural analogs. GreenScreen® criteria classify chemicals as a low hazard for carcinogenicity when adequate data are available and negative, there are no structural alerts, and they are not classifiable under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - Not on any authoritative or screening lists.
- HSDB 2013
  - According to American Conference of Governmental Industrial Hygienists (ACGIH), tri-o-cresyl phosphate was classified to group A4: (Not classifiable as a human carcinogen).
- Environmental Agency 2009
  - *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* A 2-year bioassay was conducted by the National Toxicology Program in F344/N rats and B6C3F1 mice.
    - In the rat study, the test substance was fed to the animals (95/dose/sex) at 0, 75, 150 or 300 ppm (equivalent to 0, 3, 6 or 13 mg/kg/day in males and 0, 4, 7 or 15 mg/kg/day in females, respectively). One additional group of 95 male and female rats received diets containing 600 ppm test substance (26 mg/kg/day and 30 mg/kg/day in males and females, respectively) for 22 weeks and then only control diet for the rest of the study. Interim evaluation of neurotoxicity, necropsy and histology was conducted at 3, 9 and 15 months. There were no treatment-related effects on survival, final body weight and incidences of neoplasms.
    - In the mice study, the test substance was fed to the animals (95/dose/sex) at 0, 75, 150 or 300 ppm (equivalent to 0, 7, 13 or 27 mg/kg/day in males and 0, 8 or 18 or 37 mg/kg/day in females, respectively). Interim evaluation of neurotoxicity, necropsy and histology was conducted at 3, 9 and 15 months. There were no treatment-related effects on survival, final body weight and incidences of neoplasms.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): M
Tri-o-cresyl phosphate was assigned a score of **M** for mutagenicity/genotoxicity based on classification to GHS category 3 with limited data. GreenScreen® criteria classify chemicals as a moderate hazard for mutagenicity/genotoxicity when they are classified to GHS category 3 (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative or screening lists.

- CCRIS 1995
    - An Ames test was conducted using *S. typhimurium* tester strain TA100. Tri-p-cresyl phosphate tested negative for mutagenicity in the absence of metabolic activation but positive in the presence of metabolic activation at concentrations of 0.01 – 3 μM.
- RTECS 2013
    - In an *in vivo* DNA adduct formation study, male Fischer 344 rats were exposed orally (unspecified) to tri-o-cresyl phosphate at 50 mg/kg/day for 10 days. DNA was extracted at 1, 4, 7 and 28 days after the last dosing from liver, kidney, lung, heart, brain and testes. DNA adducts as detected by ^{32}P-post-labeling was found in liver, kidney, lung and heart on day 1 post exposure. Adducts in the lungs and in the kidney persisted till the end of the study (28 days), while adducts in other organs were found only on day 1 post exposure.
    - The metabolite of tri-o-cresyl phosphate, 2-phenoxy-4-H-1,3,2-benzodioxaphosphorin 2-oxide, was studied for its mutagenicity *in vitro*. The test substance was mutagenic in *S. typhimurium* tester strain TA100, and formed DNA adducts when incubated with nucleotides, nucleosides and isolated DNA. The chemical was also found to form DNA adduct as detected by ^{32}P-post-labelling in *S. typhimurium* tester strain TA100 and in hepatoma cells.
- NTP 1994
    - *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* Two Ames tests conducted by two laboratories reported that the test substance was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 in the presence and absence of metabolic activation at concentrations of 100 – 10,000 μg/plate (precipitation formed at ≥ 3,333 μg/plate.
    - *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* No sister chromatic exchanges or chromosomal aberrations were found with the test substance in Chinese hamster ovary cells in the presence and absence of metabolic activations at concentrations of up to 5,000 μg/mL and 16 μg/mL, respectively.
- ECHA 2014
    - *Commercial mixture of tricresyl phosphate:* The test substance was not clastogenic in a GLP-compliant *in vitro* mammalian chromosomal aberration test in Chinese hamster lung fibroblasts (V79) at concentrations of up to 1,000 μg/mL in the presence and absence of metabolic activation.
- Environmental Agency 2009
    - *Commercial mixture of tricresyl phosphate:* The test substance was not genotoxic in an *in vivo* unscheduled DNA synthesis test in male rats when administered by gavage (no further details were provided).
- Tri-o-cresyl phosphate was mutagenic in one strain of bacteria with metabolic activation only. It also induced persistent (i.e. 28 days) DNA adducts in the lung and kidney of rats. Its neurotoxic metabolite 2-phenoxy-4-H-1,3,2-benzodioxaphosphorin 2-oxide was proposed to be the ultimate genotoxic species, and was found to induce DNA adducts *in vitro* in bacteria (one strain) and in mammalian cells (hepatoma). Commercial mixture of tricresyl phosphate isomers tested negative for genotoxicity (mutation and chromosome aberration) *in vitro* and *in vivo* in standard genotoxicity studies, but the mixture commonly contain less than 1% tri-o-cresyl phosphate. Based on limited evidence of genotoxicity in non-standard tests *in vitro* and *in vivo* on tri-o-cresyl phosphate, ToxServices classified it to GHS category 3 (suspected).

Reproductive Toxicity (R) Score (H, M, or L): H

Tri-o-cresyl phosphate was assigned a score of **H** for reproductive toxicity based on classification to GHS category 1B (presumed)[6]. GreenScreen® criteria classify chemicals as a high hazard for reproductive toxicity when they are classified to GHS category 1A or 1B (CPA 2012a).

