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Draft Screening Assessment

Certain Organic Flame Retardants Substance Grouping

2-Propanol, 1-chloro-, phosphate (3:1)

(TCPP)

Chemical Abstracts Service Registry Number

13674-84-5

2-Propanol, 1,3-dichloro-, phosphate (3:1) (TDCPP)

Chemical Abstracts Service Registry Number 13674-87-8

Environment Canada

Health Canada

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Canada

Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment on 2-propanol, 1-chloro-, phosphate (3:1), hereinafter referred to as TCPP, Chemical Abstracts Service Registry Number (CAS RN) 13674-84-5, and 2-propanol, 1,3-dichloro-, phosphate (3:1), hereinafter referred as TDCPP, CAS RN 13674-87-8. TCPP and TDCPP are part of the Certain Organic Flame Retardants (OFR) Substance Grouping under Canada's Chemicals Management Plan, which includes ten organic substances having similar function: application to materials to slow the ignition and spread of fire. These two substances were identified as a priority for assessment based on human health concerns (related to potential for exposure) but not for ecological concerns (met criteria for persistence but not potential for bioaccumulation or inherent toxicity to non-human organisms).

TCPP and TDCPP are discrete organic chemicals that do not occur naturally in the environment. According to information identified from a survey issued under section 71 of CEPA 1999, there is no manufacturing of either TCPP or TDCPP in Canada. Both substances were predominantly imported into Canada as pure substances or in manufactured items. The total import volumes in 2011 ranged from 1 000 000 to 10 000 000 kg of TCPP, and 100 000 to 1 000 000 kg of TDCPP.

TCPP is used as an additive flame retardant for manufacturing of building or construction materials in Canada (e.g., polyurethane spray foam insulation), and is also contained in imported products of polyurethane spray foam insulation with the same functional use. TCPP is also imported in Canada in the manufactured products of flexible polyurethane foam (used in upholstered furniture and mattresses) and as a textile waterproofing spray intended for consumer use. Available information indicates the potential for migration of flame retardants from foam objects. The commercial products, referred to as TCPP, may consist of four chain isomers of TCPP (including another three CAS RNs 76025-08-6, 76649-15-5, 6145-73-9). The composition is dominated by TCPP (up to 85%); with the balance composed by the other three isomers in varying amounts based on commercial products provided by different suppliers. The chain isomers of TCPP are considered to possess identical physical and chemical properties for the purpose of this risk assessment; data reported in studies that have been carried out using the commercial products of TCPP (i.e. a mixture of chain isomers) are considered valid for assessing TCPP.

TDCPP is used as an additive flame retardant in the manufacturing of flexible polyurethane foam in Canada (used in upholstered furniture and mattresses). The substance is imported as a pure substance and in products with the same functional use.

Globally, TCPP and TDCPP are used as flame retardants and plasticizers, in textile upholstery, paints and adhesives.

TCPP is highly soluble in water and has a low octanol-water partition coefficient, while TDCPP possesses moderate water solubility and octanol-water partition coefficient. Both substances have a low vapour pressure and do not dissociate in water. Empirical studies indicate that neither substance is rapidly biodegradable. Both substances are considered to be very stable in water, sediment and soil, but not air (gas phase). Based on findings from environmental sampling studies, TCPP and TDCPP have been found associated with particulates in air where they are considered to be very persistent. Both substances have been detected in air samples over the Arctic areas in Canada and Europe and are considered to have potential for long-range transport when adsorbed to aerosols.

Potential environmental releases of TCPP and TDCPP are from industrial activities (during their blending with a polyol) and from use of products. Releases from industrial activities are expected to primarily enter water via wastewater treatment systems. Based on physical and chemical properties, TCPP will partition to water, with insignificant amounts partitioning to sediments. On the other hand, TDCPP may be found in both sediment and water to some extent. Unlike TCPP, which is expected to remain predominantly dissolved in effluents; TDCPP, given its greater propensity to adsorb to solids, is likely to be found adsorbed to wastewater treatment system biosolids, which ultimately may be applied to soils. Emissions from manufactured items and products are expected to enter in air or to dust, and ultimately precipitate in water and soil. However, it is expected that releases to the environment via this route are minimal and diffuse.

As would be expected based on their physical and chemical properties, laboratory studies have reported low bioconcentration factors and rapid metabolism for TCPP and TDCPP, indicating that both substances have a limited potential to accumulate in aquatic biota. Significant exposure in higher trophic level organisms through the food chain is not expected for TCPP and TDCPP. Rapid excretion of biotransformation products in the mammalian studies suggests that metabolites are also unlikely to bioaccumulate.

Empirical toxicity data have been identified for both substances. TCPP has demonstrated moderate toxicity to aquatic organisms and terrestrial plants; while TDCPP has shown considerably higher toxicity to aquatic organisms including effects on the endocrine system in fish. Additional sub-lethal effects (i.e., neurotoxicity and genetic effects in birds) are also noted in both *in vivo* and *in vitro* studies. Data for endpoints from *in vitro* studies which show linkage to organism level effects have been considered in the risk assessment for these two substances.

Considering the environmental fate and available toxicity data for these two substances, risk quotient analyses were conducted in the aquatic compartment for TCPP and in the aquatic, sediment and soil compartments for TDCPP. Outcomes from the risk quotient analyses indicate that the risk associated with exposure of these two substances to organisms due to releases from industrial uses and consumer products is low at current predicted levels of release.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from TCPP or TDCPP. It is therefore proposed to conclude that TCPP and TDCPP do not meet the criteria under paragraphs 64 *(a)* or *(b)* of CEPA 1999 as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

Based on available information on concentrations in environmental media and results from a survey under section 71 of CEPA 1999, the general population is expected to be exposed to TCPP and TDCPP from environmental media (air, water, dust), from food and during the use of consumer products containing this substance (i.e. in products such as spray foam and waterproofing products and manufactured items such as foam-containing upholstered furniture).

Based on the available information and classifications by other international regulatory agencies, critical effects for characterization of the risk to human health from exposure to TDCPP are carcinogenicity and non-cancer effects on the kidneys and testes. Tumours were observed in multiple organ sites, including kidney and liver in both sexes, testes (in males) and adrenal gland (in females) in a two-year carcinogenicity study in rats. Results of genotoxicity tests were mixed *in vitro* and mostly negative *in vivo*. Results of biomonitoring studies for TDCPP are presented.

The margins of exposure between estimates of exposure from environmental media (air, water, dust and food, including breast milk) to TDCPP and the critical effect levels for cancer and non-cancer effects are considered to be adequate to address uncertainties in the health effects and exposure databases. The margins between estimates of exposure resulting from the use of manufactured items containing TDCPP and the critical effect levels for cancer and non-cancer effects are considered adequate to account for uncertainties in the exposure and health effect databases.

Based on the available information on health effects of TCPP, the critical effects for characterization of risk to human health are reproductive and developmental effects. Additionally, although no chronic or carcinogenicity studies are available, there is evidence to indicate that TCPP may be carcinogenic (read-across from analogues,

QSAR and structural alerts analyses). Limited biomonitoring data for TCPP is presented.

The margin of exposure between estimates of exposure from environmental media (air, water, dust and food, including breast milk) to TCPP and the critical effect levels are considered to be adequate to address uncertainties in the health effects and exposure databases. The margins between estimates of exposure resulting from the use of certain manufactured items containing TCPP, specifically foam-containing upholstered furniture, and the critical effect levels are considered potentially inadequate to account for uncertainties in the exposure and health effect databases.

Based on the information presented in this draft screening assessment, it is proposed to conclude that TCPP meets the criteria under paragraph 64 *(c)* of CEPA 1999 as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on the information presented in this screening assessment, it is proposed to conclude that TDCPP does not meet the criteria under paragraph 64 *(c)* of CEPA 1999 as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Overall Proposed Conclusion

It is proposed to conclude that TCPP meets one or more criteria as set out in section 64 of CEPA 1999. In addition, it is proposed that TCPP meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999.

It is proposed to conclude that TDCPP does not meet any of the criteria set out in section 64 of CEPA 1999.

Although present estimated levels of exposure of TDCPP are not indicative of harm to the environment or to human health, there may be concerns if import and use quantities were to increase in Canada.

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1. Introduction

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999), the Minister of the Environment and the Minister of Health conduct screening assessments of substances to determine whether these substances present or may present a risk to the environment or to human health.

The Substance Groupings Initiative is a key element of the Government of Canada's Chemicals Management Plan (CMP). The Certain Organic Flame Retardant Substance Grouping consists of ten substances identified as priorities for action as they met the categorization criteria under section 73 CEPA 1999, and/or were considered as a priority based on ecological and/or human health concerns (Environment Canada, Health Canada 2007). All of these substances have a similar function: the application to materials to slow the ignition and limit the spread of fire. Also, these substances are potential alternatives for other flame retardants which are presently subject to regulatory controls or phase-out globally and/or in Canada.

This draft screening assessment focuses on two substances in the Certain Organic Flame Retardants Substance Grouping: 2-Propanol, 1-chloro-, phosphate (3:1) (CAS RN 13674-84-5) and 2-Propanol, 1,3-dichloro-, phosphate (3:1) (CAS RN 13674-87-8). These substances are considered in one screening assessment on the basis of similarity in chemical structure, mode of toxic action and other assessment parameters. Both substances were identified as a priority for assessment based on other human health concerns; they also met criteria for persistence, but not for bioaccumulation or inherent toxicity to non-human organisms in the categorization of the Domestic Substances List (DSL) under subsection 73(1) of CEPA 1999.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.[1]

[1]A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) is not relevant to, nor does it preclude, an assessment against the hazard criteria for WHMIS (Workplace Hazardous Materials Information System) that are specified in the *Hazardous Products Regulations* and the *Controlled Products Regulations* for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA 1999 or other Acts.

This draft screening assessment includes consideration of information on physical and chemical properties, quantity, uses, exposure, hazards, including additional information submitted by stakeholders. Relevant data were identified until August 2014 for both human health and ecological components of this assessment. However, a cursory search was conducted to include any salient literature up to July 2015. Key studies were critically evaluated and, along with the use of modelled results, were used to reach conclusions. When available and relevant, information presented in risk and hazard assessments from other jurisdictions was considered.

This draft screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies and lines of evidence pertinent to the conclusion.

This draft screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review and/or consultation. Comments on the technical portions relevant to the environment were received from Jon Arnot at Arnot Research and Consulting, Miriam Diamond at University of Toronto, and Andy Wang at ICL IP. Comments on the technical portions relevant to human health were received from Cathy Petito Boyce, Leslie Beyer, Chris Long and David Mayfield from Gradient Corp and from Risk Assessment Division, Office of Pollution Prevention and Toxics, US Environmental Protection Agency (US EPA). While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada.

The critical information and considerations upon which the draft assessment is based are summarized below.

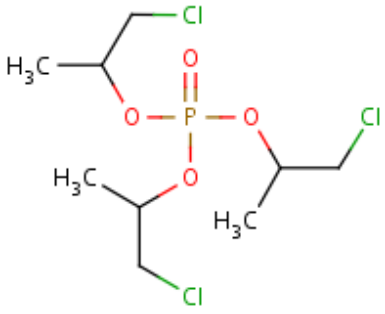
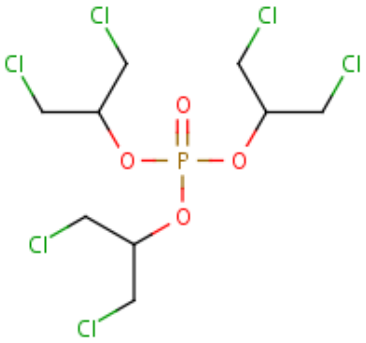
2. Substance Identity

2.1 Substance Identities of TCPP and TDCPP

This screening assessment focuses on two substances: 2-Propanol, 1-chloro-, phosphate (3:1) (CAS RN 13674-84-5), and 2-Propanol, 1,3-dichloro-, phosphate (3:1) (CAS RN 13674-87-8); herein, referred to as TCPP and TDCPP, respectively. These two substances are chlorinated alkyl phosphate esters.

The substance identities of TCPP and TDCPP are presented in Table 2.1. A list of additional chemical names and trade names of these two substances can be found in National Chemicals Inventory (2013).

Table 2.1. Substance identities of TCPP and TDCPP

CAS RN	13674-84-5 (TCPP)	13674-87-8 (TDCPP)
Chemical group (DSL Stream)	Organics	Organics
Chemical formula	$C_9H_{18}Cl_3O_4P$	$C_9H_{15}Cl_6O_4P$
Chemical structure		
SMILES[a] string	O=P(OC(CCl)C)(OC(CCl)C)OC(CCl)C	O=P(OC(CCl)CCl)(OC(CCl)CCl)OC(CCl)CCl
Molecular mass	327.57 g/mol	430.91 g/mol

[a] Simplified Molecular Input Line Entry System.

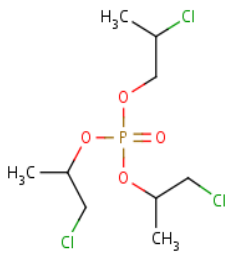
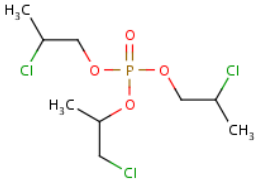
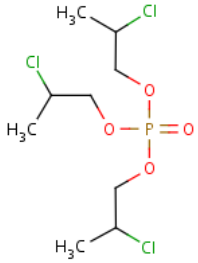
2.2 Isomers of TCPP and TDCPP

TCPP is manufactured from the reaction of phosphorous oxytrichloride with propylene oxide in the presence of a catalyst (UNEP 1990; WHO 1998). After removal of acidic impurities and residual catalyst, the final product, also referred to as TCPP, may consist of four chain isomers of TCPP (including another three CAS RNs 76025-08-6, 76649-15-5, 6145-73-9). The composition is dominated by TCPP (up to 85%); with the balance

composed by the other three chain isomers in varying amounts based on commercial products provided by different suppliers.

The chemical names and structures of three chain isomers of TCPP are illustrated in Table 2.2.

Table 2.2. Chemical structures of three chain isomers of TCPP

CAS RN	76025-08-6	76649-15-5	6145-73-9
Chemical name	Bis(1-chloro-2-propyl)-2-chloropropyl phosphate	Bis(2-chloropropyl)-1-chloro-2-propyl phosphate	Tris(2-chloropropyl) phosphate
Chemical structure			

Studies cited in this assessment on TCPP were carried out using the commercial products of TCPP, as described above. TCPP and its chain isomers have demonstrated very similar chromatographic properties and are difficult to separate (EU RAR 2008a). Predicted physical and chemical properties by a (quantitative) structure-activity relationship ((Q)SAR) model (EPI Suite v4.1) differ only to a very small extent (Environment Canada, Health Canada 2014). For the purpose of this assessment, it is assumed that all these chain isomers have identical physical-chemical and hazard properties. Given that the differences in the isomer contents of the commercial products of TCPP would not affect the physical and chemical properties and the toxicity profile of TCPP, it is considered that data reported in studies that were carried out using the commercial products of TCPP (i.e. a mixture of chain isomers) are valid for assessing TCPP.

TDCPP is produced by reaction of phosphorus oxychloride with epichlorohydrin (WHO 1998). Tris(2,3-dichloro-1-propyl) phosphate (CAS RN 78-43-3) is an isomer of TDCPP; however, there has been no report of such isomer identified in the commercial products of TDCPP.

2.3 Selection of Analogues and Use of (Q)SAR Models

Guidance on the use of a read-across approach and Quantitative Structure-Activity Relationships or (Q)SAR models for filling data gaps has been prepared by various

organizations such as the Organisation for Economic Co-operation and Development (OECD). These methods have been applied in various regulatory programs including the European Union's (EU) Existing Substances Programme. In this assessment, a read-across approach using data from analogues and the results of (Q)SAR models, where appropriate, have been used to inform the ecological and human health assessments. Analogues were selected that were structurally similar and/or functionally similar to substances within this grouping (e.g., based on physical-chemical properties, chemical structures, and toxicokinetics), and that had relevant empirical data that could be used to read-across to substances that were data poor. The applicability of (Q)SAR models was determined on a case-by-case basis.

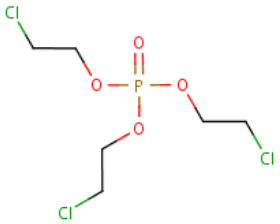
Details of the read-across data and (Q)SAR models chosen to inform the ecological and human health assessments of TCPP and TDCPP are further discussed in the relevant sections of this report.

In general, for the ecological risk assessment, TCPP and TDCPP are used as analogues of each other when there is a lack of data for certain ecological endpoints. A read-across approach is applied where available empirical information for one substance is considered suitable to fill data gap for the other substance. No additional analogues were used in the ecological risk assessment. (Q)SAR models are used for predicting environmental fate, persistence and bioaccumulation potential. Outcomes from these models are considered additional lines of evidence for assessing TCPP and TDCPP, with the relative weight assigned being dependent on reliability of the methods and results.

In the human health risk assessment, TDCPP and tris(2-chloroethyl)phosphate (TCEP) were considered qualitative analogues for assessing the carcinogenic potential of TCPP as no long-term or carcinogenicity studies of TCPP were identified (more details is available in Health Canada 2015). The identity of TCEP is presented in Table 2.3. In addition, several statistics-based (Q)SAR models were used to assess the carcinogenicity potential of TCPP (more details is available in Health Canada 2015).

Table 2.3. Analogue identity

Substance CAS RN	Substance name	Molecular Weight (g/mol)	Empirical Structure/ Molecular Formula

Substance CAS RN	**Substance name**	**Molecular Weight (g/mol)**	**Empirical Structure/ Molecular Formula**
115-96-8	tris(2-chloroethyl)phosphate (TCEP)	285.49	 $C_6H_{12}Cl_3O_4P$

3. Physical and Chemical Properties

Experimental data for physical and chemical properties of TCPP and TDCPP have been identified via literature searches and data submissions.

It is noted that there are multiple values reported for certain physical and chemical properties of TCPP and TDCPP (Environment Canada, Health Canada 2014). Upon data review and evaluation, one value was selected for characterizing each physical and chemical property (Table 3.1 and Table 3.2). These selected values are further applied in modelling in the assessment.

3.1 TCPP

Table 3.1. Physical and chemical properties for TCPP

Property	Type	Value	Temperature (°C)	Reference
Melting point (ºC)	Experimental	<-20	-	SafePharm Laboratories 2002a
Boiling point (ºC)	Experimental	288 (boil with decomposition)	-	SafePharm Laboratories 2002a
Density (kg/m^3)	Experimental	1.29×10^3	20	SafePharm Laboratories 2002a
Vapour pressure (Pa)	Experimental	0.0014	25	SafePharm Laboratories 2002b
Henry's Law constant ($Pa \cdot m^3/mol$)	Calculated	4.45×10^{-4}	25	HENRYWIN 2011
Log K_{ow} (dimensionless)	Experimental	2.68	Not specified	SafePharm Laboratories 2002c
Log K_{oc} (dimensionless)	Experimental	2.76	-	SafePharm Laboratories 2002c
Log K_{oa}	Modelled	9.43	-	KOAWIN 2010

Property	Type	Value	Temperature (°C)	Reference
(dimensionless)				
Water solubility (mg/L)	Experimental	1080	20	SafePharm Laboratories 2002c

Abbreviations: K_{oc}, organic carbon-water partition coefficient; K_{ow}, octanol-water partition coefficient; K_{oa}, octanol-air partition coefficient.

TCPP remains a viscous liquid at room temperature, with a slightly sweet odour (Santa Cruz 2010).

A dissociation model (ACD/pKaDB c1997–2012) did not identify any dissociable functional group; TCPP is a neutral organic.

3.2 TDCPP

Table 3.2. Physical and chemical properties for TDCPP

Property	Type	Value	Temperature (°C)	Reference
Melting point (ºC)	Experimental	<-20	-	SafePharm Laboratories 2002d
Boiling point (ºC)	Experimental	326	-	SafePharm Laboratories 2002d
Density (kg/m^3)	Experimental	1513	20	SafePharm Laboratories 2002d
Vapour pressure (Pa)	Experimental	5.6×10^{-6}	25	SafePharm Laboratories 2002e
Henry's Law constant (Pa·m^3/mol)	Calculated	1.33×10^{-4}	25	HENRYWIN 2011
Log K_{ow} (dimensionless)	Experimental	3.69	20	SafePharm Laboratories 2002e

Property	**Type**	**Value**	**Temperature (°C)**	**Reference**
Log K_{oc} (dimensionless)	Experimental	3.25	Not specified	Wildlife International 2005a
Log K_{oa} (dimensionless)	Modelled	10.96	-	KOAWIN 2010
Water solubility (mg/L)	Experimental	18.1	20	SafePharm Laboratories 2002f

Abbreviations: K_{oc}, organic carbon–water partition coefficient; K_{ow}, octanol–water partition coefficient.

TDCPP is a colourless or light yellow oily transparent liquid at room temperature (Alibaba 2013).

A dissociation model (ACD/pKaDB c1997-2012) did not identify any dissociable functional group for this substance; TDCPP is a neutral organic.

4. Sources

There is no reference in the published literature for the natural occurrence of TCPP or TDCPP in the environment. Sources of TCPP and TDCPP are anthropogenic, from industrial activities and use of products.

In 2013, TCPP and TDCPP were included in a notice issued pursuant to section 71 of CEPA 1999 for the Certain Organic Flame Retardants Substance Grouping (Canada 2013), aiming to identify the current sources and uses of these substances in Canada. According to responses to this notice, there is no manufacture of either TCPP or TDCPP in Canada; however, imports to Canada totalled 1 000 000 to 10 000 000 kg for TCPP and 100 000 to 1 000 000 kg for TDCPP in 2011, with most as neat substances and a small portion in consumer or commercial products (ECCC 2013-2014).

Both TCPP and TDCPP are included in the United States Environmental Protection Agency (US EPA) Chemical Data Access Tool (CDAT). The most recent data are available for 2012, reporting a national production volume of approximately 55 million lbs (approximately 25 000 000 kg) for TCPP, and 10 to 50 million lbs (approximately 4 500 000 to 22 500 000 kg) for TDCPP (US EPA 2012). A couple of major manufacturers of TDCPP discontinued their manufacturing of TDCPP recently (ECCC 2013-2014); however their reasons were unknown.

Information on use quantities of TCPP and TDCPP in Nordic countries is available up to year 2011 (SPIN 2013). TCPP has been used in all four Nordic countries (Denmark, Finland, Norway, and Sweden) in the latest 5 years and the total use quantities in these four countries ranged from 1 050 000 to 1 994 000 kg from 2007 to 2011. TDCPP has been used in some Nordic countries between 2007 and 2011; however, information on the use quantity remains confidential.

Information on the manufacturing and/or import quantity for both substances in Japan was available for recent years, 5000 tonnes in 2010 and at 7000 tonnes in 2011 for TCPP, and <1000 tonnes in 2010 and 2011 for TDCPP (CHRIP c2008).

5. Uses

According to data submissions in response to the notice issued pursuant to section 71 of CEPA 1999 for the Certain Organic Flame Retardants Substance Grouping (ECCC 2013-2014), TCPP has been used as an additive flame retardant for manufacturing of building or construction materials in Canada (e.g., polyurethane spray foam insulation); it is as well contained in imported products (e.g., polyurethane spray foam insulation) with the same functional use (ECCC 2013-2014). TCPP is also imported in Canada in the manufactured products of flexible polyurethane foam (used in furniture and mattresses) (ECCC 2013-2014; CEH 2013a,b; Stapleton et al. 2011); it has been reported as a textile waterproofing spray intended for consumer use (Empack 2014). TDCPP has been used as an additive flame retardant in Canada for manufacturing flexible polyurethane foam (used in furniture, mattresses and seating).

TCPP and TDCPP are not listed as approved food additives in the Lists of Permitted Food Additives as regulated under the *Food and Drugs Act*, nor have they been identified as being used/present in formulations of food packaging materials or incidental additives (Health Canada 2013, 2013 email from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). TCPP and TDCPP are not listed in the Drug Product Database (DPD 2013), the Therapeutic Products Directorate's internal Non-Medicinal Ingredient Database, the Natural Health Products Ingredients Database (NHPID 2013) or the Licensed Natural Health Products Database (LNHPD 2013) as a medicinal or a non-medicinal ingredient present in final pharmaceutical products, natural health products or veterinary drugs (2013 email from Therapeutic Products Directorate, Natural Health Products Directorate and Veterinary Drugs Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, TCPP and TDCPP are not anticipated to be used in cosmetic products in Canada (2013 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

6. Internationally, TCPP and TDCPP are used as flame retardants and plasticizers (Sundkvist et al. 2010). TCPP and TDCPP are also used in textile (i.e. upholstery) backcoating formulations in the Unites States and Europe; there is no confirmed textile use in Canada (US CPSC 2005 a,b; EU RAR 2008b; Danish EPA 2014).TCPP is also used in certain other coatings in small quantities (WHO 1998).

TDCPP is also used as a lacquer, paint and glue (Sundkvist et al. 2010). Releases to the Environment

Anthropogenic releases to the environment depend upon various losses occurring during the manufacture, industrial use, consumer/commercial use, service life and disposal of a substance. Releases of TCPP and TDCPP to the Canadian environment, due to the substance's use as a flame retardant, are expected to be diffuse, with some point sources (e.g., from industrial facilities and container cleaning facilities).

Direct emissions of TCPP and TDCPP to air are not expected. Instead, releases of TCPP and TDCPP to the environment occur during the industrial use stages. According to information identified in Canada (ECCC 2013-2014), TCPP and TDCPP are used to manufacture polyisocyanurate and polyurethane foams. Releases from industrial activities are expected to happen via their blending with a polyol during manufacturing processes and cleaning of tank trucks and totes. Wastewater from the industrial manufacturing facilities and cleaning facilities may receive treatment on-site before it enters publicly owned wastewater treatment systems nearby. From there, TCPP and TDCPP may be released to surface water and may partition to sediment. Having a high water solubility and moderate log K_{oc}, TCPP is not expected to appreciably partition to biosolids during wastewater treatment, and the pathway leading to TCPP soil exposure due to the application of biosolids is therefore considered unlikely. On the other hand, TDCPP with a considerably higher log K_{oc} and lower water solubility has a greater propensity to partition to solids and may reside to some extent in sediment and biosolids from wastewater treatment systems (WWTS). Due to partitioning to biosolids, exposure of TDCPP in soils would be expected due to land application of biosolids.

As additive flame retardants that are blended with the polymer product (rather than a reactive flame retardant chemically bonded to the polymer product), there is the possibility for some release of TCPP and TDCPP from consumer products to the environment (Guerra et al. 2011), likely to the air and directly to dust. Such emissions can result in atmospheric deposition to soil and water. When found in household dust, substances may end up going through the wastewater treatment systems via routine household cleaning activities. Overall, releases from products are expected to be geographically dispersed and spread out over the duration of the service life and end-of-life of these products.

Release information presented above is used to further develop exposure characterization scenarios to estimate resulting environmental concentrations (see Section 8.2).

7. Environmental Fate and Behaviour

7.1 Environmental Distribution

The environmental fate for a substance describes the processes by which it moves and is transformed in the environment. In this section, some general characteristics of TCPP and TDCPP will be discussed with respect to its environmental fate in different compartments in an effort to understand how organisms come into contact with the substance in a particular medium, the persistence of two substances in the environmental compartments, degradation, and distribution among media.

TCPP and TDCPP are expected to be released from industrial activities to wastewater and undergo migration from use of products to the air and dust.

Based on physical and chemical properties (Table 3.1 and Table 3.2), the environmental fate of TCPP and TDCPP were predicted using Level III fugacity modelling (EQC 2011) assuming steady-state emissions to air, water and soil. The Level III EQC model assumes non-equilibrium conditions between environmental compartments, but equilibrium within compartments. The results (Table 7.1 and Table 7.2) represent the net effect of chemical partitioning, inter-media transport and loss by both advection (out of the modelled region) and degradation/transformation processes, i.e. relative steady-state distribution in the physical environmental compartments.

According to the EQC model, TCPP and TDCPP demonstrate similar environmental fate and distribution. Regardless of the environmental medium to which they are released, there is negligible distribution to air, but significant distribution to water and soil compartments, depending on the release scenario. Because of its considerably lower water solubility and higher K_{oc}, partitioning to sediment is greater for TDCPP in comparison to TCPP. It is noted that the model is not able to account for the association with particulates in the atmospheric compartment; therefore the prediction of negligible partitioning in air differs from the environmental monitoring data identified for TCPP and TDCPP.

Table 7.1. Results of the Level III fugacity modelling for TCPP (EQC 2011)

Substance released to	Partitioning in air (%)	Partitioning in water (%)	Partitioning in soil (%)	Partitioning in sediment (%)
Air (100%)	Negligible	8.8	91.2	Negligible
Water (100%)	Negligible	99.7	Negligible	0.3
Soil (100%)	Negligible	7.9	92.0	Negligible

Table 7.2. Results of the Level III fugacity modelling for TDCPP (EQC 2011)

Substance released to	Partitioning in air (%)	Partitioning in water (%)	Partitioning in soil (%)	Partitioning in sediment (%)
Air (100%)	Negligible	1.6	98.3	0.1
Water (100%)	Negligible	94.6	Negligible	5.4
Soil (100%)	Negligible	1.0	99.0	0.1

7.1.1 Long-range Transport Potential (LRTP)

Measurements of organophosphate flame retardants in air indicate that both TCPP and TDCPP undergo long-range atmospheric transport. Specifically TCPP and TDCPP were detected along with 4 other organophosphate flame retardants (OPFRs) in the North Sea air, predominantly adsorbed to airborne particles (Moller et al. 2011). Both were also found in airborne particles over the Northern Pacific and Indian Ocean toward the Polar Regions (Moller et al. 2012) and at a European Arctic site (Salamova et al. 2014a). In Canada, TCPP and TDCPP were found in air samples collected in the Great Lake atmosphere (Salamova et al. 2014b) and the Canadian Arctic (Jantunen et al. 2013a).

A Long Range Transport and Persistence Level III model (TaPL3 2000) and an OECD P_{ov} and LRTP Screening Tool (Scheringer et al. 2006) were also used, aiming to provide additional information for assessing the LRTPs for these two substances (Environment Canada, Health Canada 2014).

The TaPL3 model provides the estimate for characteristic travel distance (CTD) for TCPP and TDCPP, which is the distance from the source where the initial mass in the mobile medium drops to 1/e (approximately 37%). The CTDs in air calculated for TCPP and TDCPP were below 700 km which is considered of low potential for the long-range transport. Based on the level of concern (Beyer et al. 2000), outcomes from TaPL3 indicate a low concern on the long range transport potential for both substances.

Using the OECD P_{ov} and LRTP Screening Tool, the overall environmental persistence (P_{ov}) and transfer efficiency (TE) with the CTD were estimated. P_{ov} considers environmental distribution and medium-specific half-lives in air, water, sediment and soil (Mackay 2006). This parameter is found to closely link to the potential for long-range transport but is not currently used for decision making in hazard assessment as most regulatory authorities rely on the single-media half-life approach. TE is a measure, expressed as a percentage, for the extent of the deposition of a substance onto the surface media of a target area after being transported away from the region of release (Klasmeier et al. 2006). Based on the level of concern rating system (Scheringer et al. 2006), the long-range atmospheric transport potentials for TCPP and TDCPP are expected to be of moderate concern. It is noted that the above models do not consider

TCPP and TDCPP in the particle phase associated with longer half-lives and may have underestimated the LRTPs for these substances. They also don't consider the amount of these chemicals released in the source region; since chemicals may be transported to remote regions in significant quantities if their releases in source regions are high.

Based on continuous air monitoring data in Ontario, the sampled OPFRs, including TCPP and TDCPP, in air were reported to be predominantly found in particle phase (Shoeib and Jantunen 2013; Shoeib et al. 2014). Measurements of these two compounds in other remote locations confirm that it is the particle phase with which they are associated (Moller et al. 2011; Salamova et al. 2014b).

Liu et al. (2014a) examined hydroxyl- (OH-) initiated oxidation in air of $(NH_4)_2SO_4$ particle-associated 3 organophosphate flame retardants. Keeping the OH radical concentration at a steady state in the experiment, pseudo first-order reactions are assumed. The half-life was estimated as 7.6–9.7 days for TDCPP, derived from the lifetime as 11–14 days reported in the study (Liu et al. 2014a). In another study using a different reference compound, Liu et al. (2014b) reported the half-lives of TDCPP in both gas phase and particle phase. The half-life of this substance in the particle phase is up to 5.6 days (extrapolated from the lifetime as 8.1 days), longer that it in the gas phase (the half-life at 1.3 days, extrapolated from the lifetime at 1.9 days) (Liu et al. 2014b).

Although TCPP was not included in the Liu et al. (2014a and 2014b) studies, based on structural similarity with TDCPP and other phosphate esters that were the subject of these studies (Liu et al. 2014a and 2014b), the particle phase half-life of TCPP for OH oxidation is expected to be similar to that of TDCPP. Findings in this study are in agreement with the environmental data, suggesting that particle-bound TDCPP and TCPP are highly persistent in the atmosphere with regard to OH radical oxidation and both substances undergo long-range atmospheric transport.

Atmospheric transport of these substances leads to a rapid distribution from source regions to remote areas.

7.2 Environmental Persistence

Based on monitoring studies, TCPP and TDCPP in air are predominantly associated with particles. When adsorbed to particles, both TCPP and TDCPP are expected to be highly persistent in air.

Empirical and modelled biodegradation data consistently indicate that both TCPP and TDCPP are stable in the environment and slow to degrade. Hydrolysis is not expected for either TCPP or TDCPP under the environmental conditions in Canada.

Several biodegradation studies were identified for TCPP and TDCPP. The findings suggest no rapid ready biodegradation of either substance in water; however, there is inherent biodegradation observed. The available (Q)SAR models predict slow biodegradation of both substances. Details are discussed below.

7.2.1 Degradation in Air

As mentioned above, TCPP and TDCPP have been found to be predominantly associated with particulates in air (Shoeib and Jantunen 2013; Shoeib et al. 2014). Liu et al. (2014a and 2014b) reported that the half-life of TDCPP in the particle phase ranges from 5.6 days to 9.7 days. The particle phase half-life for the OH oxidation for TCPP is expected to be similar to that of TDCPP, based on the structural similarity between them.

AOPWIN has been used to estimate the half-life of an organic substance in the gaseous phase. The model is not able to predict any reaction of TCPP and TDCPP with other photo-oxidative species in the atmosphere, such as O_3, nor are they likely to degrade by direct photolysis (AOPWIN 2010). Thus, it is expected that reactions with OH radicals will be the most important fate process in the atmosphere for these two substances. The predicted atmospheric oxidation half-life by AOPWIN was 2.9 hours for TCPP and 7.1 hours for TDCPP in the gas phase. This estimate does not take into account the association of organophosphate esters with particulates in air, which demonstrate some resistance to oxidation of OH radicals.

Weight of evidence is then given to the measured half-lives obtained from the laboratory experiments of Liu et al. (2014a and 2014b), which is more relevant to their presence in particle phase in the Canadian environment. Being present in the particle phase, TCPP and TDCPP have demonstrated resistance to the OH-initialized oxidation and do not degrade rapidly.

7.2.2 Hydrolysis

Hydrolysis of TCPP and TDCPP has been studied under a variety of pHs and temperatures (Akzo Nobel 2001a). Those findings are summarized in Table 7.3 and Table 7.4 below.

TCPP was tested at 50ºC and under three different pH conditions (pH=4, 7, and 9) (Akzo Nobel 2001a). At the end of this 5-day study, less than 1% of decrease in the concentration of the test substance was observed in all test groups. Results indicate that there is no significant hydrolysis of TCPP under the environmentally relevant pH conditions (6–9).

Table 7.3. Hydrolysis of TCPP (Akzo Nobel 2001a)

Percentage (%) of hydrolysis	Test period (day)	Test condition (pH)	Test condition (temperature)	Extrapolated half-life
<1	5	pH=4, 7 and 9	50ºC	> 1 year

Similarly to TCPP, TDCPP showed no loss to hydrolysis at 50°C and pH=4 and 7 over a 5-day study; however, at pH=9, a 6% and 16% hydrolysis of TDCPP were observed on days 2 and 4, respectively (Akzo Nobel 2001b). In a longer test of hydrolysis for 30 days, the substance was further tested at pH=9 at 20ºC and 40ºC (Akzo Nobel 2001b). Losses of 3.9% and 44.5% due to hydrolysis were observed at the end of the experiment. The findings suggest that hydrolysis of TDCPP is not significantly expected at typical environmental conditions (pH=6–9 and temperature=5–25ºC).

Table 7.4. Hydrolysis of TDCPP (Akzo Nobel 2001b)

Test period (day)	Test condition (pH and temperature)	Percentage (%) of hydrolysis	Extrapolated half-life
5	pH=4, 50ºC	No significant hydrolysis	>1 yr
5	pH=7, 50ºC	No significant hydrolysis	>1 yr
5	pH=9, 50ºC	16%	14.7 d
30	pH=9, 20ºC	3.9%	120 d
30	pH=9, 40ºC	44.5%	28 d

Considering the available empirical evidence, it is very unlikely that the rates of hydrolysis of both TCPP and TDCPP at environmentally relevant considerations are fast enough to have any influence on their environmental levels.

7.2.3 Biodegradation

Several studies have investigated the biodegradation of TCPP and TDCPP. The reported values of degradation endpoints are summarized in Tables 7.5 and 7.6 below. (Q)SAR models were also used to provide additional lines of evidence for assessing degradation of these two substances.

7.2.3.1 TCPP

According to empirical data, TCPP does not rapidly biodegrade (Table 7.5) and does not meet criteria for ready biodegradation (Environment Canada, Health Canada 2014).

Some inherent biodegradability has been shown for TCPP. In a prolonged closed bottle test under aerobic conditions, activated sludge was aerated for one week prior to the start of the test in which TCPP was present at 4 mg/L (Akzo Nobel 2002). Degradation started on day 21 based on measurement of oxygen consumption and reached 13% on day 28, indicating no rapid biodegradation of the test substance.

In a semi-continuous activated sludge study, TCPP was added to the activated sludge under aerobic conditions (Akzo Nobel 2001c). The substance was completely removed at the end of the 9-week study. Thus, TCPP was considered to be inherently biodegradable (Akzo Nobel 2001c).

In another study of inherent biodegradability, 21% degradation of TDCPP was observed at the end of a 28-day exposure to activated sewage sludge (SafePharm 1996). According to a study summary, there seems an acclimation period of around 13 days at the start of the test, followed by rapid degradation over three days (up to 13%) and then a period of slow degradation, although it had reached a total of 21% degradation by the end of the 28-day exposure. No details are available to further evaluate findings in this study (SafePharm 1996).

Table 7.5. Empirical biodegradation data for TCPP

Fate Process	Test inoculums	Method	Degradation result	Reference
Biodegradation (ready biodegradability)	Activated sludge	Equivalent to OECD 301C, MITI test	28-day degradation = 0%	MITI 1992
Biodegradation (ready biodegradability)	Activated sludge	Not specified	28-day BOD=6% 28-day TOC=2%	CHRIP c2008
Biodegradation (ready biodegradability)	Activated sludge	OECD 301E	28-day degradation= 14% (DOC removal)	Bayer 1991a
Biodegradation (ready biodegradability)	Activated sludge	USEPA TSCA 796.3100	28-day $CO_2 \leqslant$ 6.7% 28-day DOC $\leqslant$ 18.3 %	ABC Laboratories 1993
Biodegradation (inherent biodegradability)	Activated sludge	EPA OPPTS 835.3200	28-day BOD = 13% 50-day BOD = 60% 84-day BOD = 100%	Akzo Nobel 2002
Biodegradation (inherent biodegradability)	Activated sludge	OECD 302A; EEC Directive 87/302; ISO TC 147	100% removal in the end of 9 weeks	Akzo Nobel 2001c
Biodegradation (inherent biodegradability)	Activated sludge	Not specified	28-day degradation = 21% (O_2 consumption)	SafePharm 1996

Abbreviations: BOD, biological oxygen demand; TOC, total organic carbon.

7.2.3.2 TDCPP

Empirical data suggest that TDCPP does not biodegrade rapidly (Table 7.6). In general, the substance has a slower rate of biodegradation than TCPP, presumably due to chlorine replacing methyl groups. Reported values from the laboratory studies are all

below the criteria for ready biodegradation (Environment Canada, Health Canada 2014).

Degradation of TDCPP was also studied in water collected from 2 rivers and 2 coastal areas in Japan (Hattori et al. 1981) under aerobic conditions. TDCPP was reported to degrade by 18.5% in water from Oh River and 22% in sea-water from Osaka Bay after 14 days.

In an inherent biodegradation study, no degradation was observed at the end of 28 days (SafePharm Laboratories 1996a). It is noted that there was no acclimation period used in the study, and therefore, the outcome is not considered suitable to draw any conclusion with respect to biodegradation.

Table 7.6. Empirical data for biodegradation of TDCPP

Fate Process	Test inoculums	Method	Degradation result	Reference
Biodegradation (ready biodegradability)	Domestic sludge	OECD 301B OECD 301D	28-day degradation = 0% (CO_2 evolution)	Life Science Research 1990
Biodegradation (ready biodegradability)	Activated sludge	Not specified	28-day BOD = 1%	CHRIP c2008
Biodegradation (ready biodegradability)	Not specified	OECD 301C OECD 302C	28-day BOD = 0–4%	CITI 1992
Biodegradation (inherent biodegradability)	Activated sewage sludge	OECD 302C	28-day degradation = 0% (O_2 consumption)	SafePharm Laboratories 1996a
Biodegradation (anaerobic)	Anaerobic sludge	Not specified	60-day degradation = 0% (chloride release)	van Ginkel 2005
Biodegradation	Open water from Japan	Molybdenum blue colorimetric method	7-day degradation = 0–12.5% 14-day degradation = 0–22%	Hattori et al. 1981
Biodegradation	Natural soil	OECD 307	122-day degradation = 2.7–5.5% (CO_2 evolution)	Wildlife International 2005a

Abbreviation: BOD, biological oxygen demand.

(Q)SAR-based modelling (Environment Canada 2007) was also performed in order to provide additional lines of evidence for characterizing the biodegradation of TCPP and TDCPP. In summary, results for all of the BIOWIN biodegradation sub-models (BIOWIN Sub-models 3, 5, and 6) indicate no rapid biodegradation for TCPP and TDCPP; in addition, the ultimate degradation predictions from CPOPs (2012) indicate no rapid biodegradation (Environment Canada, Health Canada 2014).

7.2.4 Degradation in soil and sediment

There has been a study identified to investigate degradation of TDCPP in natural soil (Wildlife International 2005a). The substance was applied to the soil surface and the soil samples were incubated at 20 ± 2 ^{o}C for 17 weeks. At the end of the study, very little degradation (2.7-5.5% CO_2 evolution) was reported (Wildlife International 2005a).

Moreover, no additional experimental studies were found for the biodegradation of TCPP in soil or sediment or the biodegradation of TDCPP in sediment. Available modelling is limited for these two compartments. Therefore, an extrapolation ratio of 1:1:4 for water: soil: sediment biodegradation half-life based on Boethling et al. (1995) was applied. Given that the half-lives of TCPP and TDCPP in water are long and likely greater than 182 days (based on results in biodegradation studies summarized in Table 7.6), it follows that the half-life of TCPP in soil is expected to be greater than 182 days and the half-lives of TCPP and TDCPP in sediments are expected to be greater than 365 days. Both TCPP and TDCPP are likely to persist in soil and sediment.

7.2.5 Metabolism of TCPP and TDCPP

TCPP and TDCPP have been reported to undergo rapid metabolism in organisms. While data are available indicating metabolic transformation pathways in rats, the pathway in aquatic organisms remains unclear.

In the training set of BCFBAF (2010), there are data for screening level whole body primary biotransformation half-lives (day) and rate constants (k_M d^{-1}) of discrete chemicals in fish calculated according to the method of Arnot et al. (2008a and 2008b). Empirical *in vivo* biotransformation half-life estimates for a 10 g fish are 0.05 and 0.30 days for TCPP and TDCPP, respectively. QSAR predicted half-lives in a 10 g fish are 0.14 and 0.41 days for TCPP and TDCPP, respectively (EPI Suite 2000–2012). The *in vivo* and *in silico* estimates are in very good agreement with each other for both chemicals. Available evidence suggests that primary biotransformations for TCPP and TDCPP are relatively fast in fish; however, the metabolic intermediates were not specified. In a recent avian study, bis(1,3-dichloro-2-propyl) hydrogen phosphate (BDCPP, CAS RN 72236-72-7) was confirmed to be a metabolic intermediate of TDCPP (Farhat et al. 2014).

Rapid metabolism of TCPP and TDCPP has also been reported in toxicokinetics studies using rodents (see sections 9.1.3 and 9.2.2.2 for details). One study on TCPP found that an average of 89% of the administration dose of this substance by oral or intravenous means were eliminated within 72 hours after the treatment. A major metabolite was identified as 0,0-[bis(1-chloro-2-propyl)]-0-(2,propionic acid)phosphate and was found to account for over 50% of the dose (Stauffer Chemical Co. 1984). In a toxicokinetic study on TDCPP, recovery of radioactivity 168 hours after administration

was 43.2% in urine, 39.2% in feces, 16.24% in expired air (as carbon dioxide) and 2.51% in carcass (Minegishi et al. 1988). The major metabolite was a BDCPP, a diester of TDCPP (Lynn et al. 1981).

The rapid metabolism of TCPP and TDCPP suggests a low potential for accumulation in organisms (discussed further in next section). Concomitantly, this rapid metabolism results in the formation of potentially stable metabolites.

7.3 Potential for Bioaccumulation

Based on measured bioconcentration factors (BCFs), empirical data suggest low bioconcentration potential for TCPP and TDCPP in aquatic biota. As there are no available empirical bioaccumulation factor (BAF) data for TCPP or TDCPP, (Q)SAR models were used to generate estimates and the resulting modelled BAFs are low. Considering these low BAFs and the rapid biotransformation rates for these substances, biomagnification of TCPP and TDCPP through the food web is unlikely, and exposure to higher trophic level organisms are expected to be lower than exposure to lower trophic level organisms.

Details are discussed below.

7.3.1 Bioaccumulation in aquatic organisms

Empirical BCFs in aquatic organisms have been identified for TCPP and TDCPP and low BCFs have been reported for both substances (Table 7.7).

In a study using the static water test system, absorption and elimination of 4 organophosphate flame retardants (including TDCPP) was investigated (Sasaki et al. 1981). Absorption of TDCPP was observed in the Killifish and Goldfish at the similar rate, according to measured concentrations in the test water; however the bioconcentration was reported to be much higher in Killifish than it in Goldfish. Findings suggest a difference in metabolic activity for TDCPP in these two species (Sasaki et al. 1981). The half-life for elimination of TDCPP in killifish is 1.65 hours (WHO 1998).

Table 7.7. Empirical bioconcentration factor (BCF) of TCPP and TDCPP in fish

Substance	Test organism	Exposure concentration and duration	BCF (L/kg)	Reference
TCPP	Carp *Cyprimus carpio*	0.2 mg/L for 6 weeks	0.8–2.8	CITI 1992

TCPP	Carp *Cyprimus carpio*	0.02 mg/L for 6 weeks	<1.9–4.6	CITI 1992
TDCPP	Carp *Cyprimus carpio*	0.02 mg/L for 6 weeks	0.3–3.3	CITI 1992
TDCPP	Carp *Cyprimus carpio*	0.002 mg/L for 6 weeks	<2.2–22	CITI 1992
TDCPP	Killifish *Oryzias latipes*	0.3–1.2 mg/L for 96 hours (static)	31–59	Sasaki et al. 1982
TDCPP	Killifish *Oryzias latipes*	0.04–0.4 mg/L for 72–144 hours (continuous)	31–46	Sasaki et al. 1982
TDCPP	Killifish *Oryzias latipes*	0.04–0.08 mg/L for 30–32 days (continuous)	49–59	Sasaki et al. 1982

MITI (Japan) also assessed bioconcentration for TCPP and TDCPP (CHRIP c2008). Both substances were determined as "not high bioconcentration" under the Chemical Substances Control Law in Japan (CHRIP c2008); however, no further details were provided in the database.

(Q)SAR models were used to provide additional lines of evidence for characterizing bioconcentration potential for TCPP and TDCPP. Outcomes from models (BCFBAF and CPOPs) have not indicated any high BCFs (see Table 7.8).

Table 7.8. BCF predictions for TCPP and TDCPP

Substance	Test organism	Endpoint and value	Reference
TCPP	Fish	BCF = 13.26 L/kg (middle trophic level fish)	BCFBAF 2010
TCPP	Fish	BCF = 3.79 L/kg	CPOPs 2012
TDCPP	Fish	BCF = 111.6 L/kg (middle trophic level fish)	BCFBAF 2010
TDCPP	Fish	BCF = 4.52 L/kg	CPOPs 2012

BAF is also considered for assessing the bioaccumulation potential for TCPP and TDCPP.

BAF is measured under field conditions as the ratio of the whole body burden of a chemical taken up from all exposures to that of the ambient water concentrations. Measures of BAF are the preferred metric for assessing the bioaccumulation potential of substances because they incorporate chemical exposures from all routes including the diet, which predominates for substances with log K_{ow}> ~4.0 (Arnot and Gobas 2003).

No empirical BAF data were found for either TCPP or TDCPP. Considering log K_{ow} values of 2.68 for TCPP and 3.69 for TDCPP, accumulation through dietary uptake is not expected to be a relatively important process for these substances. The available (Q)SAR models were used to estimate this endpoint and estimates of BAFs are equivalent to BCFs for both substances (Table 7.9).

Table 7.9. BAF predictions for TCPP and TDCPP

Substance	Test organism	Endpoint and value	Reference
TCPP	Fish	BAF = 13.26 L/kg (middle trophic level fish)	BCFBAF 2010
TDCPP	Fish	BAF = 111.7 L/kg (middle trophic level fish)	BCFBAF 2010

The low bioaccumulation potential predicted for TCPP and TDCPP are in agreement with the low BCFs, the rapid biotransformation and low lipid (octanol) partitioning tendency of these two substances in aquatic organisms. As mentioned above, biotransformation half-lives of both substances are calculated to be shorter than 0.5 day in fish, based on empirical primary transformation rate constants (k_M) (Table 7.10). Hence, biomagnification through the food webs is unlikely, and exposure to higher trophic level organisms is expected to be lower than exposure to lower trophic level organisms.