- Authoritative and Screening Lists
  - Not on any authoritative or screening lists.
- HSDB 2013
  - A single oral dose of 500 mg/kg tri-o-cresyl phosphate was administered to Sprague-Dawley rats, and sperm was collected on day 1, 3, 7, 10, 14 and 21 after exposure from the caput, body and cauda of the epididymis. Testes and epididymis were histologically examined. Sperm neck bending was observed with high frequency starting from day 7 from all parts of epididymis. The number of tailless sperms was greatly increased at cauda epididymis from day 10 on. In addition, fusion of two or three sperms was observed on day 7. Histopathology revealed retention of Step 19 spermatid on days 3 and 7, and decreased sperm and cell debris in epididymis lumen on day 7. It was concluded that tri-o-cresyl phosphate affected spermatid at the terminal stage of spermatogenesis and induced sperm morphological abnormalities during the course of maturation in the epididymis (Hoshino N et al. 1999 as cited in HSDB 2013).
  - Tri-o-cresyl phosphate is known to adversely affect the male reproductive system in animals, and a study reported that it acted by disrupting the seminiferous epithelium in the testis and cauing a dose-dependent decrease in sperm density in the epididymis in mice. The activity of neuropathy target esterase was significantly reduced by the treatment. In addition, the metabolite of tri-o-cresyl phosphate, saligenin cyclic-o-tolyl phosphate, also inhibited the activity of this enzyme in spermatogonial stem cells. Details of the study were not provided (Chen et al. 2012 as cited in HSDB 2013).
  - A reproductive toxicity study was conducted to examine the biochemical and morphological effects on the male reproductive system in rats. In a preliminary study, male Fischer 344 rats received tri-o-cresyl phosphate orally (surrogate) at 0, or 100 – 1,600 mg/kg/day for 14 days. Doses higher than 400 mg/kg/day led to near 100% mortality within 48 hours, and the mortality at 100, 200 and 400 mg/kg/day was 0, 60 and 70%, respectively. Decreased epididymal sperm density and disruption of the seminiferous epithelium were observed (doses not specified). In the main study, rats received the compound orally at 0, 10, 25, 50, 75 or 100 mg/kg/day for 63 days. Another group of animals received 100 mg/kg/day tri-p-cresyl-phosphate. Tri-o-cresyl phosphate led to a dose-dependent decrease in sperm motility, sperm density and testicular nonspecific esterase (NSE) and acetylcholinesterase (AChE) activities, and a dose-dependent increase in the number of abnormal spermatozoa. Normal sperm morphology was observed at the lowest dose, while disrupted sperm cell architecture was observed at doses of 50 mg/kg/day and above in all animals. On the other hand, tri-p-cresyl-phosphate did not induce any signs of testicular toxicity. It was concluded that the LOAEL was 25 mg/kg/day and the NOAEL was 10 mg/kg/day for this study based on testicular toxicity (Somkuti et al. 1987 as cited in HSDB 2013).

[6] GHS category 1B reproductive toxicant: presumed human reproductive toxicant – Placing of the substance in this category is largely based on evidence from experimental animals. There should be clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or if occurring together with other toxic effects, the reproductive toxicity should not be a secondary non-specific consequence of other toxic effects.

- U.S. EPA 2010
    - *Commercial tricresyl phosphate mixture:* A one-generation reproductive toxicity study in Long-Evans rats, a modified continuous breeding protocol study in Fischer 344 rats, a continuous breeding protocol study in CD-1 mice and repeated dose toxicity studies in rats and mice, reproductive toxicity in the male reproductive system similar to those observed with tri-o-cresyl phosphate was consistently observed, with the lowest LOAEL of ~62.5 mg/kg/day (lowest dose tested) in CD-1 mice based on impaired fertility, decreased sperm motility and decreased number of litter/pair. In addition, ovarian interstitial cell hypertrophy was observed in female mice at 15 mg/kg/day and at ≥50 mg/kg/day in rats in repeated dose toxicity studies.
- Based on the weight of evidence, tri-o-cresyl phosphate induced male reproductive toxicity in animals. There is a consistent trend among animal studies identifying effects on sperm morphology, motility, and density that may lead to decreased fertility. No data were found in humans. Therefore, ToxServices classified the chemical to GHS category 1B (presumed) based on sufficient evidence in animals.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Tri-o-cresyl phosphate was assigned a score of **L** for developmental toxicity based on limited negative data in animals. GreenScreen® criteria classify chemicals as a low hazard for developmental toxicity when adequate data are available and negative, there are no structural alerts, and they are not classifiable under GHS (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- Shepard's 2014
    - In a developmental toxicity study, Long-Evans rats received tri-o-cresyl phosphate at 87.5, 175 or 350 mg/kg/day throughout organogenesis from gestation day 6 to 18. Maternal toxicity was not observed at 87.5 and 175 mg/kg/day, while increased maternal mortality was found at the high dose. There were no significant differences in the frequency of malformations between treated and control rats (Tocco et al. 1987 as cited in Shepards 2014) (Mele and Jensh 1977 as cited in Shepards 2014).
    - In a developmental toxicity study in Wistar rats aiming to examine the developmental neurotoxicity, tri-o-cresyl phosphate was administered at 500 or 750 mg/kg on gestation days 18 and 19. No fetal toxicity was found.

Endocrine Activity (E) Score (H, M, or L): *M*
Tri-o-cresyl phosphate was assigned a score of *M* for endocrine disruption based on cytoplasmic vacuolization of the adrenal gland and basophilic hypertrophy of the pituitary gland *pars distalis* in animals for the surrogate mixture. GreenScreen® criteria classify chemicals as a moderate hazard for endocrine disruption when there is evidence of endocrine activity (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- U.S. EPA 2010
    - *Commercial Tricresyl phosphate mixture*: a number of subchronic and chronic oral toxicity studies consistently observed cytoplasmic vacuolization of adrenal cortex in male

and female rats and mice with dose-dependent increase in severity and frequency. In addition, one subchronic oral toxicity study reported basophilic hypertrophy of the pituitary gland *pars distalis* at doses of 430 mg/kg/day and above in male rats. Details of these studies are described in the repeated dose toxicity section below.