Table 7.10. Primary biotransformation rate constants (kM) from the training set and corresponding half-lives for a 10 g fish (BCFBAF 2010)

Substance	Experimental k_M (/day)	Biotransformation half-life(day)	BCF (L/kg)
TCPP	14.12	0.05	8
TDCPP	2.29	0.30	12

7.3.2 Bioaccumulation in terrestrial plants

Eggen et al. (2013) conducted a study to investigate uptake and translocation of chemicals (including TCPP and another two organophosphate ester, TCEP and tributyl phosphate (TBP)) in food and forage crops. Barley (*Hordeum vulgare*), Wheat (*Triticum aestivum*), Oilseed Rape (*Brassica rapa*), Meadow Fescue (*Festuca pratense*), and four cultivars of carrot (*Daucus caroto*) were exposed to treated soil (TCPP at the measured concentration of 0.72 mg/kg dw) for 17 weeks. At the end of the study, higher concentrations of TCPP were found in leaves and roots, but lower concentrations in seeds, compared to the exposure concentration in the treated soil (Environment Canada, Health Canada 2014). The highest concentration factor was up to 25.6 (in leaves of Meadow Fescue), suggesting no significant accumulation of TCPP in plants.

7.3.3 Bioaccumulation potentials for metabolites

There has been no study identified to investigate bioaccumulation potentials for metabolites of TCPP and TDCPP in organisms; however, the findings in fish and mammalian studies on parent compounds have provided some indirect evidence (see sections 9.1.3 and 9.2.2.2 for details on metabolism in mammals). Regardless that the transformation products of TCPP and TDCPP may be somewhat different in fish and mammals, elimination of two substances and their transformation products from organisms is rapid, suggesting that metabolites of TCPP and TDCPP have low bioaccumulation potentials.

8. Potential to Cause Ecological Harm

8.1 Ecological Effects Assessment

TCPP and TDCPP are chlorinated alkyl phosphate esters that are reactive chemicals in biota. Empirical effects data suggest that TCPP possesses a lower toxicity than TDCPP with respect to survival and growth of organisms. Effects on the endocrine system have been observed only for TDCPP in fish. Effects of both substances on enzyme activities and the transcription of genes associated with a variety of biological functions have been observed in cell assays but to different extent. The difference in the overall toxicity between two substances may be due to the higher chlorination in TDCPP.

Key studies are discussed in the following sections, while details are presented in Environment Canada, Health Canada (2014). Data for endpoints of survival, growth or development of test organisms with relevance to the environmental exposure in Canada were considered in the risk characterization.

8.1.1 Toxicity to Aquatic Organisms

Acute toxicity data for TCPP and TDCPP are available for all three major taxa (fish, crustaceans and algae), while chronic toxicity data are available for crustaceans and algae (ECCC 2013-2014). In addition to *in vivo* studies, *in vitro* studies have examined effects on cells and gene transcription, in order to understand the mechanism of their effects on the endocrine system.

8.1.1.1 Effects on Survival, Reproduction, and Growth

TCPP has demonstrated moderate toxicity to aquatic organisms. The 24–96 hour EC_{50}s/LC_{50}s range from 9.8–180 mg/L for three major taxa (fish, crustaceans and algae); the chronic no observed effect concentrations (NOECs) range from 6–32 mg/L for crustaceans and algae.

TDCPP exhibits greater toxicity (exerting the same effect/response at lower exposure concentrations) to aquatic organisms than TCPP, likely due to the higher chlorination of this substance. For TDCPP, the 24–96 hour EC_{50}s/LC_{50}s range from 1.1–39 mg/L for all three taxa, and the chronic NOECs range from 0.5–10 mg/L for crustaceans and algae.

8.1.1.2 Other Effects on Aquatic Organisms

Liu et al. (2012) conducted a study to investigate effects on the endocrine system in zebrafish (*Danio rerio*) of 6 organophosphate flame retardants, including TCPP and TDCPP. The first part of the study measured 1) the concentrations of sex hormones and the transcriptions of key genes involved in steriodogenesis and 2) the binding affinity to estrogen receptors.

TCPP has a weaker effect in cell assays, as the lowest concentration (1 mg/L) of TCPP affecting 17β-estradiol (E2) and testosterone (T) in H295 cells were two orders of magnitude greater than the lowest concentration of TDCPP (0.01 mg/L), at which level comparable effects were observed. Therefore, only TDCPP was further investigated for its potential effects on the endocrine system of zebrafish (Liu et al. 2012) and results are summarized in Table 8.1 below. After exposure to TDCPP for 14 days, plasma E2 and T concentrations in adult zebrafish significantly increased in both male and female fish exposed at a concentration of 1 mg/L. Plasma 11-ketotestosterone (11-KT) concentration significantly decreased at 0.04 mg/L and above in male fish; however, there was no significant change associated with female fish in any test concentration groups. Significant effects on related gene transcriptions (CYP17, CYP19A, and VTG) in fish gonads and liver were observed only in the 1 mg/L concentration group in both male and female fish, with an additional significant downregulation of VTG at 0.2 mg/L in female fish (Liu et al. 2012). However, there was no information on semen production and density in male fish reported in this study (Liu et al. 2012).

Table 8.1. Hormonal effects of a 14-day exposure to TDCPP on adult zebrafish (Liu et al. 2012)

Endpoint	No effect concentration (mg/L)	Lowest effect concentration (mg/L)
E2 in plasma	0.2 mg/L (both male and female)	1 mg/L (both male and female)
T in plasma	0.2 mg/L (both male and female)	1 mg/L (both male and female)
11-KT in plasma	0.04 mg/L (male) No effect at all test concentrations (female)	0.04 mg/L (male) No effect at all test concentrations (female)
Gene transcriptions in gonad and liver	0.2 mg/L (male) 0.04 mg/L (female)	1 mg/L (male) 0.2 mg/L (female)

Acronym: E2, 17β-estradiol; T, testosterone; 11-KT, 11-ketotestosterone.

Wang et al. (2013) studied the effect of TDCPP on the thyroid endocrine system in zebrafish embryos. Test organisms were exposed to different concentrations of TDCPP (0.01 to 0.6 mg/L) from 2 hours post fertilization to 144 hours post fertilization. Developmental endpoints, whole-body concentrations of thyroid hormones and transcriptional profiles of genes in the hypothalamic-pituitary-thyroid (HPT) were examined (see Table 8.2). A significant effect on hatching rate and survival rate was observed in the test organism with exposure at 0.6 mg/L. A significant incidence of malformation was observed at an even lower concentration at 0.3 mg/L. Besides its effects on development endpoints, the whole body thyroxine (T4) and triiodothyronine (T3) concentrations were significantly lower in fish exposed to the substance at concentrations of 0.05 and 0.3 mg/L, respectively. Ten genes involved in the HPT axis of zebrafish embryos/larvae were also studied; mRNA expression was affected in 8 of these genes by exposure to TDCPP at or above 0.1 mg/L (Wang et al. 2013).

Table 8.2. Effects of a 14-day exposure to TDCPP on the thyroid endocrine system in zebrafish embryos (Wang et al. 2013)

Endpoint	No effect concentration (mg/L)	Lowest effect concentration (mg/L)
Hatching rate	0.3	0.6 (a significantly lower hatching rate)
Survival rate	0.3	0.6 (a significantly lower survival rate)
Heart rate	0.05	0.1 (a significantly lower heart rate)

Body weight	0.01	0.05 (a significantly lower body weight)
Malformation	0.01	0.3 (a significantly higher incidence of malformation rate, spinal curvature)
T4 concentration	0.01	0.05 (significantly lower)
T3 concentration	0.1	0.3 (significantly higher)
mRNA expressions of 10 genes	0.05	0.1 (a significant up-regulation)

Acronym: T4, thyroxine; T3, triiodothyronine.

In a chronic study, thyroid hormone homeostasis and neuronal development was studied in the progeny of adult zebrafish exposed to TDCPP for 3 months (Wang et al. 2015a) (Table 8.3). Effects on the overall development of the first generation (F1) zebrafish larvae, thyroid hormone contents, expression of genes associated with the nervous system were measured. In general, no significant effect has been observed at the concentration of 0.004 mg/L (Wang et al. 2015a).

Table 8.3. Effects of a 3-month exposure to TDCPP on the thyroid endocrine system and developmental neurotoxicity in zebrafish embryos (Wang et al. 2015a)

Endpoint	**No effect concentration (mg/L)**	**Lowest effect concentration (mg/L)**
Hatching rate	0.004	0.02 (a significantly lower hatching rate)
Malformation	0.02	0.1 (a significantly higher incidence)
Survival rate	0.004	0.02 (a significantly lower survival rate)
Body weight	0.02	0.1 (a significantly lower body weight)
F0 T4 concentration	0.004	0.02 (significantly lower)
F0 T3 concentration	0.02	0.1 (significantly lower)
Eggs T4	0.02	0.1 (significantly lower)
Eggs T3	0.1	Not applicable
F1 5-dpf T4	0.02	0.1 (significantly lower)
F1 5-dpf T3	0.01	Not applicable
F1 10-dpf T4	0.004	0.02 (significantly lower)
F1 10-dpf T3	0.02	0.1 (significantly lower)
5 genes associated with the nervous system	0.004	0.02 (a significant downregulation)
4 neurotransmitter concentrations in TDCPP-exposed F1 larvae	0.004	0.02 (a significant lower concentration)
Locomotor activity	0.02	0.1 (a significantly slower swimming

		speed)

Acronym: F0, adult fish; F1; first generation; T4, thyroxine; T3, triiodothyronine; dpf, day post fertilization.

In a longer term study, zebrafish larvae were exposed to TDCPP at 0, 0.004, 0.02, and 0.1 mg/L for 6 months (Wang et al. 2015b) (Table 8.4). Developmental parameters were recorded at 5 days post fertilization (dpf) for the first generation (F1). The hatching, survival rates and growth were not significantly changed in the F1 derived from the exposed F0 fish; however, there was a significant increase in the incidence of malformation in F1 embryos derived from parents exposed to 0.02 and 0.1 mg/L TDCPP. In adult fish (F0), there were no significant differences in survival rates; however, decreased body weight was observed at the lowest concentration at 0.004 mg/L with additional growth parameters affected at or above 0.2 mg/L.

Table 8.4. Effects of a 6-month exposure to TDCPP on the endocrine system and reproductive effects in zebrafish embryos (Wang et al. 2015b)

Endpoint	**No effect concentration (mg/L)**	**Lowest effect concentration (mg/L)**
Body weight (F0)	Not applicable	0.004 (a significantly lower body weight)
Length	0.1	Not applicable
Weight/length ratio (F0)	0.004	0.2 (a significantly lower ratio)
Gonad weight/body weight (F0)	0.02 (male) 0.004 (female)	0.1 (male) (a significantly lower ratio) 0.02 (female) (a significantly higher ratio)
Hatching (F1)	0.1	Not applicable
Survival (F1)	0.1	Not applicable
Malformation (F1)	0.004	0.02 (a significant incidence)
Egg production	0.004	0.02 (a significant lower production)
Plasma estradiol (E2) and testosterone (T) in female fish	0.004	0.02 (a significantly higher concentration)
Plasma estradiol (E2) and testosterone (T) in male fish	0.1	Not applicable
4 gene transcription levels in brain	Not applicable	0.004 (1 within 4 gene expressions assessed)
4 gene transcription	0.004	0.02 (1 within 4 gene expressions

levels in liver		assessed)
9 gene transcription levels in gonad	Not applicable	0.004 (1 within 9 gene expressions assessed)

Acronym: F0, adult fish.

In another long term study on TDCPP with the similar experimental design, zebrafish larvae were exposed to TDCPP at 0, 0.004, 0.02, and 0.1 mg/L for 6 months (Wang et al. 2015c) (Table 8.5). No effect on the overall development of the fish embryos/larvae was reported. In addition to effects on certain gene expression parameters, concentrations of two neurotransmitters were found much lower in female fish brain in all test groups; however, concentrations of those two neurotransmitters were not affected in male fish brain at any test concentration. The acetylcholinesterase activity (as a biomarker for the presence of neurotoxicants) and locomoter activity was not affected in all adult fish at any test concentration.

Table 8.5. Effects of a 6-month exposure to TDCPP on the endocrine system and reproductive effects in zebrafish embryos (Wang et al. 2015c)

Endpoint	**No effect concentration (mg/L)**	**Lowest effect concentration (mg/L)**
Development (hatching, malformation, survival, weight)	0.1	Not applicable
5 gene expression in the nervous system of zebrafish larvae	0.02	0.1 (a significantly up-regulation for 1 within 5 genes assessed)
5 gene expression in the nervous system of zebrafish adult fish	0.004	0.02 (a significantly down-regulation)
α1-tubulin in fish brain	0.004 (female) 0.02 (male)	0.02 (female) 0.1 (male) (a significantly lower production)
Myelin basic protein in fish brain	0.004 (female) 0.1 (male)	0.02 (female) (a significantly lower production) Not applicable for male
Dopamine and serotonin in female fish brain	Not applicable	0.004 (a significantly lower concentration)

Dopamine and serotonin in male fish brain	0.1	Not applicable
Acetylcholinesterase activity in adult fish	0.1	Not applicable
Locomoter activity	0.1	Not applicable

In a study by Liu et al. (2013) to investigate effects of TDCPP on zebrafish embryos/larvae, there was no change in either 72-hour post hatching rate or the 120-hour post hatching survival rate in test organisms with an exposure of the substance at 4 mg/L or lower. No malformation was observed when exposed to 2 mg/L TDCPP, which was the highest concentration used in the second part of this study (Liu et al. 2013). In addition, TDCPP was determined to affect expression of mRNAs involved in six receptor-centred gene networks at a very low concentration (0.02 mg/L).

In a study to assess overt toxicity and behavior in early life stage of zebrafish (*Danio rerio*), the test organisms were exposed to 0.033-100 µM TCPP and TDCPP from 0 to 5 days post fertilization (dpf) (Dishaw et al. 2014). Significant mortality and severe malformation were observed by 6 dpf in fish exposed to TDCPP at a concentration of 10 µM (equivalent to 4.3 mg/L); however, there was no mortality or teratogenicity in TCPP exposed fish. Larval swimming activity was used to evaluate neurobehavioral effects. Larvae exposed to TCPP (100 µM, equivalent to 33 mg/L) were hyperactive in the light phase; although their swimming ability was not impaired as exhibited by normal activity during the dark period. TDCPP elicited hyperactivity during both the light (5.6 µM, equivalent to 2.41 mg/L) and dark periods (3.14 µM, equivalent to 1.35 mg/L) in the test organisms.

According to findings reported in the above studies, TCPP has less potential to affect the hormonal system in aquatic organisms than TDCPP. For TDCPP, the lowest effect concentrations demonstrating some effects on the endocrine system are at levels below those seen to elicit effects in standard toxicity tests, which evaluate endpoints such as survival, reproduction and growth.

For the purpose of the risk assessment, data for endpoints from *in vitro* studies which show linkage to organism level effects are considered to characterize the effects of these two substances.

8.1.1.3 Selection of Critical Toxicity Value for Aquatic Organisms

Key aquatic toxicity studies are summarized in Table 8.3 for consideration in choosing a critical toxicity value for both substances.

Table 8.3. Key aquatic toxicity studies considered in choosing a critical toxicity value for water

Substance	Test Organism	Endpoint	Value (mg/L)	Reference
TCPP	Fathead Minnow *Pimephales promelas*	96-hour LC_{50}	51	Mobil 1985
TCPP	Freshwater Algae *Pseudokirchneriella subcapitata*	72-hour EC_{50} (growth rate)	88	Wildlife International 2005b
TDCPP	Rainbow Trout *Oncorhynchus mykiss*	96-hour LC_{50}	1.1	SafePharm Laboratories 1993
TDCPP	Freshwater Algae *Pseudokirchneriella subcapitata*	72-hour EC_{50} (growth rate)	4.6	Wildlife International 2005c
TDCPP	Zebrafish *Danio rerio*	6-day survival	0.6[a]	Wang et al. 2013
TDCPP	Zebrafish *Danio rerio*	6-day EC_{10}[b] (malformation)	0.3[a]	Wang et al. 2013
TDCPP	Zebrafish *Danio rerio*	90-day NOEC (survival and hatching rates)	0.004	Wang et al. 2015a
TDCPP	Zebrafish *Danio rerio*	180-day NOEC (malformation)	0.004	Wang et al. 2015b

[a] The lowest test concentration at which a significant effect was observed.

[b] 10% incidence of malformation in test organisms was estimated from Figure 6 in Wang et al. 2013.

As the lowest aquatic toxicity value identified for TCPP, the 96-hour LC_{50} of 51 mg/L for the Fathead Minnow was selected as the critical toxicity value (CTV) and in turn used to calculate a predicted no effect concentration (PNEC) for TCPP (Table 8.4).

For TDCPP, no effect on survival and hatching of zebrafish embryos and no incidence of malformation was reported in fish exposed to the substance at a concentration of 0.004 mg/L in long term studies. Therefore, the chronic NOEC = 0.004 mg/L was selected as the CTV and used to calculate a PNEC for this substance (Table 8.4).

Considering that the available dataset for TCPP and TDCPP have included a variety of species of aquatic organisms, an assessment factor of 30 was applied to extrapolate from the acute effect concentrations to the PNECs (see Table 8.4).

Table 8.4. Aquatic CTVs and PNECs for TCPP and TDCPP

Substance	CTV (mg/L)	AF	PNEC (mg/L)
TCPP	96-hour LC_{50} = 51	30[a]	1.7
TDCPP	90-day NOEC (survival and hatching rates) = 0.004	3[b]	0.0013

[a] An AF=30 is applied to calculate a long term no-effect concentration (PNEC) with consideration of the number of organism/species in the available dataset.

[b] An AF=3 is applied to calculate a long term no-effect concentration (PNEC) from a long term toxicity data, with consideration of the number of organism/species in the available dataset.

8.1.2 Toxicity to Sediment Organisms

There are no sediment toxicity data identified for TCPP. Given that TCPP and TDCPP have demonstrated different levels of toxicity on aquatic organisms and effects on the endocrine system, it is not considered appropriate to determine the effects of TCPP on sediment organisms through read-across. Therefore, a PNEC is not calculated for TCPP for this compartment.

Sediment toxicity data have been identified for TDCPP. In a few studies investigating the chronic exposure of TDCPP to midges, the reported 28-day EC_{50}s range from 16 and > 71 mg/kg dry weight (dw); the reported NOECs range from 3.9 and 71 mg/kg dw (Wildlife International 2006b, 2006c, 2006d).

Upon review of the empirical data, the 28-day EC_{50} (emergence of midge) = 16 mg/kg dw was selected as the CTV for TDCPP. Considering the organic carbon (OC) content as 5.3% was reported in this study, the CTV was adjusted to the standard 4% OC

content prior to calculating the PNEC. An assessment factor of 50 was used to derive the PNEC, to extrapolate a chronic no effect concentration from a chronic effect endpoint and to account for inter- and intra-species variability. This yields a sediment PNEC of 0.24 mg/kg dw for TDCPP.

8.1.3 Toxicity to Soil Organisms

Toxicity studies have been conducted on earthworms to investigate effects of TCPP and TDCPP in soil organisms. After earthworms (*Eisenia foetida*) were exposed to these substances for up to 8 weeks, EC_{50}s/LC_{50}s and NOECs were reported (SafePharm Laboratories 1996b and 1996c; Phytosafe 2003a and 2004a). These values are summarized in Table 8.5.

Two studies investigated the toxicity of TCPP and TDCPP on terrestrial plants. In one study, Wheat (*Triticum aestivum*), Mustard (*Sinapis alba*), and Lettuce (*Lactuca sativa*) were exposed to TCPP for 21 days, and effects on the dry plant weight and the seeding emergence were assessed at the end of the experiment (Phytosafe 2003b). The lowest NOEC of the study was 17 mg/kg dw for the seeding emergence of Lettuce. In another study, Wheat (*Triticum aestivum*), Mustard (*Sinapis alba*) and Red Clover (*Trifolium pratense*) were exposed to TDCPP and effects on emergence and plant growth were assessed (Phytosafe 2004b). The lowest NOEC in this study was 19.3 mg/kg dw for seeding emergence.

Findings in key soil toxicity studies are summarized in Table 8.5 below.

Table 8.5. Key soil toxicity studies considered in choosing a critical toxicity value for soil

Substance	Test organism	Endpoint	Value (mg/kg dw)	Reference
TCPP	Earthworms *Eisenia foetida*	14-day LC_{50}	97	SafePharm Laboratories 1996b
TCPP	Earthworms *Eisenia foetida*	14-day NOEC (mortality)	32	SafePharm Laboratories 1996b
TCPP	Earthworms *Eisenia foetida*	56-day EC_{50} (reproduction)	71	Phytosafe 2003a
TCPP	Earthworms *Eisenia foetida*	56-day NOEC (reproduction)	53	Phytosafe 2003a

TCPP	Lettuce *Lactuca sativa*	21-day NOEC (emergence)	17	Phytosafe 2003b
TDCPP	Earthworms *Eisenia foetida*	14-day LC_{50}	130	SafePharm Laboratories 1996c
TDCPP	Earthworms *Eisenia foetida*	14-day NOEC (mortality)	100	SafePharm Laboratories 1996c
TDCPP	Earthworms *Eisenia foetida*	57-day EC_{50} (reproduction)	67	Phytosafe 2004a
TDCPP	Earthworms *Eisenia foetida*	57-day NOEC (reproduction)	9.6	Phytosafe 2004a
TDCPP	Mustard *Sinapis alba*	19-day NOEC (emergence)	19.3	Phytosafe 2004b

The 56-day EC_{50} = 71 mg/kg dw and 57-day EC_{50} = 67 mg/kg dw were considered as CTVs for TCPP and TDCPP, respectively. Considering the organic carbon (OC) contents reported in these studies, the CTVs were adjusted to the standard 2% OC content prior to calculating PNECs.

An assessment factor of 50 was used to derive PNECs for both substances, to extrapolate a chronic no effect concentration from a chronic sub-lethal effect endpoint and to account for inter- and intra-species variation. Results are presented in Table 8.6 below.

Table 8.6. Soil critical toxicity values (CTV) and PNECs for TCPP and TDCPP

Substance	CTV (mg/kg dw)	OC content (%)	AF	PNEC (mg/kg dw)
TCPP	56-day EC_{50} = 71	1.4	50	2.03
TDCPP	57-day EC_{50} = 67	10	50	0.27

8.1.4 Toxicity to Birds and Mammals

In vitro and *in ovo* studies on TCPP and TDCPP have been conducted to investigate their neurotoxicity, cytotoxicity and genetic effects and the findings provide evidence of chemical reactivity and mode of action. It is noted that exposure concentrations used in these studies are several orders of magnitude greater than concentrations of both substances measured in the Canadian environment (i.e., water and eggs). Therefore, effects observed in laboratory experiments are not expected in the wild according to

their levels of environmental occurrence. As a result, the toxicity data reported from *in vitro* or *in ovo* studies were not used in the risk quotient analysis for these substances.

8.1.4.1 Neurotoxicity

Both TCPP and TDCPP have demonstrated low levels of neurotoxic effect on hens and mammals. Details are presented in sections 9.2.1.7 and 9.2.2.6.

8.1.4.2 Effects on the Endocrine System

Effects on the endocrine system for these two substances were assessed *in ovo* and *in vitro*.

In a study using primary cultures of avian neuronal cells, Crump et al. (2012) reported a higher cytotoxicity of TDCPP than TCPP. Effects on mRNA expressions associated with a variety of biological functions were studied. Both substances may demonstrate an effect on the TH pathway related gene transcription at or above 10 µM (equivalent to 3.3 mg/L and 4.3 mg/L, respectively) (Crump et al. 2012).

In an *in ovo* toxicity study (Farhat et al. 2013), chicken eggs were injected with TCPP and TDCPP separately, and the highest concentrations used were 51 600 and 45 000 ng/g wet weight (ww) of eggs, respectively. There was no lethal response to any treatment doses of either substance. Only TDCPP significantly reduced the plasma T4 levels at 7640 ng/g and higher. In addition, there was no effect on pipping success of chicken; however, a delay of pipping was observed in higher concentration groups of two substances, at 9240 ng/g and above for TCPP and at 7640 ng/g and above for TDCPP. Embryonic development (the tarsus length, the embryo mass, head and bill length, and the gallbladder length) was affected by both test substances at the highest concentration. It is noted that the exposure concentrations in the above studies are much higher than measured concentrations in avian eggs <6.7 ng/g for TCPP and up to 0.17 for TDCPP found in the environment (Chen et al. 2012; Leonards et al. 2011).

In a 21-day study, captive American Kestrels were fed with TCPP and TDCPP (and other OPFRs) at the same dose of 22 ng OPFR/g-bw per day (Fernie et al. 2015). The exposure to both substances had no significant effect on the body mass or temporal weight gain of the test organisms. Both substances were not detected in tissues, suggesting rapid metabolism. However, some biological effect, i.e. the plasma A:G ratio, was observed in kestrels expose to TCPP and TDCPP. In addition, effects on the triiodothyronine (T3) and thyroxine (T4) concentrations in plasma and changes in thyroid gland structure and related enzyme activities were observed in the test organisms exposed to TCPP and TDCPP (Fernie et al. 2015).

There have been *in vitro* studies conducted to assess effects on the endocrine system for TCPP and TDCPP using mammalian cells (Follmann and Wober 2006; Kojima et al. 2013). Details are discussed in sections 9.2.1.6 and 9.2.2.4.

8.1.4.3 Genetic effects

Genetic effects were also assessed in the Farhat et al. study (2013). Among the 9 mRNA transcripts studied, effects of these two substances on some gene expressions were observed only at the highest concentrations of TCPP and TDCPP, at 51 600 and 45 000 ng/g wet weight (ww) of eggs, respectively (Farhat et al. 2013). Farhat et al. 2013 notes that low tissue residue concentrations relative to the injected doses may be due to rapid metabolism of TCPP and TDCPP in chicken embryos, which is in agreement with the observation in rat studies, showing that the majority of dosed TCPP and TDCPP was eliminated quickly within a few days of administration (Lynn et al. 1980; Minegishi et al. 1988).

In the same study on cytotoxicity and mRNA expression in cultures of avian cells (Crump et al. 2012), both substances affected transcription of genes associated with xenobiotic metabolism (CYP2H1), the thyroid hormone pathway (TTR), lipid metabolism (L-FABP and HRSP14-α), and growth (IGF-1). Both substances demonstrated upregulation of most genes studied at a concentration of 10 µM (equivalent to 3.3 mg/L and 4.3 mg/L for TCPP and TDCPP, respectively), except TDCPP which demonstrated an effect on mRNA expression of a lipid metabolism gene (L-FABP) at all test concentrations (0.01 µM and above, equivalent to 0.0043 mg/L and above).

8.2 Ecological Exposure Assessment

8.2.1 Measured Environmental Concentrations

8.2.1.1 Environmental Monitoring Data for Canada

There are several studies reporting environmental concentrations for TCPP and TDCPP in Canada. Some of these studies measured the individual TCPP isomers (i.e. those found in the commercial products). In these studies, measured concentrations were determined for TCPP itself and/or the sum of isomers in environmental samples. A few other studies did not discuss isomers in their reports. Given the predominance of TCPP and considerably lower proportion of its chain isomers in most of the commercial products as well as their similar environmental fates, it is considered that measured concentrations reported in the environmental monitoring studies are appropriate to characterize the presence of TCPP in the environment, even in the absence of information on the TCPP isomers.

Details are presented in Environment Canada, Health Canada (2014) and key findings are summarized as follows.

Concentrations of TCPP and TDCPP in air have been reported at high levels in samples collected over Lake Superior at 1.35 ng/m^3 for TCPP and 0.034 ng/m^3 for TDCPP during 2005 (Shoeib and Jantunen 2013) and more recently in the Canadian Arctic at 0.075-0.145 ng/m^3 for TCPP and 0.005 ng/m^3 for TDCPP (Jantunen et al. 2013a). In a recent study, TCPP and TDCPP were reported at 0.67 ng/m^3 and 0.15 ng/m^3, respectively, in air samples collected in Toronto during 2012 (Shoeib et al. 2014). Both substances have been found associated with air particle in these studies (Shoeib and Jantunen 2013; Jantunen et al. 2013a; Shoeib et al. 2014).

Recent environmental studies have reported both substances in effluents of WWTS and in surface water (rivers and lakes) in Ontario. Both TCPP and TDCPP were found in samples collected at wastewater treatment plants (WWTPs) in Burlington and Hamilton (Andresen et al. 2007). The highest concentrations were reported at 78 ng/L and 35 ng/L, respectively for TCPP and TDCPP. A few studies have provided levels of TCPP and TDCPP in Canadian surface waters (Jantunen et al. 2013b; Venier et al. 2014). The surface water concentrations of TCPP and TDCPP were reported in samples collected between October 2010 and December 2011 in 13 Toronto tributaries discharging to Lake Ontario; however, the number of samples collected at each tributary was not specified (Jantunen et al. 2013b). For TCPP, mean concentrations in the 13 tributaries ranged from 26 ng/L to 844 ng/L with the two highest concentrations being1839 ng/L and 853 ng/L. For TDCPP, mean concentrations in the 13 tributaries ranged from 2 ng/L to 126 ng/L with the two highest concentrations being 1437 ng/L and 581 ng/L (Jantunen et al. 2013b). Surface water measured at different locations around the other Great Lakes (Lakes Huron, Erie and Michigan) contained mean concentrations ranging from 0.87 to 4 ng/L of TDCPP and from 2.6 to 12 ng/L of TCPP (Venier et al. 2014).

No data have been identified for TCPP or TDCPP concentrations in soil or sediment in Canada.

McGoldrick et al. (2014) reported on the levels of 6 OPFRs in the homogenized whole Lake Trout and Walleye collected from 16 water bodies across Canada ranging from remote northern lakes with minimal human influence (e.g., Kusawa Lake) to lakes in heavily populated areas with intense agricultural and industrial activities (e.g., Lake Ontario). Both TCPP and TDCPP were found above their respective limits of quantification (0.23 ng/g ww for TCPP and 0.11 ng/g ww for TDCPP) in only one individual Lake Trout from Great Bear Lake in the Northwest Territories. The low to non-detectable concentrations of TCPP and TDCPP in fish are likely due to metabolic breakdown.

Chen et al. (2012) reported levels of OPFRs in herring gull eggs collected from the Channel-Shelter Island on Lake Huron in 2010. Concentrations of TCPP were found above the detection limit in 12 out of 13 samples and the highest concentration reported was 4.1 ng/g ww. Concentrations of TDCPP were found above the detection limit in 2

out 13 samples and the highest concentration reported was 0.17 ng/g ww (Chen et al. 2012).

In another study, 16 organophosphate esters were screened in female Herring Gulls (*Larus argentatus*) and their eggs from a Lake Huron colony site (Greaves and Letcher 2014). Both TCPP and TDCPP were found in the separated yolk and albumen at the same magnitudes reported by Chen et al. (2012). Among six body compartments (fat, muscle, red blood cells, blood plasma, liver, and brain), TCPP was detected only in fat and muscle tissues with a higher concentration in fat (2.31±1.64 ng/g ww); while TDCPP was detected in all six body compartments with the highest concentration in muscle (5.04±3.69 ng/g ww) (Greaves and Letcher 2014). Measurements of TCPP and TDCPP in eggs from these studies (Chen et al. 2012; Greaves and Letcher 2014) are indicators of breeding near highly populated urban areas.

Su et al. (2014) analyzed plasma samples from herring gulls that were collected from Chantry Island, Lake Huron. Considering that organophosphate triesters are expected to degrade to OP diesters, analysis of BCPP and BDCPP was also included in the study (Su et al. 2014). TCPP and BCPP were not detected in any of 6 plasma samples. However, TDCPP was found in half of the plasma samples and measured concentrations ranged from 0.11 to 0.41 ng/g ww. Meanwhile BDCPP was found in all 6 plasma samples and measured concentrations ranged from 0.72 to 3.49 ng/g ww, thus showing metabolism of TDCPP.

In an unpublished report, low plasma concentrations of TCPP (0.9−5.5 ng/g ww) and TDCPP (0.3−1.0 ng/g ww) were reported in nestling peregrine falcons (*Falco peregrinus*) (cited in Fernie et al. 2015).

8.2.1.2 Environmental Monitoring Data for Other Jurisdictions

Both TCPP and TDCPP have also been measured in ambient air, aquatic systems, soils, sediments, plants, and aquatic biota in other countries (Appendix B2, Environment Canada, Health Canada 2014). Variations in the reported concentrations of TCPP and TDCPP country may result from different levels of use of products containing TCPP and TDCPP (Sundkvist et al. 2010).

Concentrations of OPFRs in influents and effluents of WWTPs have been reported in a few environmental monitoring studies (van der Veen and de Boer 2012; Bendz et al. 2005). Results indicated poor wastewater treatment removal efficiency for both TCPP and TDCPP at the selected WWTPs in Spain, Germany, Norway, Sweden, and Japan. (Environment Canada, Health Canada 2014). Such information is considered to estimate releases of TCPP and TDCPP in the environment.

8.2.2 Exposure Scenarios and Predicted Environmental Concentrations (PECs) in Canada

Although there are some measured concentrations of TCPP and TDCPP reported in Canadian surface waters, the available data are not considered to reflect usage throughout Canada. For the purpose of this screening assessment, environmental concentrations of TCPP and TDCPP associated with industrial uses and use of consumer products are estimated based on available information, including the use quantities, estimated release rates, and characteristics of the receiving environment. Details are provided in the following sections.

8.2.2.1 PECs of TCPP and TDCPP in the Aquatic Compartment due to Industrial Uses

Industrial uses of TCPP and TDCPP include manufacturing of polyurethane and polyisocynurate foams. Aquatic exposure to TCPP and TDCPP is estimated, assuming that both substances are released from industrial activities to a wastewater system that discharges its effluent to a receiving surface water body. Concentrations of substances in the receiving water near the discharge point of the wastewater system is used as the predicted environmental concentration (PEC), which are further used in characterizing the aquatic risk of substances.

The aquatic PEC due to releases from industrial activities ($C_{water\text{-}ind}$) can be calculated using the equation as follows.

$$C_{water-ind} = \frac{1000 \times Q \times L \times (1-R)}{N \times F \times D}$$

Where:

$C_{water\text{-}ind}$: aquatic concentration resulting from industrial releases, mg/L

Q: total substance quantity used annually at an industrial site, kg/yr

L: loss to wastewater, fraction

R: wastewater system removal rate, fraction

N: number of annual release days, d/yr

F: wastewater system effluent flow, m^3/d

D: receiving water dilution factor, dimensionless

As TCPP and TDCPP are used by industrial facilities and are expected to be released to water, several conservative aquatic industrial release scenarios were developed to cover a range of different potential industrial activities in Canada. The scenarios include blending of polyol and manufacturing polyurethane and polyisocyanurate foams. Information from the different facilities considered was collected and scenarios reflected expected practices and conditions, including type of wastewater treatment, direct or indirect releases to the receiving media and receiving environment.

Input values for estimating aquatic concentrations of TCPP and TDCPP from industrial activities are summarized in Table 8.7.

Table 8.7. Summary of input values used for estimating aquatic concentrations of TCPP and TDCPP resulting from industrial activities

Parameter	Input Value for TCPP	Input Value for TDCPP
Quantity used per site (kg)	100 000 to 2 000 000 (ECCC 2013-2014)	10 000 to 200 000 (ECCC 2013-2014)
Loss to wastewater (%)[a]	0.0011 to 0.3	0.0011
On-site wastewater system removal efficiency (%)[b]	0	0
Off-site wastewater system removal efficiency (%)	0 (van der Veen and de Boer 2012)	13 (ASTreat 2006)

Parameter	Input Value for TCPP	Input Value for TDCPP
Number of annual release days (days)[c]	200–250	250
Wastewater system effluent flow (m^3/d)	4210 to 2 100 000	2908 to 2 100 000
Dilution factor (–)[d]	1 to 10	1 to 10

[a] 0.0011% accounts for 0.00006% from curing and storage at foam production sites and 0.0005% from further processing for both TCPP and TDCPP (EU RAR 2008a and 2008b); 0.3% is the standard assumption for high-volume blending vessel cleaning, only applicable for TCPP.

[b] No on-site wastewater treatment is assumed.

[c] Site-specific information available in the NPRI data is used, otherwise a standard 250 days is considered for HPV substances (European Commission 2003).

[d] In general, the dilution factor is the ratio between the receiving environment flow rate and the site-specific WWTS flow rate. When a dilution factor was greater than 10, a maximum default value of 10 was used.

Considering the above information, PECs in surface water are calculated as 2×10^{-6} – 0.12 mg/L for TCPP and 1×10^{-7} – 2×10^{-4} mg/L for TDCPP.

8.2.2.2 PECs of TCPP and TDCPP in the Aquatic Compartment via Laundry Wastewater due to Use of Consumer Products

In additional to industrial sources, TCPP and TDCPP can be released to the environment from manufactured items and consumer products. For emissions from consumer products, the European Union reported that the total loss of either TCPP or TDCPP to air and wastewater over lifetime from indoor service is expected to be no more than 0.25%; loss to wastewater via outdoor service is anticipated to be at or below 0.75% per year for both substances; and the end-of-life foams will be deposited to landfills and releases are expected to be negligible (EU RAR 2008a and 2008b).

The presence of TCPP and TDCPP in indoor air and in dust samples in Canada and other countries strongly supports releases of both substances from consumer products to the Canadian environment (see Sections 9.1.1.2 and 9.1.1.3). Clothing and the dust collecting on it may create a pathway for TCPP and TDCPP released from household manufactured items to enter wastewater treatment systems via laundry activity (Schreder and La Guardia 2014).

Schreder and La Guardia (2014) measured the mean concentrations of TCPP and TDCPP in laundry wastewater sampled from 20 homes in the Northwestern United States between 2011 and 2012. The mean concentrations of TCPP and TDCPP in laundry wastewater were measured as 0.1 mg/L and 0.018 mg/L (originally reported as 100 000 ng/L and 17 900 ng/L), respectively (Schreder and La Guardia 2014). It is noted that the measured concentrations of both substances in laundry wastewater are below their water solubility limits.

The influent and effluent concentrations of TCPP and TDCPP at two local wastewater treatment plants serving these homes were also reported in this study (Schreder and La Guardia 2014). These wastewater treatment plants receive over 80% of their input from households, with no known flame retardant discharges from the remaining industrial contribution. Using the proportion of influent expected from laundry wastewater and the proportion of influent from households, the authors determined that laundry wastewater may be the primary source of these flame retardants to the wastewater treatment plants (Schreder and La Guardia 2014).

Laundry wastewater data from the northwestern United States from the Schreder and La Guardia study (2014) is considered sufficiently representative to construct an exposure scenario relevant to Canada. The exposure concentrations of TCPP and TDCPP in the surface water (PECs) can therefore be estimated based on releases of these substances from consumer use of manufactured items via laundry wastewater.

Environment Canada indicates that average daily domestic water use is 343 L/day/Canadian and 20% of such usage is accounted for by laundry (Environment Canada 2013). This value, multiplied by 365 days/year, 35 540 400 Canadians (Statistics Canada 2014), and the mean concentrations of TCPP and TDCPP in laundry wastewater reported above (Schreder and La Guardia 2014), yielded national estimated releases of TCPP and TDCPP in laundry wastewater from use of consumer products as 88 929 kg/year and 15 918 kg/year, respectively.

Environmental concentrations of TCPP and TDCPP near WWTS discharge points were calculated in a probabilistic manner, assuming 365 days of use, 100% release from consumer products, and the same waste water treatment system removal efficiencies employed above for the industrial scenarios. The 5^{th} and 95^{th} percentiles PECs resulting from use of consumer products were 7.7×10^{-4} and 1.3×10^{-2} mg/L for TCPP and 1.2×10^{-4} and 2.2×10^{-3} mg/L for TDCPP.

For TCPP, the highest PEC associated with releases from industrial uses (0.12 mg/L) exceeds the highest value arising from releases from use of consumer products (1.3×10^{-2} mg/L), which is aligned with the assumption that industrial point sources may result in the largest localized concentrations in the environment.

Conversely for TDCPP, the highest PEC value associated with releases from industrial uses (1.6×10^{-4} mg/L) was approximately one order of magnitude lower than the 95th percentile PEC due to releases via laundry wastewater (2.2×10^{-3} mg/L), highlighting the importance of considering releases of this substance from the use of consumer products.

It is noted that, in estimation of the environmental exposure to both substances from releases in laundry wastewater, a fraction release as 1 was applied, assuming that all flame retardants were emitted from the consumer products into wastewater; in addition, the lowest removal rates of the wastewater treatment were considered. Given that, the PECs associated with use of consumer products are considered very conservative.

8.2.2.3 PECs of TCPP and TDCPP in the Sediment Compartment due to Industrial Uses and Use of Consumer Products

An equilibrium sediment-water partition approach was used to estimate the concentration of TCPP and TDCPP in sediments. This approach is based on a partitioning principle described by the European Chemicals Agency (ECHA 2010) and incorporates two additional calculation methods. The first method is to estimate the substance's concentration in the aqueous phase (dissolved) of the overlying water from its total concentration, according to studies by Gobas (2007 and 2010). The second method is to estimate a substance's concentration in bottom sediment from its concentration in the aqueous phase of the overlying water based on an equilibrium partitioning assumption between bottom sediment and overlying water described by the US EPA's National Center for Environmental Assessment (US EPA 2003). At equilibrium, the PEC in bottom sediment is assumed to be linearly correlated with the concentration in the aqueous phase of the overlying water. Sediment exposure scenarios were developed as an extension of the industrial aquatic release scenarios described above to determine equilibrium sediment PECs, standardized to 4% organic carbon (a typical organic carbon content in bottom sediment for rivers and lakes).

Considering all of the above, PECs in sediment associated with releases from industrial uses were calculated to range from 5.4×10^{-5} to 2.8 mg/kg dw for TCPP and 1×10^{-5} to 0.011 mg/kg dw for TDCPP.

For releases of these substances from use of consumer products, such emissions will be released to the surface water after the treatment of laundry wastewater. Considering their partitioning to sediment, PECs in the sediment compartment associated with

releases from consumer products range from 1.8×10^{-2} to 0.29 mg/kg dw for TCPP and 8.5×10^{-3} to 0.16 mg/kg dw for TDCPP, based on the range of the 5th to 95th percentile probabilistic aquatic PECs.

8.2.2.4 PECs of TCPP and TDCPP in the Soil Compartment due to Industrial Uses and Use of Consumer Products

As noted in sections 8.2.2.1 and 8.2.2.2, releases of TCPP to wastewater may happen at industrial manufacturing facilities and from use of consumer products; however, it is considered that there is no removal of this substance from wastewater treatment. Given that it is not being caught in the biosolids, minimal release to soil is expected via the application of biosolids or deposition in landfills. In addition, direct release to this compartment is not likely. Therefore, a PEC in soil is not calculated for TCPP.

For industrial uses of TDCPP, it is also assumed that there is no on-site wastewater treatment; however, there may be some removal during off-site wastewater treatment. To estimate releases of TDCPP in soil, an approach described by the European Chemicals Agency (ECHA 2010) was used to quantify TDCPP sorbed to biosolids and further estimate predicted environmental concentrations in soil (soil PECs) resulting from the land application of biosolids. This approach employed the quantity of biosolids accumulated within the top 20 cm layer (ploughing depth) of soil over 10 consecutive years as the basis for soil PECs. One underlying assumption of the approach was that substances were subject to no loss due to degradation, volatilization, leaching, and soil run-off upon their entry into soil. This assumption, therefore, yields conservative soil PECs. Soil exposure scenarios were developed as an extension of the aquatic release scenarios described above, using concentrations and production rates based on site specific wastewater treatment plants.

Standard assumptions/considerations are applied as follows:

- Removal from WWTS: According to site-specific information contained in the EC database (NPRI 1994–2009), a 13% removal rate for secondary treatment was considered at most of the off-site treatment plants; meanwhile primary treatment was considered at a few other off-site treatment plants and a 10% removal rate was applied. In some cases, if a lagoon was providing the applicable wastewater treatment, a 10% removal rate was applied.
- Biosolids application rate is 8.3 tonne/ha-yr.
- Biosolids application period is 10 consecutive years.
- Soil depth and density: 0.2 m and 1200 kg/m^3.
- Soil PECs were standardized to 2% organic carbon.

For all industrial sites identified using TDCPP, soil PECs are estimated to range from 1.2×10^{-5} to 2.1×10^{-3} mg/kg dw.

TDCPP may also be released in laundry wastewater from use of consumer products. The sorption of this substance by the sludge is estimated from the total release quantity (15 918 kg per year estimated in section 8.2.2.2). Considering the same removal rate (13%) for the secondary treatment for most of the off-site wastewater treatment plants, the PEC in biosolids is calculated as 0.87 mg/kg. Applying the same standard assumptions on the biosolids application in soil as described above for the industrial uses, the resulting soil PECs are estimated as 0.03 mg/kg dw.

8.3 Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on a weight-of-evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on physical and chemical properties, sources, fate of these substances and their presence in the Canadian environment, persistence, bioaccumulation potential and inherent toxicity to non-human organisms.

8.3.1 Risk Quotient Analysis for the Aquatic Environment

A risk quotient (RQ) analysis is conducted for selected scenarios by comparing the predicted environmental exposure concentrations (PEC) to the selected predicted no-effects concentrations (PNEC) for organisms.

As discussed in Section 8.2, aquatic PECs were derived for TCPP and TDCPP to characterize their exposure to aquatic organisms resulting from releases associated with industrial uses and consumer laundry activity. Each scenario for industrial uses considered the quantity of TCPP and TDCPP used at each industrial site, the emission factor for releases to wastewater, the wastewater treatment system removal and effluent flow rates, and the dilution in the receiving water. For releases via consumer laundry activity, measured concentrations of both substances in laundry wastewater from the northwestern United States was used to represent such releases in Canada and further estimate the total releases of TCPP and TDCPP from use of consumer products. PECs of these two substances resulting from laundry wastewater were calculated in a probabilistic manner.

In addition, both substances have been found in Ontario surface water (Jantunen et al. 2013b); it is reasonable to expect that the environmental monitoring data would be reflective of releases from both industrial activities and the use of consumer products. Given that, measured concentrations of these two substances in 13 tributaries in southern Ontario (Jantunen et al. 2013b) were also considered in risk quotient analysis.

Aquatic PNECs were extrapolated from the most sensitive effect endpoint for each substance (see Section 8.1).

Results of the risk quotient analysis are presented in

Table 8.8.

For TCPP, the RQ is below 1 for all industrial sites using this substance. Considering releases of this substance in laundry wastewater, the 95th percentile PEC resulting from laundry wastewater was below the PNEC, yielding an RQ less than 1 (Table 8.8). Average measured concentrations of TCPP in 13 tributaries in southern Ontario range from 25.6 ng/L and 844 ng/L; the highest measured concentration as 1838 ng/L was reported in samples collected from one river. All are below the PNEC. These results indicate that risk in the aquatic organisms associated with releases of TCPP from industrial uses or use of consumer products is low.

For TDCPP, the RQ is below 1 for all industrial sites using this substance. Based on the probabilistic PECs associated with releases from laundry wastewater, the 87th percentile PEC is below the PNEC. With consideration of the conservatism applied in the calculation, it is expected that the number of sites where releases of TDCPP due to use of consumer products causing an environmental concentration higher than the no effect threshold is small.

According to the environmental monitoring data, average measured concentrations of TDCPP obtained in 13 tributaries in southern Ontario range from 2 ng/L and 126 ng/L and are all below the PNEC for this substance. A maximum concentration as 1437 ng/L was reported in samples collected in 1 river, while the average measured concentration was 126 ng/L for the same river. This suggests that the occasional high concentration is not representative to the realistic existence of this substance in the environment. Based on all above evidence, it is considered that risk in the aquatic organisms associated with releases of TDCPP from industrial uses or use of consumer products is low.

Table 8.8. Risk quotient analysis for the aquatic compartment

Substance	PEC or highest measured concentration[a] (mg/L)	PNEC (mg/L)	RQ
TCPP	2×10^{-6} – 0.12 (PECs associated with releases from industrial uses)	1.7	1.4×10^{-6} – 0.071

TCPP	1.3×10^{-2} (the 95th percentile PECs due to use of consumer products)	1.7	7.6×10^{-3}
TCPP	$2.6\times10^{-5} – 8.4\times10^{-4}$ (average measured concentrations in 13 tributaries in southern Ontario; a concentration as 1.84×10^{-3} mg/L was reported as the maximum measured value in one tributary)	1.7	$1.5\times10^{-5} – 4.9\times10^{-4}$
TDCPP	$1\times10^{-7} – 1.6\times10^{-4}$ (PECs associated with releases from industrial uses)	0.0013	$7.7\times10^{-5} – 0.12$
TDCPP	1.3×10^{-3} and 2.2×10^{-3} (the 87th and 95th percentile PECs due to use of consumer products)	0.0013	1 and 1.7
TDCPP	$2.0\times10^{-6} – 1.3\times10^{-4}$ (average measured concentrations in 13 tributaries in southern Ontario; a concentration as 1.4×10^{-3} mg/L was reported as the maximum measured value obtained in one river)	0.0013	$6.4\times10^{-4} – 0.1$

[a] Measured concentrations of TCPP and TDCPP in the surface water were reported in Jantunen et al. 2013b.

8.3.2 Risk Quotient Analysis for the Sediment Compartment

Due to minimal partitioning to sediments and the lack of effects data (read-across is not applicable for TCPP), a risk analysis for TCPP in sediment is not conducted.

For TDCPP, sediment PECs are calculated based on the aquatic PECs estimated for both scenarios of industrial manufacturing of polyurethane and polyisocyanurate foams and releases from routine household cleaning in laundry wastewater. The comparison of sediment PECs with PNECs and the resulting risk quotients are presented in Table 8.9. The results indicate low risk in the sediment organisms associated with releases of TDCPP to this compartment from industrial activities or releases from consumer products.

Table 8.9. Risk quotient analysis for TDCPP in the sediment compartment

Release sources	PEC (mg/kg-dw)	PNEC (mg/kg-dw)	RQ
Industrial uses	1×10^{-5} – 0.011	0.24	4.2×10^{-5} – 0.046
Consumer products	8.5×10^{-3} – 0.16	0.24	0.035 – 0.65

8.3.3 Risk Quotient Analysis for the Soil Compartment

TCPP is not expected to be released to soil due to biosolids application, and thus, a risk quotient for soil was not derived for TCPP.

Results of risk analysis for TDCPP presented in Table 8.10 indicate that there is low risk to the soil organisms due to biosolids application, which are associated with releases of this substance from industrial uses or use of consumer products.

Table 8.10. Risk quotient analysis for TDCPP in the soil compartment

Release sources	PEC (mg/kg-dw)	PNEC (mg/kg-dw)	RQ
Industrial uses	$1.2x10^{-5}$ – $2.1x10^{-3}$	0.27	$4.4x10^{-5}$ – $7.8x10^{-3}$
Consumer products	0.03	0.27	0.11

8.4 Consideration of Lines of Evidence and Conclusion

TCPP and TDCPP have been used in high volumes in Canada and internationally. Both have been found in the Canadian environment since 1970. ICL-IP has been a major manufacturer of TDCPP and the company plans to cease its production of TDCPP by 2015 (ECCC 2013-2014); furthermore, Albemarle has also indicated it will cease manufacture of TDCPP (Albemarle 2012). There is a moderate level of confidence that no significant increase in manufacture, import or use of this substance expected in the near future.