- Based on the weight of evidence, clear evidence of adrenal gland pathology was consistently observed in rodents on the surrogate, but no information was identified regarding the level of hormones secreted by the adrenal gland. Commercial mixture of tricresyl phosphate contains very low levels of tri-o-cresyl phosphate. Although the evidence of endocrine activity is weak, the potential cannot be completely ruled out.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M, or L): vH

Tri-o-cresyl phosphate was assigned a score of **vH** for acute toxicity based on being classified to DOT class 6.1 group II. GreenScreen® criteria classify chemicals as a very high hazard for acute toxicity when they belong to DOT class 6.1 group II (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Tricresyl phosphate with > 3% ortho isomer: Class 6.1 group II – Poisonous/toxic materials
  - *Screening:* WHMIS: Class D1A – Very toxic material causing immediate and serious toxic effects.
- ChemIDplus 2014
  - Oral LD_{50} = 500 mg/kg in chicken
  - Oral LD_{50} = 400 mg/kg in mammal species (unspecified)
  - Oral LD_{50} = 900 mg/kg in mice
  - Oral LD_{50} = 1,160 mg/kg in rats
  - Dermal LD_{50} = 1,500 mg/kg in cats
  - Dermal LD_{50} > 3,700 mg/kg in rabbits

The DOT classification of 6.1 group II (authoritative) classifies tri-o-cresyl phosphate to the very high hazard category, and the screening WHMIS class D1A classifies the chemical to the high hazard category, according to GreenScreen® criteria (CPA 2012a). However, available LD_{50} data in animals suggest a moderate hazards classification. Although the basis of DOT classification is unclear, ToxServices defaulted to the most conservative hazard categorization for this chemical.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

***Group II Score (single dose)* (vH, H, M, or L): vH**

Tri-o-cresyl phosphate was assigned a score of **vH** for systemic toxicity (single dose) based on adverse effects observed at the oral dose of 100 mg/kg and association with EU H370 and R39/23/24/25. GreenScreen® criteria classify chemicals as a very high hazard for systemic toxicity (single dose) when effect oral doses are ≤ 300 mg/kg in animals and/or when they are associated with EU R39/23/24/25 or H370 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* R39/23/24/25: Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed
    - *Authoritative:* EU H370: Causes damage to organs
    - *Screening:* Not on any screening lists.
- HSDB 2013
    - In humans, ingestion of tri-o-cresyl phosphate leads to sudden diarrhea and nausea or vomiting during or shortly after exposure, which are reversible within 48 days. Delayed neurological symptoms occur, which are discussed in the section for neurotoxicity.
- ChemIDplus 2014
    - In the acute dermal toxicity in cats that identified an LD_{50} of 1,500 mg/kg, gastrointestinal hypermotility and diarrhea were reported at this dose in addition to death.
    - In the acute oral toxicity study in mice that identified an LD_{50} of 900 mg/kg, gastrointestinal hypermotility and diarrhea were reported, in addition to effects on the air (unspecified).
    - In an acute oral toxicity study in rabbits, an LDLo of 100 mg/kg was established based on gastrointestinal hypermotility, diarrhea, and interstitial nephritis.
- IPCS 1990
    - Single oral doses of 100, 200, or 400 mg/kg tri-o-cresyl phosphate led to diarrhea, dehydration, metabolic acidosis and death within 6 days.
- Based on the weight of evidence, the most significant effects after acute exposure to tri-o-cresyl phosphate are neurotoxicity, and it's highly likely that the EU R phrases and H statements are based on neurotoxicity. As neurotoxicity is considered as a separate endpoint in a GreenScreen®, it is not considered for the evaluation of the current endpoint. Other effects following acute exposure are GI-related (e.g. diarrhea) as observed both in humans and in animals. The lowest effect dose identified is 100 mg/kg (oral) in rabbits based on diarrhea and interstitial nephritis.

Group II* Score (repeated dose) **(H, M, or L):** *H*

Tri-o-cresyl phosphate was assigned a score of *H* for systemic toxicity (repeated dose) based on the lowest LOAEL of 7 mg/kg/day on a surrogate mixture. GreenScreen® criteria classify chemicals as a high hazard for systemic toxicity (repeated dose) when the LOAEL is ≤ 10 mg/kg/day (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not on any authoritative lists.
    - *Screening:* Not on any screening lists.
- U.S. EPA 2010
    - *Commercial Tricresyl phosphate mixture:* A subacute oral toxicity study was conducted in Sprague-Dawley rats (10/sex/dose). The test substance was administered in the diet at doses of 0, 0.1, 0.5 or 1.0% (equivalent to 0, 50, 250 or 500 mg/kg/day, respectively). Almost all animals at the high dose died, approximately half of the animals died at the middle dose, and 1 male diced at the low dose. There was significantly reduced body weight and food consumption at the middle dose for surviving animals, and the relative liver weight was increased at this dose. EPA established the LOAEL at 250 mg/kg/day and NOAEL at 50 mg/kg/day, based on mortality and decreased body weight.
    - *Commercial Tricresyl phosphate mixture:* A subchronic oral toxicity was conducted in Sprague-Dawley rats (5/sex/dose). The test substance was given in 5% gum Arabic solution via gavage at doses of 0, 30, 300 and 1,000 mg/kg, 6 days/week for 13 weeks. At the high dose, significant body weight reduction, adrenal weight (females) increase

and adrenal cortex hypertrophy were observed. No significant findings were found regarding hematology, urinalysis or serum enzyme activities. At the middle dose, decreased albumin levels and increased potassium levels were found in both sexes. EPA established the NOAEL at 300 mg/kg/day and the LOAEL at 1,000 mg/kg/day for this study, based on decreased body weight in males and adrenal cortex hypertrophy. These doses are equivalent to 0, 26, 257 or 857 mg/kg/day after adjusting for dosing frequency[7].