Releases of TCPP and TDCPP to air are expected from industrial manufacturing of polyurethane and polyisocyanurate foams and from products and building materials to which they have been added. However, direct emissions to air from industrial uses are expected to be low due to the low vapour pressures for these substances. While emission rates from use of products appear to be minimal and diffuse, quantities in use are high and such emission volumes are not insignificant. Releases TCPP and TDCPP from consumer products have been measured in laundry wastewater, which enter the local wastewater treatment system. Therefore, it is reasonable to expect that measured concentrations in surface water would be reflective of releases from both of industrial activities and the use of consumer products. After release in air, both TCPP and TDCPP are associated with particles, where they have demonstrated higher persistence. Along with measured air concentrations in the Arctic areas of Canada and Europe, there is

sufficient evidence suggesting that both substances are very persistent in air and possess the potential for long-range atmospheric transport.

Releases of TCPP and TDCPP from uses will primarily enter the surface water after the wastewater treatment. TCPP remains in water (99.7%) and a very small percentage (0.3%) may partition to sediment. TDCPP also mainly stays in water (94.6%); while a small portion may partition in sediment (5.4%). During wastewater treatment, it is expected that this substance will partition to biosolids to some extent, and these biosolids may in turn be applied to soils.

Both substances do not hydrolyze significantly under the environmental conditions and are not rapidly biodegradable. However, both TCPP and TDCPP have been shown to biotransform quickly in various vertebrate species (fish, mammals, and birds). Empirical and modelled (Q)SAR data indicate a low bioconcentration and bioaccumulation potential for both substances. Given that, there is a high level of confidence with the limited accumulation of TCPP and TDCPP in biota. Biomagnification via food chains is unlikely and exposure to higher trophic level organisms is expected to be lower than the exposure to lower trophic level organisms.

In the ecological effect assessment, empirical data have been identified, indicating moderate toxicity of TCPP and high toxicity of TDCPP to organisms regarding survival, reproduction, and growth. While TCPP is not shown to possess a significant effect on the endocrine system in fish, empirical data have confirmed that TDCPP could alter the thyroid concentrations in zebrafish, which may be a contributing factor to the lower survival rate and a higher incidence of malformation in the test organisms. TDCPP could also change sexual hormone concentrations in fish at low levels; however, there is no report of any effect on the filial generations following parental exposure. There is a moderate to high level of confidence with key toxicity data that have been chosen to extrapolate PNECs.

Data for neurotoxicity, cytotoxicity, genotoxicity, and effects on other biomarkers for these two substances have been identified in cell assays in fish and birds. These data are useful to clarify the chemical reactivity and the mechanism of toxic action. However, it is noted the highest PECs in water (0.12 mg/L for TCPP and 0.00022 mg/L for TDCPP) estimated in this assessment are lower than exposure levels of TCPP (1 mg/L) and TDCPP (0.0033 mg/L) that can alter hormone concentrations or demonstrate effects on enzyme activities and mRNA expression in cell assays. Hypothetically speaking, the lowest exposure concentrations used in the cell assays (1 mg/L for TCPP and 0.0043 mg/L for TDCPP) extrapolates to tissue concentrations of TCPP and TDCPP in fish at approximately 3 mg/kg and 0.0043 mg/kg, respectively (assuming density at 1 kg/L for aquatic organisms). Such tissue concentrations are much higher

than the measured concentrations reported in any of the fish samples collected from Canadian water bodies. Considering the measured concentrations of (and the high frequency of not detecting) TCPP and TDCPP in aquatic organisms, there is a high level of confidence as to the effects of these two substances on hormone pathways, gene transcription, or receptor-mediated effects that are not expected at their current levels of occurrence in fish.

Both TCPP and TDCPP were found in herring gull eggs. These findings are in agreement with the protein binding-potentials associated with these two substances. *In ovo* toxicity data suggest that chicken embryos are also sensitive to TCPP and TDCPP. The timing of pipping and embryonic development were affected by both substances at magnitudes of 10^3 ng/g, while the hormonal effect was only associated with TDCPP at the same level. Such exposure concentrations associated with an effect in the toxicity study are three orders of magnitude higher than the measured concentrations of both substances in eggs.

Considering the above, a higher weight is applied to the effects data from *in vitro* and *in vivo* studies which are directly linked to organism level effects for the estimation of PNECs in this assessment.

The exposure assessment has focused on releases of both substances from the production of polyurethane and polyisocyanurate foams and the use of consumer products via laundry activities. Environmental concentrations have been estimated for compartments with a high level of confidence where substances are most likely to be found based on the environmental fate analysis.

Risk characterization was conducted for the aquatic compartment for TCPP and the aquatic, sediment, and soil compartments for TDCPP. Outcomes from risk quotient analysis for TCPP in the aquatic compartment are below 1, indicating that risk associated with exposure to substance in the environment due to industrial uses or releases from the use of consumer products is low. Considering all lines of evidence, it is proposed that current releases of TCPP are not causing harm to the Canadian environment. It is proposed to conclude that they do not meet the criteria as set out in section 64 *(a)* or *(b)* of CEPA 1999.

For TDCPP, outcomes from risk quotient analysis for this substance in the sediment and soil compartments are below 1. In the aquatic compartment, PECs associated with all industrial uses are below the PNEC; the probability that any one site where releases of TDCPP due to use of consumer products causing an environmental concentration higher than the PNEC is small. Given that, the risk associated with exposure to TDCPP in the environment due to industrial uses or releases from the use of consumer products is considered low. Based on all lines of evidence, it is proposed that current releases of

TDCPP are not causing harm to the Canadian environment. It is proposed to conclude that they do not meet the criteria as set out in section 64 *(a)* or *(b)* of CEPA 1999.

8.5 Uncertainties in Evaluation of Ecological Risk

The exposure assessment focuses on industrial point sources as being most relevant for TCPP and TDCPP in the environment. From their use as additive flame retardants, both substances may migrate from products over time to the air and directly to dust, as evidenced by concentrations in air samples of both outdoor air and indoor dust. Diffuse emissions from use of products are at a very low rate. Quantities of these substances imported in manufactured items have not been well captured in responses to the notice issued pursuant to section 71 of CEPA 1999. TCPP and TDCPP quantity in products (considering all products imported and in use) could be high; however, it assumed that major TCPP and TDCPP pathways of release from products are reflected in measured environmental concentrations. The environmental releases due to use of consumer products have also been characterized by considering the measured concentrations of these substances in laundry wastewater in a residential area. Similarly, releases from industrial transport container cleaning were not considered in a quantitative manner due to a high degree of uncertainty. Conservative assumptions were made in the exposure assessment and there is a moderate level of confidence with the exposure scenarios used to calculate PECs.

According to its physical and chemical properties, TCPP is water soluble and the majority of this substance is expected to remain in the aquatic compartment. Outcomes from the Level III EQC only suggest 0.3% of the total release of this substance may reside in sediment, if released to water. Sediment PECs for TCPP were derived from the conservative PECs in the surface water and have been estimated at up to 2.8 mg/kg dw. There has been no empirical sediment toxicity data identified for this substance. Considering the difference in aquatic toxicity between TCPP and TDCPP and other phosphate esters, read-across is not considered applicable to determine the value of a toxicity endpoint; therefore, a PNEC for sediment is not calculated for TCPP and a risk quotient analysis is not conducted for this compartment. The lack of sediment effect data for TCPP is considered a critical data gap in this assessment and leaves the possibility for false negatives regarding risk to sediment-dwelling and terrestrial organisms.

9. Potential to Cause Harm to Human Health

9.1 Exposure Assessment

9.1.1 Environmental Media and Food

Both TCPP and TDCPP are additive flame retardants and therefore not chemically bound to the polymer matrix, increasing the potential for environmental release over the service lifetime of a product containing it.

Concentrations of TCPP and TDCPP reported in air, water, dust and food are further described below (see also Section 8.2.1, Appendix A; Environment Canada, Health Canada 2014). Based on monitoring data, the highest estimate of potential exposure of the general population to TCPP and TDCPP through environmental media and food is 0.33 and 0.35 µg/kg-bw per day, respectively, for ages 0–6 months (Appendix C).

9.1.1.1 Ambient Air

TDCPP and TCPP have been detected in outdoor air in Canada and elsewhere (Section 8.2.1). Both TDCPP and TCPP were measured via high-volume active air samplers around the Great Lakes and Toronto from 2011 to 2013. Mean concentrations from Lake Superior, Lake Ontario and Lake Huron ranged between 4.3×10^{-3} and 6×10^{-3} ng/m^3 for TDCPP and 0.08 and 0.20 ng/m^3 for TCPP (Shoeib et al. 2014, Jantunen 2014). As mentioned in Section 8.2.1, mean concentrations of 0.15 ng/m^3 for TDCPP and 0.67 ng/m^3 for TCPP were measured in Toronto (n= 32) (Shoeib et al. 2014). TDCPP was also measured with a concentration of 9.5×10^{-3} ng/m^3 in outdoor air samples (n=20) in another Toronto study from January 2011 to February 2012 using a high-volume active air sampler (Diamond et al. 2013). TCPP was not monitored by Diamond et al. (2013).

Ambient TDCPP air levels were also measured in Chicago and Cleveland and mean concentrations were 0.079 ng/m^3 (n=27) and 0.11 ng/m^3 (n=22), respectively (Salamova et al. 2013). Ambient air samples for TCPP were collected in Chicago (n=27) and Cleveland (n=22) in 2012. Median concentrations were 0.41 ng/m^3 (Chicago) and 0.32 ng/m^3 (Cleveland) based on the sum of vapour and particle phases (Salamova et al. 2013). A study in Sweden reported a level of 0.81 ng/m^3 of TCPP at a single location (Marklund et al. 2005a). In Norway, 10 samples in an urban area were analyzed for TCPP with concentrations between 240 and 3700 ng/m^3 (Green et al. 2007). Concentrations of TCPP and TDCPP are found in remote areas such as the Arctic and Antarctic, suggesting that both may undergo long-range atmospheric transport (Moller et al. 2012; Green et al. 2007). This is consistent with findings based on physical chemical properties of the substances.

Mean concentrations of 0.15 ng/m^3 and 0.67 ng/m^3 from the same Toronto study were selected to estimate daily intakes of TDCPP and TCPP, respectively, from exposure to ambient air (Shoeib et al. 2014).

9.1.1.2 Indoor Air

Indoor air was monitored for TCPP and TDCPP in homes in one Canadian study but methodology difficulties were encountered and results could not be used (Diamond et

al. 2013). These substances have been measured in homes in Sweden. In two studies of 10 homes, TCPP and TDCPP were detected in air at levels ranging from 2.4–160 ng/m^3 and from below the detection limit (1 ng/m^3) to 17 ng/m^3, respectively (Staaf and Ostman 2005; Bergh et al. 2010). For TDCPP, the majority of the samples were below the detection limit of 1 ng/m^3 (Bergh et al. 2011) (Appendix A).

Indoor time may be spent in locations other than the home, such as an office for adults, or vehicle, daycare, school or gym, for adults or children. Concentrations of TCPP and TDCPP in office environments in Sweden and Norway ranged from 10 to 240 ng/m^3 and 0.2 to 150 ng/m^3, respectively (Marklund et al. 2005b; Staaf and Ostman 2005; Green et al. 2007; Bergh et al. 2010; Hartmann et al. 2004). More recently, TCPP and TDCPP were measured in 10 offices in China with maximum concentrations of 81 and 14 ng/m^3, respectively, much lower than those offices in Europe (Yang et al. 2014). Indoor air from daycare centres and early childcare education (ECE) centres has been sampled recently in North America. In a study of 40 ECE centres, Bradman et al. (2012) detected TDCPP with a mean concentration of 0.59 ng/m^3 and 95th percentile of 1.25 ng/m^3. TCPP was not measured in this study (Bradman et al. 2012). Levels in air in 10 Swedish daycares were measured; the mean concentration was 6.7 ng/m^3 of TDCPP. The mean concentration in daycares in Stockholm was 19 ng/m^3 for TCPP (Bergh et al. 2010). Gymnasiums in Boston were monitored for TDCPP and TCPP given the prevalence of foam pits; concentrations were 12.5 ng/m^3 and 2.68 ng/m^3 for a single sample near the foam and 8.41 ng/m^3 and 0.74 ng/m^3 for a single sample away from the pit, for TDCPP and TCPP, respectively (Carignan et al. 2013).

Time spent in automobiles and aircraft may also represent potential sources of exposure to TCPP or TDCPP. Indoor air measured in vehicles contained levels ranging from not detected (LOD = 0.12 ng/m^3) to 2300 ng/m^3 of TCPP (Hartmann et al. 2004; Staaf and Ostman 2005). Hartmann et al. (2004) sampled 4 cars of varying age in Switzerland, where the maximum TCPP concentration of 260 ng/m^3 was measured in a 9 year-old car. Concentrations in the other cars, both less than 1 year old, were below 23 ng/m^3. TDCPP was measured in cars, but not detected above the analytical detection limit of 0.11 ng/m^3 (Hartmann et al. 2004). Staaf and Ostman (2005) measured a collection of personal and public vehicles (1 car, 2 public buses and 1 subway car) from Stockholm resulting in a TCPP concentration of 1800 ng/m^3 in the car, 330 and 2300 ng/m^3 in the buses and 2000 ng/m^3 in the subway car. Only TDCPP was detected in the car at a concentration of 5 ng/m^3 (concentrations were not detected in buses and subway [LOD = 1 ng/m^3]) (Staaf and Otsman 2005). Given the potential variability of TCPP and TDCPP concentrations across various transportation vehicles, the limited number of study samples, and the increased air changes from opening doors frequently (and windows depending on the season), there is uncertainty in estimating exposures in vehicles.

Daily intake of TCPP from exposure in indoor air for the Canadian general population was estimated based on the highest concentrations of 160 ng/m^3 in a home in Sweden (Staaf and Ostman 2005). A concentration of 17 ng/m^3 in indoor air from Sweden was used to estimate the daily intake of TDCPP (Bergh et al. 2010). These air levels are considered to take into account the variability in environmental concentrations associated with different settings (e.g., daycare, office, gym, vehicles). These potential sources of exposure are expected to be lower than those conservatively estimated for homes based on lower frequency and duration of exposure.

9.1.1.2 Dust

TCPP and TDCPP have been measured in dust in several studies in homes, offices and other indoor environments in Canada and globally (Appendix A).

TCPP was measured in the Canadian House Dust Study (CHDS) during 2007–2008 in the dust of 818 homes in Ottawa, ON resulting in mean and 95th percentile concentrations of 1.62 mg/kg and 18.2 mg/kg, respectively (Canadian House Dust Study preliminary data; Kubwabo et al., manuscripts in preparation, Environmental Health Science Bureau, Health Canada, unreferenced). Results from studies from the United States and Europe are consistent with the Canadian data, where TCPP has been measured in household dust with mean concentrations ranging from 0.5 to 3.1 mg/kg (Van den Eede et al. 2011; Brommer et al. 2012; Dodson et al. 2012; Bergh et al. 2011; Stapleton et al. 2009; Marklund et al. 2003).

TDCPP was reported in two Canadian studies monitoring dust in Toronto and Ottawa resulting in the highest mean and 95th percentile concentrations of 3.08 mg/kg and 12.7 mg/kg (Canadian House Dust Study preliminary data; Kubwabo et al., manuscripts in preparation, Environmental Health Science Bureau, Health Canada, unreferenced; Diamond et al. 2013). European and American studies monitoring TDCPP in household dust report similar mean concentrations as seen in Canada ranging from 0.08 to 2.8 mg/kg (Van den Eede et al. 2011; Brommer et al. 2012; Dodson et al. 2012; Stapleton et al. 2009; Ali et al. 2012).

Dust was also monitored for its TDCPP and TCPP content in early childcare education environments (ECE). In Sweden, TDCPP was measured in 10 daycare centres with a mean concentration of 28 mg/kg, while TCPP was found at a mean concentration of 4.5 mg/kg (Bergh et al. 2011). In California, USA, TDCPP in dust was detected in 49 early childcare education centres ranging from 0.79 mg/kg to 71 mg/kg, with a mean concentration of 6 mg/kg and 95th percentile of 37 mg/kg (Bradman et al. 2012). TCPP was not monitored as part of this study. Dust was also sampled in gymnasiums in Boston, Massachusetts (Carignan et al. 2013). The median concentration of TDCPP and TCPP inside the gymnastics facilities was found to be 13 mg/kg and 2.48 mg/kg, respectively, by Carignan et al. (2013).

TCPP and TDCPP have also been frequently detected in offices and different vehicles. Webster et al. (2010) measured TDCPP in office dust and cars in the Boston area, USA, in 2009, where mean concentrations were found to be 9.8 and 26 mg/kg, respectively. In Germany, TCPP and TDCPP mean concentrations were reported in office dust (n=10; 3 mg/kg and 0.15 mg/kg, respectively) and cars (n=12; 3.1 mg/kg and 130 mg/kg, respectively) (Brommer et al. 2012). Concentrations in both the office and cars exceeded the concentrations of TCPP and TDCPP in the homes sampled in the same study. Other studies have also reported higher concentrations of TCPP and TDCPP in car dust compared to household dust in Europe and the Middle East (Ali et al. 2011; Ali et al. 2013; Brandsma et al. 2014). In addition, TDCPP was also measured in dust from aircraft cabins, with median levels in carpet of 2100 ng/g, and of 5600 ng/g in air vents (Allen et al. 2013). TCPP was not measured in aircraft.

As no Canadian dust data were identified for ECE facilities, the 95th percentile concentration of 37 mg/kg from daycare centres in California was used as a conservative level of TDCPP in dust for estimating exposure of Canadian children and adolescents (i.e. all age groups below 20 years) (Bradman et al. 2012). This approach is considered appropriate for estimating exposures for children because the concentration in dust sampled from California ECE facilities is reported to be higher than that measured in Canadian house dust. Therefore, this is considered a reasonable worst-case scenario that accounts for exposure in an environment in which children may spend a significant amount of time. The 95th percentile of TDCPP (12.7 mg/kg) from the Canadian house dust study (personal communication from Environmental Health Science and Research Bureau, Health Canada, dated August 22, 2014) was used to estimate the daily intake for adults. The 95th percentile concentration of TCPP (18.2 mg/kg) in household dust from Ottawa was used to estimate the daily intake from dust by the Canadian general population (personal communication from Environmental Health Science and Research Bureau, Health Canada, dated August 22, 2014).

9.1.1.3 Soil and Sediment

There is no soil monitoring data for TCPP or TDCPP in Canada. However, both substances were measured in one study in Europe. Mihajlovic et al. (2011) measured a mean concentration of 0.0012 mg/kg of TCPP in six German soil samples. TDCPP was below the detection limit of 9×10^{-5} mg/kg. Both the mean soil concentration and the detection limit were used to estimate an intake from soil for TCPP and TDCPP.

9.1.1.4 Drinking Water

Reported levels of TDCPP and TCPP in water were recently identified in Canada (Venier et al. 2014; Jantunen et al. 2013b) (Section 8.2.1, Environment Canada, Health Canada 2014). TCPP was measured in a pilot study on tap water study in Barrie,

Ontario (n=2) with a concentration of 11 ng/L (Jantunen 2014). Data on TDCPP concentrations in tap water were not identified.

As previously described in Section 8.2.1, TDCPP and TCPP were measured in surface water from rural and urban tributaries draining into Lake Ontario, with upper concentrations of 1437 ng/L and 1839 ng/L in urban areas, respectively. TCPP was reported at lower concentrations between 4.64 and 180 ng/L in rural areas (Jantunen et al. 2013b). In another study, Venier et al. (2014) measured lower concentrations for both TDCPP and TCPP at different locations around the Great Lakes (Environment Canada, Health Canada 2014).

TCPP and TDCPP were measured in Europe from different deposition types, including snow and rain, in addition to surface water from rivers, estuaries and the ocean. Concentration of TCPP in rain was detected at higher levels than snow with a mean concentration of 372 ng/L compared to 233 ng/L in Germany (Mihajlovic and Fries 2012). TDCPP was detected at mean levels of 46 ng/L in rain and 100 ng/L in snow (Mihajlovic and Fries 2012). Both substances were found to be less concentrated further north with lower snow concentrations ranging between 68–210 ng/kg (TCPP) and 4–29 ng/kg (TDCPP) in Sweden (Marklund et al. 2005a).

TCPP was measured in river water between 24 and 570 ng/L in Germany, in higher concentrations than those found in the ocean or estuaries (Bollman et al. 2012). Measurements of waterways near wastewater treatment plants (WWTP) in Germany, Austria and Norway have shown that concentrations are approximately 10-fold higher downstream (Meyer and Bester 2004; Andreson et al. 2004; Green et al. 2007; Martinez-Carballo et al. 2007). Similar river concentrations of TCPP (100–310 ng/L) were detected in rural areas of South Korea, Asia (Yoon et al. 2010). TDCPP has been measured in rivers in Germany at concentrations ranging between 5 and 67 ng/L (Bollman et al. 2012). This is lower than water concentrations (20-740 ng/L) measured near WWTPs in Germany and Norway (Meyer and Bester 2004; Andreson et al. 2004; Green et al. 2007).

Of all the available water monitoring data, the surface water concentrations from tributaries to Lake Ontario of 1437 ng/L and 1839 ng/L for TDCPP and TCPP, respectively, were considered to be the most relevant data to use in calculating an estimate of daily intake from drinking water for the Canadian general population.

9.1.1.5 Food

No reports of studies monitoring TCPP or TDCPP in Canadian food were identified. TDCPP and TCPP have been monitored in food basket surveys by the US FDA since

the 1980s. There are no reported amounts of TDCPP; TCPP was detected in fruits with peels at concentrations ranging from 0.05 to 0.82 µg/kg (ATSDR 2012).

Monitoring of TCPP and TDCPP in fish and shellfish was conducted in four European studies (Environment Canada, Health Canada 2014). Levels in fish tissue (perch, cod, salmon and char) and bivalve shellfish (mussel) were reported from freshwater and marine locations in Sweden and Norway. Levels of TCPP and TDCPP were below the detection threshold of 10 µg/kg in mussels in Norway, but TCPP was detected in concentrations up to 15.6 µg/kg in mussels in Sweden (Green et al. 2007; Sundkvist et al. 2010). TCPP and TDCPP concentrations in finfish from Nordic countries ranged from not detected (detection limit = 0.1µg/kg) to 5.7 µg/kg and 0.3 – 8.1 µg/kg, respectively (Green et al. 2007; Evenset et al. 2009; Sundkvist et al. 2010). In a Swedish study, fish purchased from a grocer were sampled and neither substance was found above detection limits of 1 µg/kg and 9 µg/kg for TCPP and TDCPP, respectively (Campone et al. 2010).

Upper bound concentrations of 5.7 µg/kg from shellfish in Sweden and 8.1 µg/kg from arctic finfish in Norway were selected to estimate the daily intake from food for TCPP and TDCPP, respectively, for the general population (Sundkvist et al. 2010; Evenset et al. 2009). Upper bound concentration in fruit (0.82 µg/kg) was selected as another food source to estimate daily intake for TCPP. Upper-bounding estimates of daily intake from food for the Canadian general population were estimated to be 0.068 and 0.028 µg/kg-bw per day for TCPP and TDCPP, respectively (for children aged 0.5–4 yrs). These are conservative estimates assuming that all seafood and fish consumed would contain TCPP or TDCPP. Although certain northern populations or other subpopulations in Canada may consume larger quantities of seafood or game in their diet, this estimate is considered conservative enough to account for this variability.

9.1.1.6 Breast Milk

No data were identified on concentrations of TDCPP and TCPP in breast milk in Canada or the U.S. TDCPP and TCPP were measured in breast milk in 6 cohort studies in Sweden. The concentration of 0.186 µg/L of TDCPP in breast milk is based on the highest lipid weight concentration (5.3 ng/g) measured in 90 women, corrected with the lipid content in breast milk (3.4%) and the density of breast milk. TCPP concentration in breast milk was derived from the highest measured lipid weight concentration of 57 ng/g from 50 women, and corrected in the same manner to give a concentration of 1.99 µg/L (Sundkvist et al. 2010).

9.1.2 Consumer Products

TCPP and TDCPP are additive flame retardants with a variety of uses and applications (see Section 5), some of which may result in general population exposure. Dermal and

oral exposure estimates were derived using conservative approaches for scenarios considered relevant for the general population. TCPP and TDCPP are non-volatile substances; therefore, they are not expected to appear in their gaseous form under normal conditions. Additionally, releases to air are expected to be accounted for through indoor air and dust exposure estimates (see Sections 9.1.1.1 and 9.1.1.3).

9.1.2.1 Manufactured Items

TCPP and TDCPP are used in flexible foam products (for example in furniture such as foam mattresses or seating), nap mats, car seats and in building construction in Canada (ECCC 2013-2014; CEH 2013a,b; Stapleton et al. 2011). TCPP and TDCPP can each be found in the foam of furniture at a concentration up to 9% w/w (Kemmlein et al. 2003; Stapleton et al. 2009; Stapleton et al. 2011; Stapleton et al. 2012; Ionas et al. 2014; US CPSC 2005a,b; ECCC 2013-2014). In addition, TCPP and TDCPP have also been measured in several children's products containing foam in the U.S., including nap mats (CEH 2013b), foam chairs (including one containing TCPP purchased in Canada) (CEH 2013a), car seats, changing table pads, portable mattresses and rocking chairs, ranging from 0.11 to 1.4% for TCPP and 0.24 to 12.4% for TDCPP in concentration (reported as 1.11 to 14.4 mg/g and 2.4 to 124 mg/g, respectively) (Stapleton et al. 2011). As a result of product testing conducted by Health Canada on 23 children's products (e.g., nursing pillows, polyurethane foam chair, toys) purchased in retail stores in Ottawa, Ontario in 2014), TDCPP was detected in a foam toy at a mean concentration of approximately 7%; TCPP was not detected above the limit of quantification (LOQ of 0.3%) in any of the foam samples (Health Canada 2014).

Flame retardants can also be found in coatings to the inside face of the cover fabric of furniture (e.g., couch) as "backcoating". The use of TDCPP or TCPP as backcoating in furniture upholstery has not been identified specifically for Canada but is a known use in the United States and Europe (US CPSC 1998, 2005a,b; EU RAR 2008b; Danish EPA 2014), and it is considered reasonable to assume that the general population of Canada can be exposed to TCPP or TDCPP in furniture. The Upholstered Furniture Action Council (UFAC), a voluntary coalition of furniture manufacturers, outlined the potential for dermal exposure to backcoating, either via direct contact with the substance from contamination of the outside surface of the fabric (from wet backcoating when textile is rolled up post-production), or from degradation of the backcoating, or through the textile weave (cited in US CPSC 1998).

Dermal exposure intakes were estimated for children and adults in contact with foam mattresses as a representative upper bounding scenario of potential exposure (Appendix E). Given the conservativeness of this scenario, the estimate would cover potential exposure from textile backcoating from furniture. This exposure was modelled using the algorithm presented in the report from the US Consumer Product Safety Commission (US CPSC) in 2006. Other jurisdictions have used similar algorithms to

estimate dermal exposure to a substance migrating from foam or textile backcoating (NRC 2000; Danish EPA 2014, Arcadis EBRC 2011).

Extraction studies measuring migration of TDCPP and TCPP from furniture foam have been conducted previously (US CPSC 2005a; TNO Quality of Life 2005 cited in EU RAR 2008a). TNO Quality of Life (2005) conducted an extraction test of a foam block containing 10% TCPP, resulting in a migration rate of 4.6×10^{-3} mg/cm^2/hr. The migration rate of 5.6×10^{-5} mg/cm^2/hr for TDCPP was used to estimate dermal exposures is based on a migration study of treated furniture foam by the U.S. CPSC (U.S. CPSC 2005a). No TCPP or TDCPP-specific skin contact factor was identified in the literature. Therefore, a skin contact factor of 0.13 (Also used by the U.S. CPSC (US CPSC 2006) as the best estimate based on an average of several substances with data available) is applied to account for the dermal contact of TCPP or TDCPP that may migrate to the surface of the fabric or foam (US CPSC 2006).

Dermal absorption of TCPP and TDCPP through the skin has been investigated. The EU RARs for TCPP and TDCPP (TNO Quality of Life 2005, 2006b cited in EU RAR 2008a,b) describe *in vitro* dermal absorption studies using human skin membranes with direct application of radiolabelled TCPP and TDCPP giving a maximum total absorption of 23% and 40% of TCPP and 15% of TDCPP. The two absorption values of 23 and 40% for TCPP were derived from studies testing different doses. The dermal absorption of 40% was based on doses considered most representative of exposure from dermal contact with foam and was used in estimating dermal exposure from contact with furniture (TNO Quality of Life 2005). The dermal absorption value of 15% for TDCPP derived from an *in vitro* study was based on a dose which was not considered representative of exposure from furniture and therefore was adjusted by the EU RAR (2008b). The ratio of absorption values from the *in vitro* studies conducted on TCPP (23% and 40%) was applied to the 15% absorption rate of TDCPP resulting in an adjusted dermal absorption value of 30% for TDCPP (EU RAR 2008b).

Although the European Union risk assessment for TCPP did not evaluate dermal exposure from foam objects (EU RAR 2008a), some flame retardants have been reported to migrate from various foam objects (US CPSC 2005a, EU RAR 2009, Arcadis EBRC 2011). Additionally, the US CSPC has shown that TDCPP can migrate to the surface of foam covered with fabric, under simulated perspiration and pressure conditions (i.e. to simulate sitting) (U.S. CPSC 2005a).

Therefore, given that various jurisdictions have developed models and algorithms to evaluate exposure from this source and given that flame retardants can migrate from foam objects, dermal exposure from contact with mattresses was assessed for TDCPP and TCPP.

The highest estimated intakes for chronic exposure to TCPP and TDCPP from dermal contact with mattresses containing polyurethane flexible foam is 0.21 mg/kg-bw/d and 1.9 $\times 10^{-3}$ mg/kg-bw/d, respectively, for infants. An estimate of exposure from mouthing a foam object was determined based on the same migration rates of 0.056 µg/cm^2/hr (US CPSC 2006) and 4.6 µg/cm^2/hr (EU RAR 2008a) for TDCPP and TCPP, respectively, in the absence of mouthing migration rates. Assuming a foam object mouthed over a surface area of 20 cm^2 during a mouthing event of 24.5 min per day (Norris and Smith 2002 cited in US EPA 2011), results in an estimate of exposure of 0.030 µg/kg-bw per day and 2.4 µg/kg-bw per day for TDCPP and TCPP, respectively. Further details of assumptions used to derive the dermal and oral exposure estimates are provided in Appendix D).

Table 9.1. Estimated exposure to TCPP and TDCPP from dermal contact with flexible polyurethane manufactured items.

Exposure Route and Duration	Source	Age Group	Uptake of TCPP	Uptake of TDCPP
Dermal (daily)	Foam in children's mattresses	Infant (0–6 mos; 7.5 kg)	0.21 mg/kg-bw/d	1.9×10^{-3} mg/kg-bw/d
Dermal (daily)	Foam in children's mattresses	Toddler (0.5–4 yr; 15.5 kg)	0.15 mg/kg-bw/d	1.3×10^{-3} mg/kg-bw/d
Dermal (daily)	Foam mattresses	Adult (70.9 kg)	5.5×10^{-2} mg/kg-bw/d	5.0×10^{-4} mg/kg-bw/d
Oral (Intermittent)	Foam in children's products	Toddler (0.5–4 yr; 15.5 kg)	2.4×10^{-3} mg/kg-bw/d	3.0×10^{-5} mg/kg-bw/d

TCPP and TDCPP are used in other manufactured items, such as specialized textiles for TDCPP (i.e., tent material) and various automotive parts found in the interior of vehicles for both substances (ECCC 2013-2014). One study detected TDCPP in the textile of three of 11 tents tested, in compliance with CPAI-84, an industry tent flammability standard (Keller et al. 2014). While exposure to TCPP or TDCPP can occur via these products, the overall exposure potential (i.e. combined frequency, duration and magnitude) for these scenarios are not expected to result in higher exposures than those quantitatively presented for flexible polyurethane foam.

9.1.2.2 Products

In Canada, TCPP is reported to be used as an additive in several types of polyurethane (PU) spray foam insulation (ECCC 2013-2014). According to the U.S. EPA's website on SPF, although two-component low pressure kits and one-component foam are used by professional applicators, these types of products are also available for do-it-yourself (DIY) applicators (U.S. EPA 2015). As such, two scenarios were developed for homeowners conducting DYI SPF projects, i.e., a one-component can for smaller scale tasks; and a two-component low-pressure kit for larger scale tasks. While SPF product labels specify personal protection measures, such as the use of gloves or respiratory protection, exposure estimates derived do not consider that individuals are wearing personal protective equipment, given such equipment may not be readily accessible to consumers, or may not be properly handled by consumers. Application of these product types is expected to occur infrequently (i.e. once every ten years).

For a one-component small scale project (i.e., sealing gaps around windows and doors), inhalation and dermal exposure to TCPP was estimated using ConsExpo v.4.1 software (RIVM 2012). Air concentration of TCPP for the small scale project was found to be 185 µg/m^3, equivalent to an Inhalation exposure of 0.88 µg/kg-bw/event. Dermal exposure to TCPP during this same activity was estimated to be 2.7 µg/kg-bw/event. Details regarding this scenario are described further in Appendix E, Tables E1 and E3.

For a two-component large scale project (i.e., insulating an attic by a homeowner), inhalation and dermal exposure to TCPP were estimated also. No studies were identified in which air concentrations of TCPP; however, one study is available in which air concentrations of TCPP were measured during the application of two-component SPF application of a large scale project by professionals (full wall spraying; ACC 2012). Monitoring results for the low-pressure system from this study were considered representative of a homeowner scenario. Concentrations of TCPP in air were reported to be between 477 and 2,940 µg/m^3 (ACC 2012), resulting in an inhalation exposure ranging from 2.3 and 14 µg/kg-bw/event (Appendix E, Table E4). This study also reported that post-spray measurements resulted in TCPP concentrations which were much lower (27 to 45 µg/m^3; ACC 2012). These concentrations are associated with uncertainty however, given that professionals are likely to be trained and perform a "cleaner" application than an untrained user. TCPP dermal exposure for this scenario was estimated to be 630 µg/kg-bw/event during application of the two-component product based on the use of ConsExpo. Details regarding this scenario are described further in Appendix E Table E2.

TCPP can also be found in a waterproofing spray intended for use as a Do-It-Yourself spray for the exterior of tents (Empack 2014). This product is intended for outdoor application, once the tent is assembled (Empack 2014). Given that this application is done outdoors, inhalation exposure from the sprayed product is expected to be minimal.

The waterproofing spray may contact 50% of the hands (455 cm^2) resulting in a dermal load of 0.071 mg/cm^2.equivalent to 4.7 µg/kg-bw/event (Appendix E, Table E5)

9.1.3 Biomonitoring

TDCPP is extensively metabolized in the human body, resulting in a major metabolite, the diester of TDCPP, BDCPP (Van den Eede et al. 2013). BDCPP has been identified as the major metabolite (over 60% in rat urine) in *in vivo* rat toxicokinetic studies (Nomeir et al. 1981; Lynn et al. 1980, 1981). BDCPP has been monitored in five studies in the U.S. for its presence in human urine, including office workers and pregnant women (Carignan et al. 2013; Cooper et al. 2011; Meeker et al. 2013; Hoffman et al. 2014; Butt et al. 2014). No biomonitoring studies of BDCPP or TDCPP were identified for Canada. Since BDCPP is the diester form of TDCPP, it is considered to be a specific metabolite of TDCPP and an appropriate biomarker for TDCPP. Additional information on this metabolite is provided in Section 9.2.1.3.

The method for detecting BDCPP in urine was first developed by Cooper et al. (2011). Subsequent biomonitoring studies adapted the same method of detection (Carignan et al. 2013; Meeker et al. 2013; Hoffman et al. 2014; Butt et al. 2014). In order to account for hydration status and adjust for urine dilution, authors of these biomonitoring studies have used specific gravity (SG) to correct BDCPP concentrations from spot urine samples.

In the Cooper et al. (2011) biomonitoring study, the BDCPP concentration was measured from spot urine samples collected from 9 volunteers (5 women, 4 men), aged 23–46 years, in 2011 (Cooper et al. 2011). The authors identified these individuals as people who live in the US with no known occupational exposure to TDCPP. No further details were available. BDCPP was detected in all urine samples, and SG-corrected concentrations in urine ranged from 0.088 to 3.469 ng/mL, with a geometric mean of 0.410 ng/mL.

Carignan et al. (2013) collected spot urine samples from 29 office workers (number of men and women not specified), located in Boston, U.S., during work hours in June–July 2009. BDCPP was detected in all urine samples, and SG-corrected concentrations ranged from 0.0621 to 1.760 ng/mL with a geometric mean of 0.408 ng/mL. Dust samples were collected from the homes, offices and vehicles of these 29 individuals in January–March 2009. There was a positive trend between urinary BDCPP and TDCPP in office dust, which was not observed in the other environments (i.e. homes and vehicles).

Another study in Boston measured BDCPP levels in urine and correlated those concentrations with dust levels in the individual homes (Meeker and Stapleton 2010; Meeker et al. 2013). Dust samples and spot urine samples were collected within a

month (median 14 days) between 2002 and 2007 from 45 men (between 18 and 54 years of age). In a subset study, 7 men provided 9 repeated urine samples over 3 months. BDCPP was detected in 91% of samples (total of 106 samples including 61 samples from the subset study) and concentrations corrected for SG were as high as 19.4 ng/mL with a 95th percentile of 4.3 ng/mL and a geometric mean of 0.20 ng/mL (Meeker et al. 2013; July 2014 email from John Meeker to Existing Substances, Health Canada, unreferenced). The author noted the large variability in concentration among samples, concentrations spanning 4 orders of magnitude, suggesting exposure level may be highly variable among individuals of a population. The homes of the 45 men had TDCPP levels in dust with a maximum concentration of 56 µg/g (Meeker et al. 2013). A statistical analysis concluded a weak (r_S = 0.31) but statistically significant (p = 0.03) correlation between concentrations of BDCPP in urine (uncorrected for SG) and concentrations of TDCPP in house dust (Meeker et al. 2013). Pooled urine samples from Australia were also studied by the same methods used above (Van den Eede et al. 2015). The authors noted that the concentrations in adults were comparable to Cooper et al. (2011), Carignan et al. (2013) and Meeker et al. (2013), suggesting the exposure of the Australian population is similar to the population in the United States.

Urine samples were collected from 8 pregnant women (age from 28 to 36 years old at conception) in Chapel Hill, North Carolina, U.S., between December 2011 and May 2012, during pregnancy and after birth (Hoffman et al. 2014). A total of 39 urine specimens were collected (3 samples during the 18th week of pregnancy, 1 during the 28th week and 1 shortly after the child's birth, one woman did not provide a sample shortly after birth). BDCPP was detected in 38 of 39 urine samples, and the maximum SG-corrected concentration was 34.3 ng/mL, with a 95th percentile of 7.1 ng/mL and a geometric mean of 2.1 ng/mL) (personal communication Hoffman to Health Canada, 2014 June). Based on analysis of the urine samples, the authors suggest that exposure to TDCPP is variable for pregnant women and that a single measure of BDCPP, taken in the second trimester, likely captures information on the rank order of exposure throughout pregnancy.

In a paired mother and toddler study, spot urine samples were collected from 22 mothers and 26 "paired" children (5 mothers were paired with 2 children; one mother did not provide child's urine) from Princeton, New Jersey and analyzed for BDCPP (Butt et al. 2014). BDCPP was detected in 100% of samples for both mothers and toddlers. Maximum concentrations corrected for SG were 11.0 ng/mL for mothers and 251 ng/mL for toddlers with geometric means of 2.4 ng/mL and 5.6 ng/mL for mothers and toddlers, respectively. The authors determined a positive correlation between the mothers and toddlers for BDCPP and this trend may indicate that a shared environment is an important determinant of TDCPP exposure (Butt et al. 2014). In Australia, BDCPP concentrations in infants were also found to be higher than adults, a correlation suggested by Stapleton et al. (2011) given the wide use of TDCPP in children's products (Van den Eede et al. 2015).

Reverse dosimetry was used to derive estimates of daily intakes from urine concentrations from these studies, and results are shown in Table 9.2. A correction factor for incomplete excretion of BDCPP of 21% was applied to the estimate. This was based on toxicokinetic studies conducted in rats, showing a recovery of TDCPP radioactivity 24 hours after administration of closer to 35% in urine (percentage was estimated in figure in reference) (Minegishi et al. 1988), and a 60% urine recovery of metabolite BDCPP when TDCPP was intravenously administered (Nomeir et al. 1981; Lynn et al. 1980, 1981). The metabolism of TDCPP and excretion in urine from rats is relatively rapid, with a urinary half-life of approximately 12 hours (Minegishi et al. 1988). In addition, the relatively rapid metabolism is consistent with the *in vitro* human study by van den Eede et al. (2013). More details of toxicokinetic information are described in Section 9.2.1.3. Details regarding the reverse dosimetry are provided in Appendix F.

Table 9.2 Urinary BDCPP concentrations and reverse dosimetry intake estimates

Study	Participants	Location	Urinary concentrations[a] (ng/mL)— Geometric mean [Maximum]	Reverse dosimetry Intake estimates (µg/kg-bw/day) — Geometric mean [Maximum]
Hoffman et al. 2014	Pregnant Females (n=8)	Chapel Hill, North Carolina, U.S.	2.1 [34.3]	0.51 [8.3][b]
Butt et al. 2014	Women (i.e., mothers paired with toddlers) (n=22)	New Jersey, U.S.	2.4 [11]	0.44 [2.0][c]
Butt et al. 2014	Toddlers (paired with mothers) (n=23)	New Jersey, U.S.	5.6 [251]	1.6 [72][d]
Carignan et al. 2013	Females and Males (n=29)	Boston, MA, U.S.	0.41 [1.8]	0.07 [0.33][b]
Meeker et al. 2013	Males (n=45)	Massachusetts, U.S.	0.20 [19.4]	0.04 [3.5][b]

Study	Participants	Location	Urinary concentrations[a] (ng/mL)— Geometric mean [Maximum]	Reverse dosimetry Intake estimates (µg/kg-bw/day) — Geometric mean [Maximum]
Cooper et al. 2011	Females (n=5) Males (n=4)	North America	0.41 [3.5]	0.07 [0.64][b]

[a] Concentration are normalized to specific gravity (as reported in the studies).

[b] These estimates are based on the upper bound (2.7 L/d) of the range of mean total daily urinary volume for pregnant females.

[c] These estimates are based on the upper bound (2.03 L/d) of the range of mean total daily urinary volume for adults.

[d] These estimates are based on the upper bound (0.7 L/d) of the range of mean total daily urinary volume for toddlers.

A single biomonitoring study was recently identified for TCPP, where bis(1-chloro-2-propyl) phosphate (BCPP) urinary concentrations were measured in paired mother-toddler pairs from Princeton, New Jersey (Butt et al. 2014). Compared to high detections of BDCPP, BCPP was detected in 8% of urine samples (Butt et al. 2014). The low detection level may be from the low formation yield of BCPP from TCPP (Hoffman et al. 2014). The authors suggested that more research is needed to determine a suitable biomarker for TCPP (Butt et al. 2014).

There are a number of uncertainties associated with the use of this biomonitoring data. First, there is uncertainty with the data since the studies represent a relatively small number of participants for each subpopulation category (adults, pregnant women, children), and only depict individuals from the United States and thus may not be demographically representative. The applicability of the above data to the Canadian population is another uncertainty given the different manufactured items in each market. There is also an uncertainty in selecting the maximum urine concentration for each subpopulation given that the data is comprised of spot samples and may contain outliers.

Finally there are uncertainties associated with the parameters used to derive the estimates. Although BDCPP is a major metabolite and an appropriate biomarker for TDCPP, there is the uncertainty of direct exposure to BDCPP as a possible environmental breakdown product of TDCPP. There is uncertainty associated with specific gravity and applying generic mean urine volumes corrections. Another uncertainty in the dose conversion of spot urine samples for all age groups is the assumption that absorption, distribution, metabolism and elimination parameters are the same for all individuals (including pregnant women) and remain constant within individuals over time. Estimates of daily intake derived from the biomonitoring data are uncertain due to the limited data on toxicokinetics (differences in rat and human metabolism not fully elucidated) and lack of an excretion rate for humans.

9.2 Health Effects Assessment

9.2.1 TDCPP

9.2.1.1 Carcinogenicity

The European Commission has classified TDCPP as a Category 2 carcinogen (suspected human carcinogen) (European Commission 2013).

A two-year carcinogenicity study was conducted in Sprague Dawley rats (60/sex/group) where animals were fed diets (ad libitum) containing TDCPP (Stauffer Chemical Co. 1981a). The administered dose levels were 0, 5, 20 or 80 mg/kg-bw/day. Ten animals per sex per group were sacrificed after 12 months of treatment as an interim group.

Non-cancer effects are described in Section 9.2.1.5. The mortality rates were comparable between treatment groups and controls except for males in the high-dose group, for which mortality rate was significantly higher than controls after 12 months of treatment. Terminal body weights of male and female rats in the high-dose groups were significantly lower than the control animals (>20%).

For the 12-month interim group, the number of incidences of tumours in kidney, testes, liver, brain, as well as thyroid and adrenal glands is presented in Table 9.3. The adrenal gland, brain and thyroid gland were not examined at the low and mid doses in both sexes. No significant increase of any tumour types in the treatment groups compared to controls was observed.

Table 9.3. Tumour incidences of the 12-month interim group.

Table 9.3A. Tumour incidences in male rats of the 12-month interim group

Dose levels (mg/kg-bw/day)	**0**	**5**	**20**	**80**
Testicular interstitial cell tumour	0/14	0/12	3/13	3/11
Hepatocellular adenoma	0/15	0/12	0/13	3/14

Adrenal cortical adenoma	0/15	N/A	N/A	2/13
Brain gliomas (astrocytoma/ oligodendrogloima)	0/15	N/A	N/A	0/14
Thyroid gland adenoma/parafollicular cell adenoma	0/14	N/A	N/A	0/11

N/A-Not assessed in the study

Table 9.3B. Tumour incidences in female rats of the 12-month interim group

Dose levels (mg/kg-bw/day)	**0**	**5**	**20**	**80**
Hepatocellular adenoma	0/11	0/13	0/9	1/10
Adrenal cortical adenoma	5/11	N/A	N/A	1/10
Brain gliomas (astrocytoma/ oligodendrogloima)	0/11	N/A	N/A	0/10
Thyroid gland adenoma/parafollicular cell adenoma	0/9	N/A	N/A	0/6

N/A-Not assessed in the study

In the 24-month group, cancer effects were observed. The incidences of renal cortical adenomas (both sexes) and testicular interstitial cell tumours (males) were significantly increased in the mid- and high-dose groups compared to controls. At the high dose, significant increase incidences of hepatocellular adenomas (both sexes) and adrenal cortical adenomas (females) were observed. Tumour incidences for this group are presented in Table 9.4.

Table 9.4. Tumour incidences of the 24-month group.

Table 9.4A. Tumour incidences in male rats of the 24-month group

Dose levels (mg/kg-bw/day)	**0**	**5**	**20**	**80**
Renal cortical adenoma	1/45	3/49	9/48*	32/46*
Testicular interstitial cell tumour	7/43	8/48	23/47*	36/45*
Hepatocellular adenoma	2/45	7/48	1/48	13/46*
Hepatocellular carcinoma	1/45	2/48	3/48	7/46
Brain gliomas (astrocytoma/ oligodendrogloima)	0/44	0/4	1/1	5/46
Thyroid gland adenoma/ parafollicular cell adenoma	0/40	2/2	1/2	5/41

* Significantly different when compared to control animals ($p<0.05$).

Table 9.4B. Tumour incidences in female rats of the 24-month group

Dose levels (mg/kg-bw/day)	0	5	20	80
Renal cortical adenoma	0/49	1/48	8/48*	29/50*
Adrenal cortical adenoma	8/48	5/27	2/33	19/49*
Hepatocellular adenoma	1/49	1/47	4/46	8/50*
Hepatocellular carcinoma	0/49	2/47	2/46	4/50
Brain gliomas (astrocytoma/ oligodendrogloima)	1/46	1/4	2/5	1/48
Thyroid gland adenoma/ parafollicular cell adenoma	3/42	0/2	N/A	9/49

* Significantly different when compared to control animals ($p<0.05$).

N/A-Not assessed in the study

Freudenthal and Henrich published a journal article on the Stauffer Chemical carcinogenicity study for TDCPP years after it was completed (2000). The tumour incidences reported in Freudenthal and Henrich (2000) was based on combined tumour incidences for the interim and main groups, which was different from the original study report.

A retrospective cohort study examining mortality of workers employed in a TDCPP manufacturing plant was identified (Stauffer Chemical Co. 1983a). The study followed 289 workers, who were employed for a minimum of 3 months between 1956 and 1977, through to 1980. Over half of the workers worked fewer than 5 years and only 42 workers worked 15 or more years. The measured TDCPP levels, based on breathing zone samples measured between 1978 and 1981, were below the limit of detection of 8 ppb (140 µg/m^3). The overall standardized mortality ratio (SMR) based on observed death versus expected death of all causes was 0.75. SMR for all malignant neoplasms was 1.31 based on 3 observed over 2.3 expected. The 3 observed cases were employees who died from lung cancers and who were known to be moderate to heavy cigarette smokers.

9.2.1.2 Genotoxicity

A number of *in vitro* and *in vivo* genotoxicity studies were identified.

Most of these studies are described in detail in the EU RAR for TDCPP (EU RAR 2008b). Results were mostly negative for *in vitro* gene mutation assays in bacteria and yeasts, in the presence or absence of metabolic activation (S9) (Mortelmans et al. 1986; Soderlund et al. 1985; Stauffer Chemical Co. 1981b, 1983b; Nakamura et al. 1979;

Safepharm Laboratories Ltd 1984, 1985a; Ishidate 1983). Positive results were observed in particular strains of *Salmonella typhimurium*, TA97, TA100 and TA1535, in the presence of S9 (Stauffer Chemical Co. 1983b; Soderlund et al. 1985). In mammalian cells, results of some *in vitro* assays (point mutation assay, sister chromatid exchange assay and a limited unscheduled DNA synthesis assay) were negative (Stauffer Chemical Co. 1977; Soderlund et al. 1985). Other *in vitro* assays (mouse lymphoma assay, chromosomal aberration assay, transformation assay) generated mixed results (Stauffer Chemical Co. 1977, 1981b; Ishidate 1983; Inveresk Research International 1985; Soderlund et al. 1985; Covance Laboratories Inc. 2004). In *in vivo* testing, results were negative for a sex-linked recessive lethal mutations assay in *Drosophila,* an unscheduled DNA synthesis (UDS) assay in rats, a micronucleus assay in mice and a chromosomal aberration assay in mice (Stauffer Chemical Co. 1978a, 1981b; Brusick et al. 1980; Safepharm Laboratories Ltd 1985b; Covance Laboratories Inc. 2005a).