- *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* A subchronic oral toxicity study was conducted by NTP in Fischer 344/N rats (10/sex/dose). Animals received the test substance by gavage at 0, 50, 100, 200, 400 or 800 mg/kg/day for 13 weeks. There was a significant reduction in final body weight in males at 200 mg/kg/day and higher doses. Cytoplasmic vacuolization of the adrenal cortex was found at all doses in both sexes with a dose-dependent severity. EPA established the LOAEL at 50 mg/kg/day based on cytoplasmic vacuolization of the adrenal cortex.
- *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* A subchronic oral toxicity study was conducted by NTP in B6C3F1 mice (10/sex/dose). Animals received the test substance by gavage at 0, 50, 100, 200, 400 or 800 mg/kg/day for 13 weeks. Final body weight reduction was observed in males at 200 mg/kg/day and above, and in females at 400 mg/kg/day and above. Cytoplasmic vacuolization of the adrenal cortex was found at all doses in both sexes with a dose-dependent severity. EPA established the LOAEL at 50 mg/kg/day based on cytoplasmic vacuolization of the adrenal cortex.
- *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* A subchronic oral toxicity study was conducted by NTP in F344/N rats (10/sex/dose). Animals received the test substance in the diet at 0, 90, 1,700, 3,300, 6,600 or 13,000 ppm (equivalent to 0, 55, 120, 220, 430 or 750 mg/kg/day in males and 0, 65, 120, 230 or 770 mg/kg/day for females, respectively) for 13 weeks. Final body weight reduction was observed in males at 430 mg/kg/day and above, and in females at 230 mg/kg/day and above. Cytoplasmic vacuolization of the adrenal cortex was found at all doses in both sexes. There was renal papillary edema and renal papillary necrosis at the doses of 750 mg/kg/day in males and 430 mg/kg/day and above in females. In addition, there was basophilic hypertrophy of the pituitary gland *pars distalis* at doses of 430 mg/kg/day and above in males. EPA established the LOAEL at 55 – 65 mg/kg/day based on cytoplasmic vacuolization of the adrenal cortex.
- *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* A subchronic oral toxicity study was conducted by NTP in B6C3F1 mice (10/sex/dose). Animals received the test substance in the diet at 0, 250, 500, 1,000, 2,100 or 4,200 ppm (equivalent to 0, 45, 110, 180, 380 or 900 mg/kg/day in males and 0, 65, 130, 230, 530 or 1,050 mg/kg/day for females, respectively) for 13 weeks. Final body weight reduction was observed in males at 900 mg/kg/day and above, and in females at 530 mg/kg/day and above. Cytoplasmic vacuolization of the adrenal cortex was found at all doses in both sexes, with the exception of males at 45 mg/kg/day. There was papillary hyperplasia of the gallbladder at 110 mg/kg/day and higher doses in males

[7] 30 mg/kg for 6 days per week is equivalent to 30 x 6/7 mg/kg/day = 26 mg/kg/day

and 230 mg/kg/day and higher doses in females. Additionally, renal tubule degeneration was found at 900 mg/kg/day in males. EPA established the LOAEL at 65 mg/kg/day based on cytoplasmic vacuolization of the adrenal cortex in females.

- *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* In the 2-year NTP feeding study in Fischer 344/N rats detailed in carcinogenicity section, cytoplasmic vacuolization of the adrenal cortex was observed at 26 mg/kg/day in males and at 7 mg/kg/day and higher doses in females at 3 months. At 9 and 15 months, this effect was mainly found in females at 15 mg/kg/day, with significant increase in incidence and severity at the study termination. EPA established a LOAEL at 7 mg/kg/day based on cytoplasmic vacuolization of the adrenal cortex in females.
- *79% Commercial tricresyl phosphate (21% tri-m-cresyl phosphate, 4% tri-p-cresyl phosphate, <1% tri-o-cresyl phosphate, and other unidentified tricresyl phosphate esters):* In the 2-year NTP feeding study in B6C3F1 mice, detailed in the carcinogenicity section, there was ceroid pigmentation was found in the adrenal cortex in all exposure groups throughout most of the study, except in 8 and 18 mg/kg/day females sacrificed at 3 months. The severity of this effect was greatly increased in females at 37 mg/kg/day. In addition, there was increased incidence of clear cell foci, fatty change and ceroid pigmentation in the liver of males at doses of 13 mg/kg/day and above. EPA established the LOAEL at 7 mg/kg/day based on ceroid pigmentation of the adrenal cortex in males.

Neurotoxicity (N)

***Group II Score (single dose)* (vH, H, M, or L): vH**

Tri-o-cresyl Phosphate was assigned a score of **vH** for neurotoxicity (single dose) based on classification to GHS category 1 based on sufficient human and animal data. GreenScreen® criteria classify chemicals as a very high hazard for neurotoxicity (single dose) when they are classified to GHS category 1 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not on any authoritative lists
  - *Screening:* GHS-Japan: Systemic toxicity (single exposure) – Category 1
  - *Screening:* G&L: Known to be neurotoxic in man
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- IPCS 1990
  - The neurotoxicity is tri-o-cresyl phosphate is well known and extensively studied. In dogs, monkeys, cats and chickens, a single or multiple doses of the compound can lead to paralysis of the hindlegs after a delay period of 2-3 weeks. The delayed neuropathy associated with tri-o-cresyl phosphate and other organophosporus compounds are collectively termed organophosphorus induced delayed neuropathy (OPIDN).
  - A single oral or dermal dose of tri-cresyl phosphate at 250, 500 or 1,000 mg/kg led to neurological signs ranging from ataxia to partial paralysis in all dermally dosed groups and mild ataxia in 1,000 mg/kg orally dosed group in European ferrets, indicating dermal exposure was more effective than oral exposure in inducing neurotoxicity.
  - Chicken is highly susceptible to ataxia and therefore has been used as an experimental model to study OPIDN. A single oral dose of 58 – 580 mg/kg induced mild to severe paralysis in the hen.
  - In humans, ingestion of tri-o-cresyl phosphate leads to delayed neurotoxicity leading to paralysis and pyramidal signs (e.g., spasticity), but the sensitivity varies greatly between individuals. Severe symptoms were reported with the dose of 0.15 g in one individual,