Morales and Matthews (1980) examined covalent binding of TDCPP to macromolecules in mice intravenously treated with TDCPP. Animals were sacrificed 6 hours after treatment. It was found that TDCPP readily bound to DNA in the liver and kidney. TDCPP also bound to RNA and proteins in liver, kidney and muscle.

Overall, results from *in vitro* genotoxicity studies were mixed. Results from a number of *in vivo* genotoxicity studies were negative.

9.2.1.3 Toxicokinetic

Three oral toxicokinetic studies conducted in rats were identified (Minegishi et al. 1988; Nomeir et al. 1981; Matthews and Anderson 1979). Overall, oral absorption from the gastrointestinal tract was greater than 90%. TDCPP was rapidly distributed in the body with high levels in kidneys, liver and lungs. The average Tmax was 9.6 h for TDCPP in blood and tissues in an oral toxicokinetic study (Minegishi et al. 1988). Metabolic degradation was extensive. Recovery of radioactivity 168 hours after administration was 43.2% in urine, 39.2% in faeces, 16.24% in expired air (as carbon dioxide) and 2.51% in carcass. Recovery of radioactivity 24 hours after administration was closer to 35% in urine (percentage was estimated in figure in reference) (Minegishi et al. 1988). Approximately 40% of the radioactivity was excreted via the bile. Bioaccumulation was expected to be low. The half-life of TDCPP clearance in tissues was between 1.5 and 5.4 hours depending on the tissue from a rat toxicokinetic study where TDCPP was intravenously administered (Nomeir et al. 1981).

TDCPP metabolites were recovered from rat urine in toxicokinetic studies where TDCPP was intravenously administered (Nomeir et al. 1981; Lynn et al. 1980, 1981).

The major metabolite identified was a diester of TDCPP, BDCPP (>60%). Lynn et al. (1981) identified 1,3-dichloro-2-propanol (1,3-DCP), the halo-alcohol that would be generated from hydrolysis of TDCPP to diester BDCPP, 1,3-dichloro-2-propyl phosphate (monoester of TDCPP) and a trace amount of un-metabolized TDCPP. Nomeir et al. (1981) noted that an unidentified polar metabolite (32%) was found in the urine, in addition to trace amounts of 1,3-dichloro-2-propyl phosphate (0.29%) and 0.45% un-metabolized TDCPP. Ulsamer et al. (1980) reported 1,3-DCP as the only metabolite detected in the urine of TDCPP-treated animals (rats and rabbits) but did not provide further experimental details.

An *in vitro* metabolism study tested in liver samples resulted in identification of the following metabolites: BDCPP (64%), 3-monochloro-1,2-propanediol (3-MCPD) (20%), 1,3-DCP (5.7%) and an unknown metabolite (11%) (Nomeir et al. 1981). Nomeir et al. (1981) suggested that the absence of 3-MCPD and 1,3-DCP metabolites in urine or expired air in their *in vivo* study was probably due to further metabolism of these intermediate metabolites. Another *in vitro* metabolism study identified glutathione conjugate of TDCPP(substitution of Cl) and derived metabolites (Gly-Cys-adduct and Cys-adduct) (Study Submission 2013).

In vitro metabolism studies using rat liver fractions suggested that TDCPP was metabolized by a NADPH-dependent microsomal mixed-function oxidase system and a glutathione-dependent transferase system in the soluble fraction (Sasaki et al. 1984; Nomeir et al. 1981), Blood plasma was found to have low capacity to metabolize TDCPP in the presence or absence of cofactors, where results were in contrary to a number of organophosphate insecticides (Nomeir et al. 1981).

In a recent *in vitro* metabolism study using human liver fractions (Van den Eede et al. 2013), consistent with other metabolism studies, BDCPP (45%) and the glutathione conjugate (20%) of TDCPP were identified. Metabolites that were possible products of a different pathway, oxidative dehalogenation, were identified. They were diester (20%) or triester (10%) forms of TDCPP with an alcohol (substitution of Cl) and triester form (5%) of TDCPP with a carboxylic acid (substitution of Cl). Oxidative dehalogenation involves the formation of an intermediate hydroxylated metabolite, from which HCl is eliminated to form an aldehyde which, in turn, is further oxidized to a carboxylic acid or reduced to an alcohol.

In vitro dermal absorption study tested on human skin, conducted according to OECD guidelines (TNO Quality of Life 2006a) is described in Section 9.1.2.1. In an *in vivo* study, Nomeir et al. (1981) stated that TDCPP was readily absorbed through rat skin but the absorption rate was not stated. Distribution pattern showed the highest concentration in the liver, followed by lungs, skin, blood, kidneys, adipose tissue and muscle.

9.2.1.4 Mode of Action

The mode of action for the tumours observed in rodents has not been fully elucidated.

Two metabolites identified based on *in vivo* and *in vitro* studies were 1,3-DCP and 3-MCPD (Nomeir et al. 1981; Lynn et al. 1981; Ulsamer et al. 1980) (see Section 9.2.1.2 for details). 1,3-DCP and 3-MCPD were classified as Category 2B carcinogens by the International Agency for Research on Cancer (IARC) (IARC 2012a,b). As described in the IARC monographs for 1,3-DCP and 3-MCPD, proposed metabolic pathways suggested that 1,3-DCP can metabolize to 3-MCPD and the metabolism of 1,3-DCP and 3-MCPD can generate several known mutagen and genotoxic carcinogens (1,3-dichloroacetone, epichlorohydrin and glycidol). Based on the identified potential genotoxic metabolites and evidence of *in vivo* DNA binding in mice, the US California EPA (2011) concluded that TDCPP may be carcinogenic through a genotoxic mechanism. A recent *in vitro* metabolism study (Van den Eede et al. 2013) identified metabolites from another pathway (oxidative dehalogenation) which involves the generation of an aldehyde intermediate. Although aldehyde can further metabolize to carboxylic acid or alcohol, it has the potential to bind to DNA or protein.

The EU RAR (2008b) has not identified any mode of action, but stated that testicular interstitial cell tumours could be induced by chemicals via a non-genotoxic mode of action through alternations in the Hypothalmus-Pituitary-Testis (HPT) Axis. Also, hyperplasia is often considered to be a pre-cancer lesion and the EU RAR (2008b) hypothesized that kidney tumours could have developed through hyperplastic changes.

9.2.1.5 Repeated-dose Toxicity

Kamata et al. (1989) conducted a 3-month oral subchronic study in mice (12/dose group) where animals were orally fed TDCPP in diets. The no-observed-adverse-effect level (NOAEL) for female mice was 15.3 mg/kg-bw/day based on a significant increase in absolute and relative kidney weights at the next dose level of 61.5 mg/kg-bw/day. The NOAEL for male mice for the 3-month groups was 47.3 mg/kg-bw/day based on a significant increase in relative liver and kidney weights at the next dose level of 171.0 mg/kg-bw/day.

In the two-year carcinogenicity study described earlier in Section 9.2.1.1, there were non-cancer effects observed in both 12-month and 24-month treated animals (Stauffer Chemical Co. 1981a; Freudenthal and Henrich 2000). In the 12-month interim, the lowest-observed-adverse-effect level (LOAEL) was 80 mg/kg-bw/day based on a significant decrease in body weights, significant increase in absolute and relative liver weights and significant increase in absolute and relative kidney weights observed in both male and female rats. For the 24-month treated animals, the LOAEL was 5 mg/kg-bw/day, the lowest dose level tested, based on hyperplasia of the convoluted tubule

epithelium in the kidneys and histological abnormalities in the testes in male rats at 5 mg/kg-bw/day and higher. At the next dose level of 20 mg/kg-bw/day, a significant increase in absolute and relative kidney weights and a significant increase in relative liver weights were observed in both males and females. In males, there was also a significant increase in absolute liver weight, an increased incidence of chronic nephropathy and an increased incidence of testicular enlargement at this mid-dose level. At the high dose of 80 mg/kg-bw/day, there was a significant decrease in body weight (>20%) and a significant increase in absolute and relative thyroid weights in both male and female rats compared to control animals. Macroscopic changes of the liver, erythroid/myeloid hyperplasia of the rib marrow and erythroid/myeloid metaplasia of the spleen were also observed.

9.2.1.6 Reproductive and Developmental Toxicity

A reproductive toxicity study was identified, which was conducted in male Dutch rabbits, where animals (10/dose group) were administrated 0, 2, 20 or 200 mg/kg-bw/day of TDCPP via oral gavage for 12 weeks (Stauffer Chemical Co. 1983c). The NOAEL was 20 mg/kg-bw/day based on a significant increase in absolute kidney and relative liver weights at the next dose level of 200 mg/kg-bw/day. There were no effects on mating behaviour, male fertility, sperm quality or sperm quantity. No histological lesions were observed in kidneys, liver, pituitaries, testes or epididymides.

In the two-year carcinogenicity study described earlier in Sections 9.2.1.1 and 9.2.1.5 (Stauffer Chemical Co. 1981a; Freudenthal and Henrich 2000), non-cancer effects in the male reproductive system were examined. Histopathological observations included oligospermia, eosinophic material/lumen, sperm stasis, polyarteritis nodosa in the testes, oligospermia and degenerated seminal product in the epididymis and decreased secretory product and atrophy in the seminal vesicle. The original report did not indicate that statistical analyses were performed. However, the National Research Council (NRC 2000) presented the same data with statistical analysis where histopathological observation for the 12- and 24-month treatment groups were combined. Effects in the seminal vesicle (decreased secretory product and atrophy) reached statistical significance starting from 5 mg/kg-bw/day, the lowest dose level tested. Effects observed in the male reproductive system might be secondary to an effect on the testicular interstitial cell tumours. Female reproductive organs were not analyzed in this study.

No reproductive toxicity studies conducted in female animals were identified. TDCPP, TCPP and TCEP, are closely related substances with similarities in chemical structures, physiochemical properties and toxicokinetics (more detail is available in Health Canada 2015). However, the reproductive effects observed in female animals tested with TCPP and TCEP were inconsistent (Appendix G). The EU (EU RAR 2008b) considered it not

appropriate to read-across from female fertility data on either TCPP or TCEP to address any possible effects on female fertility of TDCPP.

In a cross-sectional study, house dust samples and blood samples were collected from 50 male participants (18–54 years old) recruited through a U.S. infertility clinic (Meeker et al. 2010). Details of house dust are described in Section 9.1.3. TDCPP in dust was associated with a 3% decline in free thyroxine and a 17% increase in prolactin levels in blood. This study is considered to provide limited information as the sample size was small, control subjects were lacking and the association could be due to unmeasured confounders or coexposure to other chemicals.

In an *in vitro* study using Chinese hamster ovary cells (CHO-K1), Kojima et al. (2013) used cell-based transactivation assays to examine potential agonistic or antagonistic activities of TDCPP against a number of human nuclear receptors. Results showed that TDCPP exhibited PXR agonistic, AR antagonistic and GR antagonistic activities. The activities were 5-, 100- and 300-fold, respectively, lower than known PXR agonist (rifampicin), AR antagonist (hydroxyflutamide) and GR antagonist (mifepristone).

In a developmental toxicity study, pregnant Sprague-Dawley rats (20/dose group) were administrated 0, 25, 100 or 400 mg/kg-bw/day of TDCPP by oral gavage during gestation day 6 to 15 (Stauffer Chemical Co. 1978b). The maternal NOAEL was 25 mg/kg-bw/day based on a significant decrease in food consumption and in body weights and clinical signs of toxicity at the next dose level of 100 mg/kg-bw/day. The developmental NOAEL was 100 mg/kg-bw/day based on a significant increase in the rate of resorption, a significant decrease in the fetal viability index and retarded skeletal development at the next dose level of 400 mg/kg-bw/day. These developmental effects could be secondary due to maternal toxicity.

Another study was conducted with pregnant Wistar rats (15-24/dose group) administrated 0, 25, 50, 100, 200 or 400 mg/kg-bw/day of TDCPP by oral gavage during gestation day 7–15 (Tanaka et al. 1981 cited in EU RAR 2008b, only abstract is in English). The maternal NOAEL was 100 mg/kg-bw/day based on a significant increase in absolute and relative kidney weights at the next dose level of 200 mg/kg-bw/day. Increased mortality (11/15 dams) and clinical signs of toxicity were observed at 400 mg/kg-bw/day. The developmental NOAEL was 200 mg/kg-bw/day based on a significant increase in foetal deaths at the next dose level of 400 mg/kg-bw/day. Performance of functional tests including open field, water maze, rota rod, inclined screen, pain reflex and preyer's reflex were comparable to controls in the pups at dose levels of 200 mg/kg-bw/day and below.

9.2.1.7 Neurotoxicity

In three independent studies conducted in hens, animals treated orally with TDCPP for an acute duration, 5 consecutive days and 90 days did not show any significant signs of paralysis or neurotoxicity (Stauffer Chemical Co. 1978c, 1981b; US EPA 2008).

Plasma cholinesterase activity and erythrocyte cholinesterase activity were measured at 18 and 24 months in the two-year carcinogenicity study in rats (see Section 9.2.1.1, Stauffer Chemical Co. 1981a). In the high-dose females, plasma cholinesterase activity was significantly decreased at 18 months and non-significantly decreased at 24 months. In males, no dose-response trend was observed for plasma cholinesterase activity at 18 months and the levels were comparable to controls at 24 months. Erythrocyte cholinesterase activity, measured at 18 and 24 months, was comparable between treated and control groups in both male and female rats.

9.2.1.8 Sensitization

No skin sensitization was observed in guinea pig maximization tests (CIT 2001 cited in EU RAR 2008b).

9.2.1.9 Epidemiological studies

A total of 124 workers in a TDCPP manufacturing plant were part of a retrospective morbidity study (Stauffer Chemical Co. 1983d). This study served as an adjunct to the mortality study (Stauffer Chemical Co. 1983b) described in Section 9.2.1.1. Workers were all men, worked full-shift, were employed for a minimum of three months between 1956 and 1977. A follow-up was conducted in 1981. Based on payroll information from 1975 to 1981, workers were classified as TDCPP-exposed (93 workers) or non-exposed (31 workers). Breathing zone sampling taken in the plant during December 1978 to May 1979 indicated that TDCPP levels in the air were always near or below the limit of detection of 8 ppb (140 µg/m^3). A self-administered health questionnaire, a physical examination, a pulmonary function test, a chest x-ray and electrocardiogram and a spectrum of clinical and biochemical analyses were performed on these workers. Overall, there were no increased risk of adverse respiratory effects from exposure to TDCPP and no abnormal clinical findings. An excess of benign neoplasms (primarily lipomas) (5.4% vs. 0%), dermatitis (6.5% vs 3.2%) and gynaecomastia (3.3% vs 0%) were observed in the exposed group compared to the non-exposed group.

9.2.2 TCPP

9.2.2.1 Carcinogenicity and Genotoxicity

No chronic or carcinogenicity studies of TCPP were identified. Currently, the US National Toxicology Program (NTP) (2014) is conducting 90-day and two-year oral

toxicity and carcinogenicity studies in both rats and mice. The concern for potential carcinogenicity was due to structural similarity to other organophosphate esters that showed carcinogenic effects in two-year carcinogenicity studies in experimental animals.

Several other lines of evidence were investigated to characterize the carcinogenic potential of TCPP (more detail is available in Health Canada 2015), including the analogue approach, the quantitative structural activity (QSAR) approach and the structural alerts approach. It was considered that TCEP and TDCPP may be used for qualitative read-across for carcinogenicity. The Government of Canada has published a final screening assessment for TCEP (Environment Canada, Health Canada 2009) and concluded that TCEP demonstrated carcinogenic potential, and that it could not be precluded that the induction of tumours could be via a mode of action involving direct interaction with genetic material. The human health effects assessment for TDCPP described in Section 9.2.1 shows that TDCPP is associated with carcinogenic potential. Overall, the evidence suggests that TCPP may be carcinogenic in rodents.

A number of *in vitro* and *in vivo* genotoxicity studies were identified.

Most of these studies are described in detail in the EU RAR for TCPP (EU RAR 2008a). *In vitro* genotoxicity studies (Ames assays) showed little evidence of mutagenic potential in bacteria and fungi (Stauffer Chemical Co. 1976, 1978d; Parmar 1977; Tenneco Chemicals Inc 1977a, b; Nakamura et al. 1979; Anon 1980; Mobil Environmental and Health Safety Laboratory 1980a; SafePharm Laboratories Ltd 1992; Zeiger et al. 1992; Follmann and Wober 2006). *In vitro* studies tested in mammalian cells (mouse lymphoma assays, unscheduled DNA synthesis [UDS] assays, comet assays) generated equivocal or mixed results (Stauffer Chemical Co. 1978e,f, g, 1980a; Environmental Affairs and Toxicology Department 1981; Covance Laboratories Inc. 2005b; Bayer 1991b; Williams et al. 1989; Follmann and Wober 2006). One of the *in vitro* mouse lymphoma assays conducted according to OECD guidelines generated positive results in the presence of S9, suggesting clastogenicity potential of a metabolite. Results of some *in vivo* assays (micronucleus assays and comet assays) were negative (Bayer 1991c; Covance Laboratories Inc. 2006). Other *in vivo* studies (UDS assays, chromosomal aberration assays) generated equivocal results or negative results associated with limitations to the studies (Stauffer Chemical Co. 1978h; Bayer Healthcare 2005).

The US National Toxicology Program (NTP) recently conducted *in vivo* micronucleus assays in male and female B6C3F1 mice and Sprague-Dawley rats (NTP 2009). Cells were collected from peripheral blood of animals that were orally fed 0, 1250, 2500, 5000, 10000 or 20000 ppm TCPP in diet, 5 days a week for 90 days. The corresponding intakes were 0, 163, 325, 650, 1300 and 2600 mg/kg-bw/day, respectively. The final report is not yet available, but original data are presented on the NTP website. Positive

results were observed in male mice. Results were negative in male and female rats and in female mice.

9.2.2.2 Toxicokinetics

Several oral or intravenous dosing toxicokinetic studies conducted on experimental rats were identified (Minegishi et al. 1988; Stauffer Chemical Co. 1984). Based on these studies, oral absorption of TCPP appears to be at least 75%. TCPP is widely distributed in tissues including liver, kidney, lung and adipose tissue. The actual amount detected in these tissues was very low suggesting low bioaccumulation. The biliary/faecal excretion ratio suggested enterohepatic re-circulation from the GI tract after oral administration. TCPP is extensively metabolized prior to excretion. Urinary excretion is the primary route of elimination of TCPP, but both urinary and faecal excretions are dose-dependent and route dependent (oral and i.v.). One study (Stauffer Chemical Co. 1984) found that for the same dose level (20 mg/kg) administered orally or by i.v., the urine excretion was 49% for oral and 63% for i.v. routes. The faecal excretion was 40% for oral and 27% for i.v. routes. The total elimination via the 2 routes was rapid and constant, averaging 89% of the dose at 72h. In the same study, Stauffer Chemical Co. (1984) also administered a higher oral dose level (200 mg/kg). It was found that the urine excretion was 70% and faecal excretion was 22% suggesting dose-dependent excretion pattern. Approximately 2% of TCPP is excreted unchanged. A major metabolite identified in both urine and faeces, accounting for over 50% of the dose, is 0,0-[bis(1-chloro-2-propyl)]-0-(2,propionic acid)phosphate (triester form of TCPP with carboxylic acid substituting a chlorine atom). It was suggested that this major metabolite is responsible for the dose-dependent excretory pattern. At low doses, this metabolite was excreted approximately equally in the urine and faeces. At high doses, it was excreted predominantly in the urine. Other metabolites identified include possible products from hydrolysis reaction: diester form of TCPP, bis(1-chloro-2-propyl)monophosphoric acid and halo-alcohol, 1-chloro-2-propanol. 1-chloro-2-propanol, is a demonstrated mutagen in *in vitro* genotoxicity studies, but did not induce any tumours in two-year drinking water carcinogenicity studies conducted in both rats and mice (NTP 1998).

In vitro metabolism study using liver S9 fraction and liver slices from male Wistar-Han rats identified another metabolic pathway. TCPP was metabolized to a hydroxylated metabolite by chlorine substitution in liver S9 fraction and liver slices, followed by glucuronic acid conjugation in liver slices (Study Submission 2013). In a recent *in vitro* metabolism study using human liver fractions (Van den Eede et al. 2013), consistent with *in vivo* studies, the carboxylic acid metabolite (0,0-[bis(1-chloro-2-propyl)]-0-(2,propionic acid)phosphate) (30%) and the diester form of TCPP (20%) were identified. Another metabolite identified was a triester form of TCPP with an alcohol (40%) substituting a chlorine atom. The carboxylic acid and the alcohol metabolites were

possible products of oxidative dehalogenation. In addition, one hydroxylated metabolite (10%) of TCPP where the position of the hydroxyl is uncertain was identified.

Two *in vitro* dermal absorption studies, conducted according to OECD guidelines, were identified (TNO Quality of Life 2005, 2006b) (see section 9.1.2.1).

9.2.2.3 Repeated Dose Toxicity

Repeated dose toxicity studies via the oral route (gavage or fed TCPP in their diet) were identified.

In a 14-day study, Sprague-Dawley male and female rats (10/sex/dose) were treated with 0, 4200, 6600, 10600 or 16600 ppm of Fyrol PCF in diet (Stauffer Chemical Co 1980b). According to the OECD SIDS Initial Assessment Report for TCPP (OECD 2002), the composition of Fyrol PCF contained about 70% of TCPP and about 22% of 2-chloropropanol phosphate. The corresponding intakes were 0, 417, 648, 1015 and 1636 mg/kg-bw/day of Fyrol PCF for males and 0, 382, 575, 904 and 1517 mg/kg-bw/day for females, respectively. For males, a NOAEL of 10 600 ppm (1015 mg/kg-bw/day) was identified based on reduced weight gain during the first week of treatment compared to controls at 16 600 ppm. Weight gain was not different from controls during week two. Food consumption was significantly reduced in the first 3 days of the study in male rats in the two highest treatment groups. For the remainder of the study, food consumption of all treated groups was similar to control groups. For females, the NOAEL was 16 600 ppm (1517 mg/kg-bw/day), the highest dose tested.

In an oral gavage study, male and female Wistar rats (6/sex/dose group) were treated with 0, 10, 100 or 1000 mg/kg-bw/day of TCPP for 28 days (Bayer 1991d). The study was conducted according to EC guidelines. A preliminary 7-day study was first conducted on male rats indicating no treatment-related effects observed when animals were dosed up to 1000 mg/kg-bw/day for 7 days. In the main study, a NOAEL of 100 mg/kg-bw/day was identified. Three animals died at 1000 mg/kg-bw/day (1 male rat died probably due to treatment error and 2 female rats died that could be treatment-related). Absolute and relative liver weights were significantly increased in both males and females at 1000 mg/kg-bw/day. All male rats in the 100 mg/kg-bw/day dose group except one exhibited minimal periacinary hepatocyte hypertrophy. The one animal at 100 mg/kg-bw/day and all male rats at 1000 mg/kg-bw/day dose group developed slight hypertrophy of the periacinary hepatocytes. TCPP treated female rats did not exhibit any hepatic alterations. Clinical chemistry indicated significant decrease in alanine aminotransferase activity in both male and female rats in the 1000 mg/kg-bw/day dose group.

The EU (EU RAR 2008a) described an unpublished 13-week study where Sprague-Dawley male and female rats (20/sex/dose) were treated with 0, 800, 2500, 7500 or 20

000 ppm of TCPP in diet (Stauffer Chemical Co. 1981c cited in EU RAR 2008a). The corresponding intakes were 0, 52, 160, 481 and 1349 mg/kg-bw/day for males and 0, 62, 171, 570 and 1745 mg/kg-bw/day for females, respectively. For males, a LOAEL of 800 ppm (52 mg/kg-bw/day), the lowest dose level tested, was determined based on all treated males exhibiting a significant increase in absolute and relative liver weights, accompanied by mild thyroid follicular cell hyperplasia. The incidences of thyroid follicular cell hyperplasia were 0/20, 2/20, 2/20, 5/20 and 8/20 at 0, 800, 2500, 7500 or 20000 ppm, respectively. At 2500 ppm, a significant increase in relative kidney weight was observed, accompanied with mild renal cortical tubule degeneration (hyaline droplet formation). For females, a NOAEL of 2500 ppm (171 mg/kg-bw/day) was identified with a LOAEL of 7500 ppm based on significant increase in absolute and relative liver weights. At 20 000 ppm, mild renal cortical tubule vacuolative degeneration (4 animals, compared to 1 control animal) and mild thyroid follicular cell hyperplasia (5/20 treated vs 0/20 control) were observed in the female rats. Periportal hepatocyte swelling (hypertrophy) was observed at 20 000 ppm in both males (7/20 treated vs. 0/20 control) and females (8/20 treated vs. 5/20 control). The mean body weights of male and female rats in the high dose groups were significantly lower than the control animals. There were no significant alternations in clinical chemistry, haematology or urinalysis parameters. No treatment-related changes in plasma, erythrocyte or brain cholinesterase activity were observed.