while others were not affected by 1 – 2 g. Recovery rate also varies, from complete recovery to severe symptoms after years at the same exposure level. A single large dose or tri-cresyl phosphate leads to initial reversible GI symptoms (characterized by vomiting) followed by delayed (3 – 28 days) symptoms including sharp, cramp-like pains in the calves, some numbness and tingling in the feet and hands, and subsequent increased weakness of the lower limbs and inability to maintain balance.
    - Tri-o-cresyl phosphate can be metabolized to saligenin cyclic o-tolyl phosphate, which is a derivative of o-hydroxymethyl metabolites. This metabolite is believed to be the active neurotoxic agent.
- Based on the weight of evidence, there is clear evidence of delayed neuropathy in humans, which is considered significant toxicity in severity. In addition, a single dose of 58 mg/kg induced similar symptoms in the hen. Therefore, ToxServices classified tri-cresyl phosphate to GHS category 1.

Group II* Score (repeated dose) **(H, M, or L): H**

Tri-o-cresyl phosphate was assigned a score of **H** for neurotoxicity (repeated dose) based on classification to GHS category 1 based on sufficient human and animal data. GreenScreen® criteria classify chemicals as a high hazard for neurotoxicity (repeated dose) when classified to GHS category 1(CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not on any authoritative lists.
    - *Screening:* GHS-Japan: Systemic toxicity (repeated exposure) – Category 1 (neurotoxicity)
    - *Screening:* G&L: Known to be neurotoxic in man
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- IPCS 1990
    - The neurotoxicity is tri-o-cresyl phosphate is well known and extensively studied. In dogs, monkeys, cats and chickens, a single or multiple doses of the compound can lead to paralysis of the hindlegs after a delay period of 2-3 weeks.
    - In humans, the symptoms of chronic low dose exposure do not involve GI symptoms, unlike those of acute exposure, but neurotoxicity symptoms are similar to those observed in acute poisoning cases, including initial cholinesterase inhibition and subsequent delayed neuropathy characterized by severe paralysis. It was concluded that there is no safe level for tri-o-cresyl phosphate ingestion (due to inter-individual variance in sensitivity), and exposure through dermal and inhalation routes should be minimized.
- Based on the weight of evidence, tri-o-cresyl phosphate is clearly neurotoxic in humans, with no safe exposure levels that can be established. Therefore, the sufficient evidence classifies tri-o-cresyl phosphate to GHS category 1

Skin Sensitization (SnS) Group II* Score (H, M, or L): M

Tri-o-cresyl phosphate was assigned a score of **M** for skin sensitization based on classification to GHS category 1B. GreenScreen® criteria classify chemicals as a moderate hazard for skin sensitization when classified to GHS category 1B (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- IPCS 1990
    - Irritant and allergic dermatitis have been reported in humans.

- HSDB 2013
    - Organophosphorus compounds are mostly weak sensitizers.
- Environmental Agency 2009
    - *Commercial tricresyl phosphate mixture*: Human patch tests indicated that tricresyl phosphate has the potential to induce dermal sensitization.
- ECHA 2014
    - *Commercial tricresyl phosphate mixture*: A GLP-compliant mouse local lymph node assay (LLNA) was conducted according to OECD Guideline 429. The stimulation indices (SIs) were 3.7, 3.4 and 5.4 for concentrations of 25%, 50% and 100%. The Sis of larger than 3 indicate that the test substance is a skin sensitizer, but there is no dose-response relationship. Therefore, the results were inconclusive.
- Based on the weight of evidence, tri-o-cresyl phosphate is likely to be a weak dermal sensitizer, classifying it to GHS category 1B (low to moderate frequency of occurrence).

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): DG
Tri-o-cresyl phosphate was assigned a score of DG for respiratory sensitization based on lack of data.

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- No data were identified.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): *L*
Tri-o-cresyl phosphate was assigned a score of *L* for skin irritation/corrosivity based on none to slight irritation potential of the surrogate. GreenScreen® criteria classify chemicals as a low hazard for skin irritation/corrosivity when there are adequate data available and negative, there are no structural alerts, and they are not classifiable under GHS (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- HSDB 2013
    - Organophosphorus compounds can produce dermal irritation.
- ECHA 2014
    - *Commercial tricresyl phosphate mixture*: A non-GLP, non-guideline study was conducted in New Zealand White rabbits. 0.5 g test substance was applied under occlusive conditions to the clipped intact and abraded skin for 24 hours (irritation test, 6 animals) or 4 hours (corrosion test, 6 animals). The primary dermal irritation index was 0.5. The results indicate that it is a slight dermal irritant, which does not meet EU classification requirements.
    - *Commercial tricresyl phosphate mixture*: A non-GLP study was conducted according to the Standard Federal Hazardous Substances Labeling Act test guideline. The test substance (0.5 g) was applied under occlusive condition to the saved and partially abraded skin of 6 albino rabbits for 24 hours. The overall irritation score was 0.04, which is less than the cutoff of 0.5 to be classified as a skin irritant based on the Draize scoring criteria.
- Based on the weight of evidence, the surrogate is at most a slight dermal sensitizer.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): *L*
Tri-o-cresyl phosphate was assigned a score of *L* for eye irritation/corrosivity based on negative data on the surrogate. GreenScreen® criteria classify chemicals as a low hazard for eye

irritation/corrosivity when there are adequate data available and negative, there are no structural alerts, and they are not classifiable under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative or screening lists.
- HSDB 2013
  - Vapor of tricresyl phosphate may irritate the eyes, but only at high temperatures.
- ECHA 2014
  - *Commercial tricresyl phosphate mixture:* A non-GLP, non-guideline study was conducted in New Zealand Albino rabbits. 0.1 mL test substance was instilled to one eye of 9 animals for 24 hours. The maximum mean total scores were 0.7, 0.3 and 0 observed at 24, 48 and 72 hours, respectively. Therefore, the substance was considered not irritating.
  - *Commercial tricresyl phosphate mixture*: A non-GLP study was conducted according to the Standard Federal Hazardous Substances Labeling Act test guideline. The test substance was not irritating to the eye.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): *vH*

Tri-o-cresyl phosphate was assigned a score of *vH* for acute aquatic toxicity based on acute L/EC_{50} values of less than 1 mg/L on the surrogate. GreenScreen® criteria classify chemicals as a very high hazard for acute aquatic toxicity when the acute L/EC_{50} values are ≤ 1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* R51/53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
  - *Screening:* Not on any screening lists.
- HSDB 2013
  - 96h LC_{50} = 7,000 mg/L in bluegill sunfish
  - 96h LC_{50} = 8,700 mg/L in inland silverside
- ECOTOX
  - 28h EC_{50} = 1.7 – 2.5 mg/L in algae
- U.S. EPA 2010
  - *Commercial tricresyl phosphate mixture:*
    - 96h LC_{50} = 0.75 mg/L in rainbow trout
    - 48h LC_{50} = 0.27 mg/L in daphnia
    - 96h EC_{50} = 0.56 mg/L in green algae (growth rate)
- The data presented in HSDB 2013 were highly abbreviated and of questionable reliability. Therefore, evaluation was heavily reliant on data on the surrogate. Although association with EU R51/53 classifies tri-o-cresyl phosphate to high hazard for acute aquatic toxicity, the L/EC_{50} values of less than 1 mg/L for the surrogate classify tri-c-cresyl phosphate to the very high hazard category.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *vH*

Tri-o-cresyl phosphate was assigned a score of *vH* for chronic aquatic toxicity based on a LOEC of 0.018 mg/L on the surrogate. GreenScreen® criteria classify chemicals as a very high hazard for chronic aquatic toxicity when effect levels are ≤ 0.1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative or screening lists.

- No data were found on tri-o-cresyl phosphate
- U.S. EPA 2010
    - *Commercial tricresyl phosphate mixture:* 21 day LC_{50} = 0.1 – 0.3 mg/L in daphnia
- ECHA 2014
    - *Commercial tricresyl phosphate mixture:* A number of studies were identified, but only the key study was presented below, which is sufficient to classify the chemical to the highest chronic hazard category.
        - 28 day NOEC – 0.01 mg/L (LOEC = 0.018 mg/L) based on mortality and quantitative growth (length and weight) in fish *Jordanella floridae*.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL
Tri-o-cresyl phosphate was assigned a score of **vL** for persistence based on being expected to meet the 10-day biodegradation window. GreenScreen® criteria classify chemicals as a very low hazard for persistence when they meet the 10-day window in ready biodegradation tests (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists
- HSDB 2013
    - Biodegradation half-lives are 12 - 13 days at 14ºC and 10 days at 25ºC in river water. After incubation with water from Lake Ontario, tri-o-cresyl phosphate was completely degraded.
    - At the tri-o-cresyl phosphate addition rate of 3 and 13 mg/L every 24 hours, 97% and 99% biodegradation were reached using the activated sludge seed after 4 and 7 weeks, respectively.
    - Tri-o-cresyl phosphate at the concentration of 26 mg/L reached 79%, 82% and 86% biodegradation after 7, 28 and 48 days, respectively in a river die-away test.
- Based on the weight of evidence, tri-o-cresyl phosphate is readily biodegradable and is expected to meet the 10 day biodegradation window.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *M*
Tri-o-cresyl phosphate was assigned a score of *M* for bioaccumulation based on a measured BCF of 800 in fish for the surrogate. GreenScreen® criteria classify chemicals as a moderate hazard for bioaccumulation when BCFs are between 500 and 1,000 (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- HSDB 2013
    - An estimated BCF of 1,060 was derived in fish based on an estimated log Kow of 6.34 in EPISuite. This indicates bioconcentration potential, provided that the compound is not metabolized in the organism.
- U.S. EPA 2012
    - EPISuite estimated a BAF of 1,381 based on a measured log Kow of 5.11. See Appendix D for details.
- Environmental Agency 2009
    - *Commercial tricresyl phosphate mixture:* In a 32-day bioconcentration study in fathead minnows, A BCF of 165 L/kg was determined. Another study reported a BCF of 10 for muscle and 169 for gut in rainbow trout.

  - *Tri-p-cresyl phosphate and tri-m-cresyl phosphate:* Bioconcentration was investigated in fathead minnows and rainbow trout on ^{14}C-labelled tri-p-cresyl phosphate and tri-m-cresyl phosphate separately. The BCFs were calculated to be 310 L/kg and 462 L/kg in rainbow trout and fathead minnows, respectively, for tri-m-cresyl phosphate, and 770 and 109 L/kg for the two species for tri-p-cresyl phosphate.
  - *Tri-p-cresyl phosphate:* The chemical was reported to accumulate in several aquatic organisms. Ecological magnification factors were 320,000 for algae, 28,000 for snail, 3,700 for mosquito, 3,700 for fish and 2,900 for daphnia. However, it is not clear how these factors were derived.
  - *Tri-p-cresyl phosphate:* A BCF was determined to be 1,589 L/kg in bluegill. However, this high number may reflect uptake via both water and food due to the way food was administered to the fish. Therefore, this may be an overestimation of the true BCF (via water alone).
  - In summary, several studies showed bioconcentration potential for tricresyl phosphate in fish. Uncertainties exist due to limitations in these studies, including not maintaining constant concentration during the study (resulting in BCFs not representative of a steady-state value), using ^{14}C measurements (leading to overestimation of BCF by measuring metabolites as well), or toxic effects on feeding/growth. Of all the studies evaluated, more reliable studies which analyzed only the parent compound concentrations reported the BCFs around 310 – 800 L/kg.

- Based on the weight of evidence, although EPISuite predicted BAFs of over 1,000 for tri-o-cresyl phosphate, metabolism is expected to decrease the level of its bioaccumulation in fish. ToxServices used the highest BCF of 800 that was considered to be from reliable measured data in fish for the mixture of tricresyl phosphate isomers as the basis to evaluate the bioaccumulation potential of tri-o-cresyl phosphate.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Tri-o-cresyl phosphate was assigned a score of *L* for reactivity based on the surrogate lacking explosivity. GreenScreen® criteria classify chemicals as a low hazard for reactivity when they are not explosive (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative and screening lists.
- ECHA 2014
  - *Commercial tricresyl phosphate mixture:* A structural evaluation and oxygen balance calculate determined that the substance were not explosive. In addition, on the same basis, it was determined that the substance does not have oxidizing potentials.
- Based on the weight of evidence, tri-o-cresyl phosphate is not likely to be reactive.

Flammability (F) Score (vH, H, M, or L): L
Tri-o-cresyl phosphate was assigned a score of **L** for flammability based on high flashpoint. GreenScreen® criteria classify chemicals as a [score] hazard for flammability when [explain reasoning here] (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative and screening lists.

- HSDB 2013
    - Flash point = 225ºC
    - Boiling point = 410ºC
    - NFPA flammability: 1 (must be preheated before ignition will occur)
- Based on the weight of evidence, tri-o-cresyl phosphate does not meet GHS criteria to be classified as a flammable liquid (flash point ≤ 93ºC).

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Tri-o-cresyl Phosphate (CAS #78-30-8)

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**Tri-o-cresyl phosphate**	**78-30-8**	L	M	H	L	M	vH	vH	H	vH	H	M	DG	L	L	vH	vH	vL	M	L	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	Yes		
2	STOP						
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Tri-o-cresyl phosphate	1

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

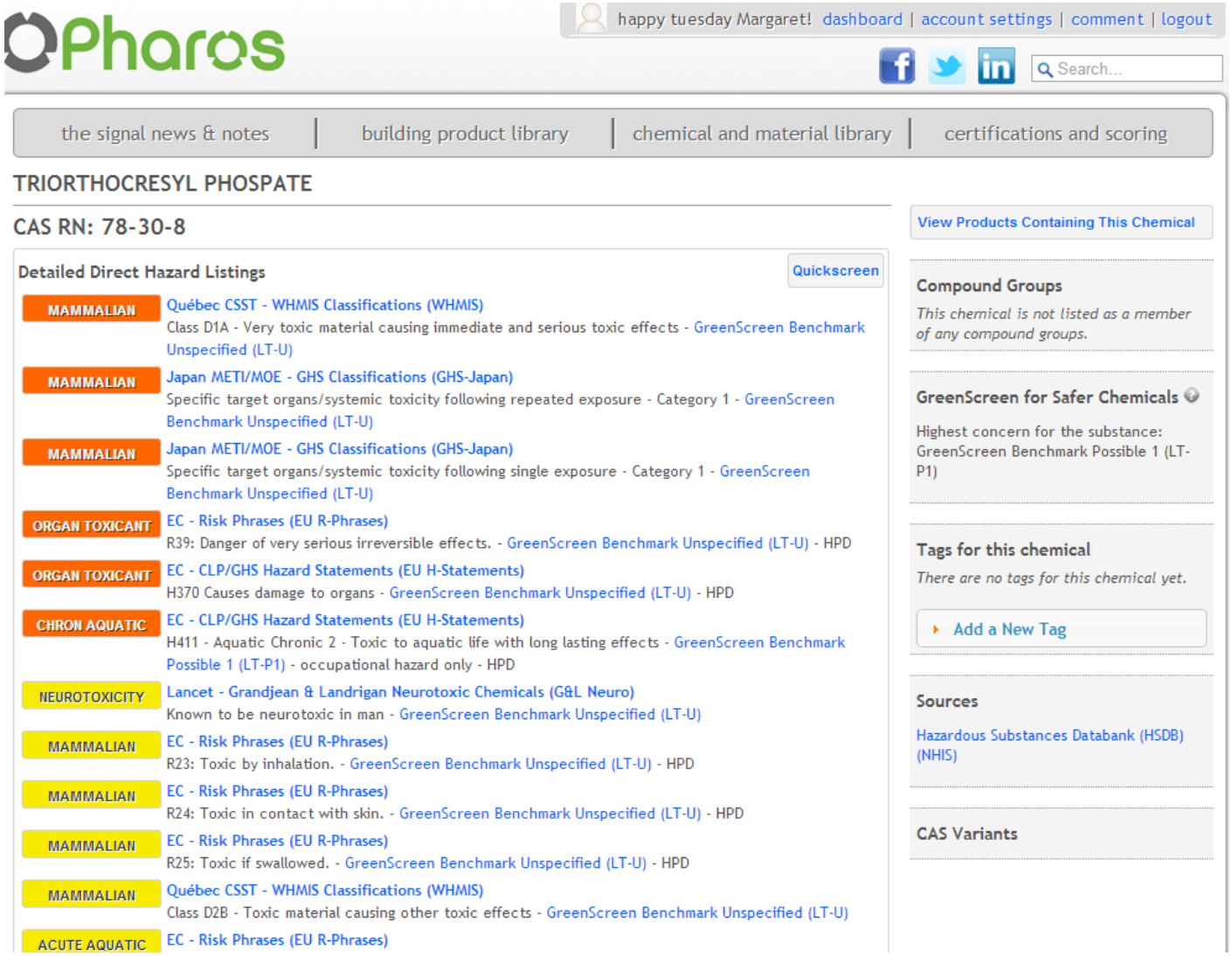
Chemical Name	Final GreenScreen® Benchmark Score
Tri-o-cresyl phosphate	1

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												1
2												
3												
4												

APPENDIX C: Pharos Output for Tri-o-cresyl Phosphate (CAS #78-30-8)



ORGAN TOXICANT
EC - CLP/GHS Hazard Statements (EU H-Statements)
H370 Causes damage to organs - GreenScreen Benchmark Unspecified (LT-U) - HPD

CHRON AQUATIC
EC - CLP/GHS Hazard Statements (EU H-Statements)
H411 - Aquatic Chronic 2 - Toxic to aquatic life with long lasting effects - GreenScreen Benchmark Possible 1 (LT-P1) - occupational hazard only - HPD

NEUROTOXICITY
Lancet - Grandjean & Landrigan Neurotoxic Chemicals (G&L Neuro)
Known to be neurotoxic in man - GreenScreen Benchmark Unspecified (LT-U)

MAMMALIAN
EC - Risk Phrases (EU R-Phrases)
R23: Toxic by inhalation. - GreenScreen Benchmark Unspecified (LT-U) - HPD

MAMMALIAN
EC - Risk Phrases (EU R-Phrases)
R24: Toxic in contact with skin. - GreenScreen Benchmark Unspecified (LT-U) - HPD

MAMMALIAN
EC - Risk Phrases (EU R-Phrases)
R25: Toxic if swallowed. - GreenScreen Benchmark Unspecified (LT-U) - HPD

MAMMALIAN
Québec CSST - WHMIS Classifications (WHMIS)
Class D2B - Toxic material causing other toxic effects - GreenScreen Benchmark Unspecified (LT-U)

ACUTE AQUATIC
EC - Risk Phrases (EU R-Phrases)
R51: Toxic to aquatic organisms. - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD

CHRON AQUATIC
EC - Risk Phrases (EU R-Phrases)
R53: May cause long-term adverse effects in the aquatic environment. - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only

There are no tags for this chemical yet.

Add a New Tag

Sources

Hazardous Substances Databank (HSDB) (NHIS)

CAS Variants

Life Cycle Research

Research Status: No life cycle research started
The Pharos team has not yet researched the life cycle of this substance and has no information about chemicals of concern that may be associated with its life cycle.

VOC designation: Non-volatile (Boiling point: 410 degrees Celsius)

APPENDIX D: EPISuite Modeling Results for Tri-o-cresyl Phosphate (CAS #78-30-8)

CAS Number: 78-30-8
SMILES : O=P(Oc(c(ccc1)C)c1)(Oc(c(ccc2)C)c2)Oc(c(ccc3)C)c3
CHEM : Phosphoric acid, tris(2-methylphenyl) ester
MOL FOR: C21 H21 O4 P1
MOL WT : 368.37
---------- EPI SUMMARY (v4.11) ----------

Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.68 estimate) = 6.34
Log Kow (Exper. database match) = 5.11
Exper. Ref: SAEGER,VW ET AL. (1979)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 476.06 (Adapted Stein & Brown method)
Melting Pt (deg C): 89.89 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.0121 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.62 (Mean VP of Antoine & Grain methods)
MP (exp database): -33 deg C
BP (exp database): 265 deg C
VP (exp database): 6.00E-07 mm Hg (8.00E-005 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.2073
log Kow used: 5.11 (expkow database)
no-melting pt equation used
Water Sol (Exper. database match) = 0.36 mg/L (25 deg C)
Exper. Ref: SAEGER,VW ET AL. (1979)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 0.14004 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters
Esters (phosphate)

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 5.35E-008 atm-m3/mole (5.42E-003 Pa-m3/mole)
Group Method: Incomplete

Exper Database: 8.08E-07 atm-m3/mole (8.19E-002 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.829E-002 atm-m3/mole (2.867E+003 Pa-m3/mole)
VP: 0.0121 mm Hg (source: MPBPVP)
WS: 0.207 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 5.11 (exp database)
Log Kaw used: -4.481 (exp database)
Log Koa (KOAWIN v1.10 estimate): 9.591
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.0501
Biowin2 (Non-Linear Model) : 1.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.3143 (weeks-months)
Biowin4 (Primary Survey Model) : 3.5760 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : -0.0061
Biowin6 (MITI Non-Linear Model): 0.0098
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.8974
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 8E-005 Pa (6E-007 mm Hg)
Log Koa (Koawin est): 9.591
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.0375
Octanol/air (Koa) model: 0.000957
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.575
Mackay model : 0.75
Octanol/air (Koa) model: 0.0711

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 13.6991 E-12 cm3/molecule-sec
Half-Life = 0.781 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 9.369 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

0.663 (Junge-Pankow, Mackay avg)
0.0711 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 4.711E+004 L/kg (MCI method)
Log Koc: 4.673 (MCI method)
Koc : 3352 L/kg (Kow method)
Log Koc: 3.525 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Phosphorus esters hydrolysis rates available (see Full Output)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 2.214 (BCF = 163.6 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.6717 days (HL = 4.696 days)
Log BCF Arnot-Gobas method (upper trophic) = 3.107 (BCF = 1280)
Log BAF Arnot-Gobas method (upper trophic) = 3.140 (BAF = 1381)
log Kow used: 5.11 (expkow database)

Volatilization from Water:
Henry LC: 8.08E-007 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 1393 hours (58.03 days)
Half-Life from Model Lake : 1.535E+004 hours (639.7 days)

Removal In Wastewater Treatment:
Total removal: 80.90 percent
Total biodegradation: 0.70 percent
Total sludge adsorption: 80.20 percent
Total to Air: 0.01 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 96.13 percent
Total biodegradation: 42.15 percent
Total sludge adsorption: 53.98 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.434	18.7	1000
Water	10.9	900	1000
Soil	60.4	1.8e+003	1000
Sediment	28.3	8.1e+003	0

Persistence Time: 1.52e+003 hr

Authorized Reviewers

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