Freudenthal and Henrich (1999) published a journal article on a subchronic toxicity study, in which the data were very similar to the Stauffer Chemical Co. study (1981c) described in the EU RAR (2008a), and are likely from the same study. Sprague-Dawley male and female rats (20/sex/dose) were treated with 0, 800, 2500, 7500 or 20 000 ppm of Fyrol PCF in diet. Fyrol PCF consists of about 70% of TCPP and about 23% of 2-chloropropanol phosphate. Similar changes in absolute and relative liver weights, relative kidney weights and mean body weights at the same dose levels as reported in the EU RAR (2008a) were described. However, the reported incidences of histopathology observations were not identical in those described in EU RAR (2008a). Histopathology observations reported by Freudenthal and Henrich (1999) are presented in Table 9.5 and Table 9.6. Since mild thyroid follicular hyperplasia was observed in both treated and control groups, the authors considered the effects were not treatment-related. The authors considered the swelling of periportal hepatocytes and very mild degenerative changes in the renal cortical tubules non-adverse, in the absence of changes in clinical chemistry and concluded that a NOEL of 2500 ppm for the study based on minimal morphological alternations observed at 7500 ppm and above. A LOAEL of 800 ppm based on a significant increase in absolute and relative liver weights is considered more appropriate for this study.

Table 9.5. Histopathology observations in male rats (Freudenthal and Henrich 1999)

Dose (ppm)	Thyroid follicular hyperplasia	Liver periportal swelling	Renal cortical tubular degeneration*
0	5	0	0
800	5	0	0
2500	3	0	0
7500	10	0	13
20 000	8	9	7

*Combined tubular vacuolative degeneration and tubular hyaline droplet degeneration

Table 9.6. Histopathology observations in female rats (Freudenthal and Henrich 1999)

Dose (ppm)	Thyroid follicular hyperplasia	Liver periportal swelling	Renal cortical tubular degeneration*
0	0	5	1
800	2	0	0
2500	2	0	0
7500	9	0	0
20 000	5	8	4

*Combined tubular vacuolative degeneration and tubular hyaline droplet degeneration

NTP (2014) is currently conducting a 90-day study where B6C3F1 male and female mice were orally fed with 0, 1250, 2500, 5000, 10 000 or 20 000 ppm of TCPP in diet. The corresponding intakes were 0, 163, 325, 650, 1300, 2600 mg/kg-bw/day respectively. A study report is not yet available. Preliminary results indicated male mice exhibited a significant decrease in body weight starting from 2500 ppm. A similar effect was observed in female mice, but at higher dose of 10 000 ppm. Histopathology observations reported incidences of liver hypertrophy in male mice starting from 2500 ppm, which was also observed in female mice starting from 5000 ppm. In male mice, but not in female mice, incidences of cytoplasmic alteration of the renal tubule in the kidney were observed starting from 2500 ppm.

9.2.2.4 Reproductive Toxicity

An oral two-generation reproductive toxicity study in rats was conducted in accordance with OECD guidelines (TNO Quality of Life 2007 cited in EU RAR 2008a). This study included a preliminary range-finding study of a one-generation reproductive toxicity study. It was noted that there was a deviation from the study plan, the corpora lutea were not counted at scheduled sacrifice.

In the preliminary study, male and female rats were treated for 5 weeks prior to mating and during mating. Females were treated during gestation and lactation to post-natal (PN) day 21. Dams were sacrificed for necropsy at PN21. Males were sacrificed after at least 42 days of exposure. Rats (10/sex/dose) were orally fed 0, 1500, 5000 or 15 000 mg/kg diet containing TCPP. The administered doses were equivalent to 0, 95, 325 and 1000 mg/kg-bw/day, respectively, in male rats. In female rats, the administered doses were equivalent to 0, 108, 370 and 1176 mg/kg-bw/day, respectively, during premating; 0, 100, 314 and 963 mg/kg-bw/day, respectively, during gestation; and 0, 193, 680 and 1930 mg/kg-bw/day, respectively, during lactation. In parental (F0) females, the LOAEL was 1500 mg/kg diet (108-193 mg/kg-bw/day) based on a significant decrease in mean absolute and relative uterus weights at all treatment doses. This effect was independent of weight loss as a significant decrease in mean terminal body weight was observed in the high dose group only. In parental F0 males, the LOAEL was 1500 mg/kg diet based on a significant decrease in mean absolute prostate weight. Statistically significant decrease absolute prostate weight was observed in the low- and high- dose groups, with a non-significant decrease in mid-dose animals. No effects on motility or count of epididymal sperm or sperm morphology were observed. Changes in organ weights were not associated with any gross or histopathological changes. In terms of reproductive parameters, there were no effects on pre-coital time, mating index and male and female fertility index. The number of pups delivered and the sex ratio were not affected by treatment. Pup mortality was significantly higher in the high-dose group, including all 8 pups of one dam.

In the main study, the F0 parents, 28 Wistar rats per sex per group received TCPP in their daily diet for at least 10 weeks during premating and mating. Females were also treated throughout gestation (approximately 3 weeks) and lactation (3 weeks) until sacrifice. At weaning (PN21), F1 offspring (28 animals per sex per group, selected at random) were treated with TCPP for at least 10 weeks of exposure during their growth into adulthood and during mating. Female F1 animals continued to be treated during gestation and lactation until the F2 generation was weaned on PN21. The reported overall intakes were 0, 85, 293 or 925 TCPP mg/kg-bw/day in males and 0, 99, 330 or 988 mg/kg-bw/day in females.

In terms of effects on reproductive parameters, no treatment-related differences were observed in pre-coital time, mating index, female fecundity index, male and female

fertility index and duration of gestation in both generations. A non-significant increase in post-implantation loss in the F1 generation was observed. All dams survived the delivery and there were no dams with stillborn pups in any of the groups. The mean number of pups delivered was decreased in the mid dose of F1 and in the high dose of F0 and F1, including the loss of one litter (10 pups) of a single dame in the high-dose group. In males, there was no treatment-related effect on epididymal sperm motility or sperm count, sperm morphology or mean testicular sperm count in F0 and F1 at necropsy.

The LOAEL for the F0 generation of females was the lowest dose tested of 99 mg/kg-bw/day based on a significant decrease in mean absolute and relative uterus weights and effects on oestrus cycle in females. Effects on oestrus cycle were observed, including a significant increase in the mean length of the longest oestrus cycle at all doses. At high dose, a significant decrease in the number of oestrus cycle per animal and a significant increase in the number of acyclic animal were observed. In F1 females, a similar effect on uterus weights and oestrus cycles reached statistical significance at the high dose. The LOAEL for F1 females was 99 mg/kg-bw/day based on a significant decrease in absolute pituitary weight at all doses. In F0 males, the NOAEL was 85 mg/kg-bw/day based on a significant decrease in mean terminal body weight and mean absolute seminal vesicles at the next dose level of 293 mg/kg-bw/day. In F1 males, the LOAEL was 85 mg/kg-bw/day based on a significant decrease in mean absolute kidney weight observed at all treatment doses. No treatment-related macro- or microscopical changes were observed in the F0 or F1 animals.

Follmann and Wober (2006) conducted *in vitro* studies to examine potential estrogenic or anti-estrogenic effects of TCPP. No estrogenic or anti-estrogenic effect was observed in a recombinant yeast reporter gene assay tested in human endometrial cancer Ishikawa cells. Kojima et al. (2013) used cell-based transactivation *in vitro* assays to examine potential agonistic and/or antagonistic activities of TCPP against a number of human nuclear receptors. Overall, TCPP had no agonistic or antagonistic activities against nuclear receptors except a weak agonistic activity against PXR.

9.2.2.5 Developmental Toxicity

In the preliminary range-finding study of the two-generation reproductive toxicity study described in Section 9.2.2.4 (TNO Quality of Life 2007 cited in EU RAR 2008a), it was reported that a significant number of runts was observed at all treatment doses on PN21. The EU RAR (2008a) did not provide their definition of runt. The OECD SIDS initial assessment profile for TCPP (OECD 2009) defined runt as a pup with a weight less than the mean pup weight of the control group minus 2 standard deviations. In F0 animals, there was a significant decrease in body weight in the mid-dose group (5000 mg TCPP/kg diet) during premating. A similar body weight effect was observed in the mid- (5000 mg TCPP/diet) and high-dose (15 000 mg TCPP/diet) groups during

gestation and lactation. Overall, the LOAEL was 1500 mg TCPP/kg diet based on a significant increase in the number of runts.

In the main two-generation reproductive toxicity study described in Section 9.2.2.4 (TNO Quality of Life 2007), parameters related to developmental effects were examined in F0, F1 and F2 generations.

In F0 generation, a significant increase in the number of runts was observed at 99 mg/kg-bw/day or higher on PN1. The mean number of pups delivered was decreased in the high dose group. There was a significant increase in pup mortality during PN1-4 in the low- and high-dose groups, but it did not reach statistical significance in the mid-dose group. The mean pup weights were normal on PN1, but significantly decreased from PN14 onwards in the high-dose group. A significant decrease in absolute and relative spleen weights was observed in the mid- and high-dose groups. Maternal body weight was decreased in high dose females during gestation. Mean food consumption was decreased in F0 females in mid- and high-dose groups.

In the F1 generation, a significant increase in the number of runts was reported from F1 females treated with 99 mg/kg-bw/day and higher on PN21. The mean number of pups delivered and the mean number of live pups per litter were decreased in mid- and high-dose groups. In the high-dose group, there was a loss of all 10 pups in one litter from a dam on PN4. The mean pup weights were normal on PN1, but significantly decreased from PN7 onwards in the high-dose group and on PN21 in the mid-dose group. A significant decrease in absolute and relative spleen weights was observed in the mid- and high-dose groups. Maternal body weights were decreased in mid- and high-dose animals in F1 generation throughout premating, gestation and during lactation. Mean food consumption was decreased in F1 females of mid- and high-dose groups.

Anogenital distance was measured in all F2 pups on PN1, which was found to be comparable to controls. Sexual maturation parameters (vaginal opening and preputial separation) were assessed in 1 male and 1 female F2 pup per litter. A non-significant delay of the vaginal opening and a significantly delayed preputial separation were observed at the high dose. These effects could be secondary to systemic toxicity as the body weights of the high-dose male and female F2 pups were significantly decreased from PN28 until PN42.

In both generations, the pups that were found dead showed no abnormalities. No treatment-related macroscopic findings were observed in the pups at necropsy.

Overall, a developmental LOAEL of 1500 mg TCPP/kg diet (99 mg/kg-bw/day) was identified in this study based on a significant increase in the number of runts observed in F0 generation on PN1. Similar effects were observed in F1 generation on PN21 but not on PN1. The EU (EU RAR 2008a) established the same LOAEL for this study based

on a weight-of-evidence approach and considered this to be a relatively precautionary LOAEL as the effects on runts was not observed in both generations on PN1.

9.2.2.6 Neurotoxicity

In an acute neurotoxicity study, 4 female hens were orally administered 13 200 mg/kg-bw of TCPP (Sprague et al. 1981). No inhibition of plasma cholinesterase or brain neurotoxic esterase (NTE) was observed in the treated animals. In the second part of the study, 18 female hens were orally administered 13 200 mg/kg-bw of TCPP for 2 times, 21 days apart. Animals showed signs of systemic toxicity (significant reduction in food consumption, decreased mean body weights, feather loss and cessation of laying). One out of 18 hens died on day 4. Histological examination showed 2 hens with minimal axonal degeneration in dorsal funiculi of the cervical, ventro-lateral funiculi of thoracic or ventromedial funiculi of the sacro-lumber spinal cord, tracts known to be sensitive to organophosphate-induced degeneration. One of these hens also showed impaired walking behaviour. The administered dose of 13 200 mg/kg-bw was excessively above the recommended dose limit of 2000 mg/kg-bw for acute OPIDN study in OECD guidelines (OECD 1995). Only isolated incidences of minimal axonal degeneration was observed in 2/18 hens and no plasma cholinesterase and NTE inhibitions were observed; overall, the EU (EU RAR 2008a) considered that there is no concern for acute delayed neurotoxicity.

The 13-week rat study (Stauffer Chemical Co. 1981c) described in Section 9.2.2.3, measured cholinesterase activities. No treatment-related changes in plasma, erythrocyte or brain cholinesterase activity were observed.

9.2.2.7 Sensitization

No skin sensitisation was observed in a Buehler's test in guinea pigs and in a mouse local lymph node assay (SafePharm Laboratories 1979, 2005).

9.3 Characterization of Risk to Human Health

9.3.1 TDCPP

Based on the classification from the European Commission and on the available health effects data, the critical effect for characterization of risk to human health associated with exposure to TDCPP is carcinogenicity. A statistically significant increase in the incidence of tumours (adenomas) was observed in both male and female rats exposed to TDCPP for two years. Tumours were observed in multiple organ sites, including kidney and liver in both sexes, testes (in males) and adrenal gland (in females) (Stauffer Chemical Co. 1981a). Hyperplasia in the kidney and histological abnormalities in the testes were observed, which could be associated with the adenomas developed in these organs starting in the mid dose. The excessive body weight effects in the high-

dose groups suggested maximum tolerated dose had been exceeded. In terms of genotoxicity, mixed results were observed *in vitro* and negative results were observed *in vivo;* however, there is evidence that TDCPP can covalently bind to DNA in mice.

Using the two-year carcinogenicity study where TDCPP was administered to male and female rats via the diet (Stauffer Chemical Co. 1981a; Freudenthal and Henrich 2000), benchmark dose (BMD) modelling was applied to derive a point of departure (POD) for critical cancer effects from oral exposure. A dose-response curve was used to derive a lower-bound one-sided 95% confidence limit for the benchmark dose (BMDL) corresponding to a 10% incidence of tumours ($BMDL_{10}$). The model selection criteria and results are provided in Appendix H.

A $BMDL_{10}$ was derived for each tumour type, and a model was selected on the basis of fit amongst the nine models available in the US EPA Benchmark Dose Software (BMDS v.24). A dose-response analysis of each tumour site by BMDS shows that the testis (interstitial cell tumour in male rats) is the most sensitive organ with a $BMDL_{10}$ of 6.74 mg/kg-bw per day. A similar $BMDL_{10}$ of 6.84 mg/kg-bw per day was identified for renal cortical adenoma in males. In female rats, the $BMDL_{10}$ for renal cortical adenoma was 8.29 mg/kg-bw per day. Given that the differences between the renal cortical adenoma $BMDL_{10}$ levels for male and female rats were minimal, it is considered that TDCPP does not induce gender-specific effects in the kidney.

For non-cancer effects, a chronic critical LOAEL of 5 mg/kg-bw was identified, where hyperplasia of the epithelium of the convoluted tubule in the kidneys, and histological abnormalities in the testes, were observed in males at the lowest dose tested in a two-year chronic toxicity study in rats (Stauffer Chemical Co. 1981a).

Potential exposure to TDCPP for the general population is expected to be mainly from environmental media (air, water, dust and food, including breast milk) and from the use of manufactured items and consumer products. Total daily intake from environmental media was estimated for each age group (Table 9.7, Appendix C). For the purpose of estimating the risk of cancer from exposure to TDCPP, a lifetime average daily dose (LADD) from environmental media was calculated as follows:

LADD = [exposure rate × exposure duration] / Lifetime

= (0.35 × 0.5/71) + (0.20 × 4.5/71) + (0.12 × 7/71) + (0.048 × 8/71) + (0.047 × 40/71) + (0.044 × 11/71)

= 0.066 µg/kg-bw/day

Comparison of the LADD estimate of total daily intake from environmental media of 0.066 µg/kg-bw/day to the $BMDL_{10}$ of 6.74 mg/kg-bw/day for cancer effects results in a

lifetime margin of exposure (MOE) of 100 000. For non-cancer effects, comparison of the highest environmental media estimate of an infant (0.35 µg/kg-bw/day, Table 9.7) to the critical effect level of 5 mg/kg-bw/day resulted in a MOE of 14 000. These MOEs are considered to be adequate to account for uncertainties in the exposure and health effect databases for cancer and non-cancer effects.

Table 9.7 Exposure estimates by age group

Age Group	**0y–0.5y**	**0.5y–4y**	**5y–11y**	**12y–19y**	**20y–59y**	**⩾60–71y**
Body weights[a] (kg)	7.5	15.5	31.0	59.4	70.9	72.0
Environmental media intake (µg/kg-bw/day)	0.35	0.20	0.12	0.048	0.047	0.044
Dermal exposure from lying on foam mattresses[b] (µg/kg-bw/day)	1.90	1.34	0.71	0.58	0.50	0.49

[a] Body weights of age groups according to Health Canada (1998).

[b] Intake estimated based the TDCPP adjusted dermal absorption value of 30% obtained by using the ratio of the TCPP *in vitro* absorption values (23% and 40%) to the 15% TDCPP absorption rate (EU RAR 2008b).

Manufactured items (foam mattresses and couches, furniture with upholstery backcoating) may contain TDCPP. Dermal exposure through contact with foam-containing furniture was estimated for each age group (Table 9.7). For the purpose of estimating the risk of cancer from exposure to TDCPP, a LADD from dermal exposure to foam-containing furniture was calculated as follows:

LADD = [exposure rate × exposure duration] / Lifetime

= (1.90 × 0.5/71) + (1.34 × 4.5/71) + (0.71 × 7/71) + (0.58 × 8/71) + (0.50 × 40/71) + (0.49 × 11/71)

= 0.59 µg/kg-bw/day

Comparison of the LADD estimate from dermal exposure to foam-containing furniture of 0.59 µg/kg-bw/day with the $BMDL_{10}$ of 6.74 mg/kg-bw/day results in a lifetime MOE of 11 000 for cancer effects.

For non-cancer effects, dermal exposure through contact with foam-containing furniture was estimated to be 1.9 µg/kg-bw/day for an infant and 0.50 µg/kg-bw/day for an adult (Table 9.7). Comparison of these estimates with the chronic oral critical effect level of 5 mg/kg-bw/day resulted in MOEs of 2600 for infants and 10 000 for adults (Table 9.8). Toddler exposure through mouthing of a foam product (e.g., toy) was estimated to be 0.030 µg/kg-bw/day. Comparison of this estimate with the chronic oral LOAEL of 5 mg/kg-bw/day result in a MOE of 170 000 (Table 9.8).

Table 9.8 Margins of exposure from use of consumer products containing TDCPP, for non-cancer effects

Scenario	Exposure concentration (µg/kg-bw/day)	MOE for non-cancer effects (based on a chronic oral LOAEL of 5 mg/kg-bw/day)
Infant dermal contact from lying on foam mattresses	1.9*	2600
Adult dermal contact from lying on foam mattresses	0.50*	10 000
Toddler mouthing a foam object	0.030	170 000

* intake estimated based on TDCPP adjusted dermal absorption value of 30% obtained by using the ratio of the TCPP *in vitro* absorption values (23% and 40%) to the 15% TDCPP absorption rate (EU RAR 2008b).

Estimates of daily exposure intake were also calculated using reverse dosimetry from biomonitoring studies (Cooper et al. 2011; Carignan et al. 2013; Meeker et al. 2013; Butt et al. 2014; Hoffman et al. 2014) in which concentrations of BDCPP, as a biomarker of TDCPP, were measured in urine spot samples. Although estimates of daily intake derived from biomonitoring data are associated with a number of uncertainties (see Section 9.1.3), biomonitoring provides a direct measure of the internal dose of the chemical and is reflective of uptake from all routes of exposure (NRC 2006). The estimates of daily exposure intake based on geometric means of BDCPP concentrations ranged from 0.04–1.6 µg/kg-bw/day for children and adults. These concentrations though variable are overall consistent with estimates of exposure from environmental media and the use of consumer products derived with the use of modelling. Therefore the range of margins of exposure to these estimated of daily intake

would be considered to be adequate to account for uncertainties in the exposure and health effect databases for cancer and non-cancer effects.

Overall, the MOEs for the use of manufactured items containing TDCPP are considered to be adequate to account for uncertainties in the exposure and health effect databases.

9.3.2 TCPP

Based on the overall data available on health effects of TCPP, the critical effects for characterization of risk to human health associated with exposure to TCPP are reproductive and developmental toxicity. Although no chronic or carcinogenicity studies are available, there is evidence to suggest that TCPP may have carcinogenic potential.

The initial concern for carcinogenicity is due to the structural similarity of TCPP to other organophosphate esters (eg. TCEP, TDCPP) that showed carcinogenic effects in carcinogenicity studies in experimental animals. Initiated in 2012, the NTP is conducting 90-day and two-year oral toxicity and carcinogenicity studies in both rats and mice. In the absence of a chronic study, several other lines of evidence were investigated to assess the carcinogenic potential of TCPP. Overall, the evidence suggests that TCPP may be carcinogenic in rodents; this is based on a qualitative read-across from TCEP and TDCPP which are considered to be structurally similar to TCPP, as well as QSAR and structural alerts analyses.

A two-generation reproductive toxicity study in rats was available. In this study, a LOAEL of 99 mg/kg-bw/day, the lowest dose level tested, was identified for both reproductive and developmental effects (TNO Quality of Life 2007 cited in EU RAR 2008a). For reproductive effect, this effect level was based on a significant decrease in uterus weights and effects on estrus cycle in F0 females. The effect on uterus weights was also observed in the preliminary one-generation reproductive toxicity study. At this effect level, there was also a significant decrease in absolute pituitary weight in F1 females in the two-generation study. In terms of developmental effects, a significant increase in the number of runts was observed at 99 mg/kg-bw/day or higher on PN1 in the F0 generation. Similar effects were observed in F1 generation and in the preliminary one-generation reproductive toxicity study on PN21 but not on PN1. It is not clear whether the developmental effects occurred *in utero* or from exposure after birth.

In a 13-week dietary study (Stauffer Chemical Co. 1981c cited in EU RAR 2008a and likely published by Freudenthal and Henrich 1999), a significant increase in liver weights in male rats was reported starting from the lowest dose tested of 52 mg/kg-bw/day. Although the same liver effects were not observed at higher doses in the two-generation study (TNO Quality of Life 2007), there are uncertainties in the purity of TCPP in the treatments used in each study and a range of critical effect levels based on both studies is used for the characterization of risk from exposure to TCPP.

A short-term critical NOAEL of 1015 mg/kg-bw/day was identified based on reduced weight gain at the next dose level of 1636 mg/kg-bw/day in male rats that were treated with TCPP for 14 days (Stauffer Chemical Co. 1980b cited in EU RAR 2008a).

The principal routes of exposure to TCPP for the general population are expected to be environmental media (air, water, dust and food, including breast milk) and the use of consumer products. Comparison of the estimate of total daily intake from environmental media (0.33 µg/kg-bw/day) to the range of subchronic critical effect levels of 52 to 99 mg/kg-bw/day, resulted in MOEs ranging from 160 000 to 300 000. These MOEs are considered to be adequate to account for uncertainties in the exposure and health effect databases.

The use of consumer products (foam products furniture/foam mattresses, spray foam insulation and waterproofing spray) containing TCPP may result in general population exposure via the dermal and oral routes. Exposure from dermal contact when lying on a piece of foam-containing furniture was estimated to be 210 µg/kg-bw/d for an infant and 55 µg/kg-bw/d for an adult. Comparison of these estimates with the range of subchronic LOAELs (52 to 99 mg/kg-bw/day) resulted in MOEs ranging from 250 to 470 for infants and 950 to 1800 for adults (Table 9.9). Comparison of the estimate of exposure for a toddler mouthing a foam object (e.g., a toy) with the subchronic LOAELs ranging from 52 to 99 mg/kg-bw/day resulted in MOEs from 22 000 to 41 000 (Table 9.9).

Margins of exposure based on the use of consumer products containing TCPP, specifically from foam-containing furniture, are considered to be potentially inadequate to account for uncertainties in the exposure and health effect databases, including the absence of a cancer study.

Table 9.9. Margins of exposure from foam articles containing TCPP

Scenario	**Exposure concentration (µg/kg-bw/day)**	**MOEs**
Infant dermal contact from lying on foam mattresses	210*	250–470 (based on subchronic critical LOAELs of 52–99 mg/kg-bw/day)
Adult dermal contact from lying on foam mattresses	55*	950–1800 (based on subchronic critical LOAELs of 52–99 mg/kg-bw/day)

Mouthing foam object (e.g., toy)	2.4 (toddler)	22 000–41 000 (based on subchronic critical LOAELs of 52–99 mg/kg-bw/day)

* assumption that 40% of TCPP is absorbed. based on doses considered most representative of exposure from dermal contact with foam (TNO Quality of Life 2005).

The use of spray insulation and waterproofing tent spray may result in oral and dermal exposure for an infrequent short-term duration. Margins of exposure were estimated based on upper-bounding oral and dermal estimates of exposure compared to the short-term critical NOAEL of 1015 mg/kg/day (Table 9.10). These MOEs are considered to be adequate to account for uncertainties in the exposure and health effect databases.

Table 9.10. Margins of exposure from use of spray foam and waterproofing products containing TCPP

Scenario	**Exposure concentration (µg/kg-bw/event)**	**MOEs**
Applying spray foam insulation (small project)	2.7* (dermal)	3.7×10^5 (based on a short-term oral NOAEL of 1015 mg/kg-bw/day)
Applying spray foam insulation (small project)	0.88 (inhalation)	1.2×10^6 (based on a short-term critical NOAEL of 1015 mg/kg-bw/day)
Applying spray foam insulation (large project)	630* (dermal)	1610 (based on a short-term oral NOAEL of 1015 mg/kg-bw/day)
Applying spray foam insulation (large project)	2.3 to 14.0 (inhalation)	7.25×10^4 to 4.4×10^5 (based on a short-term critical NOAEL of 1015 mg/kg-bw/day)

Applying waterproofing tent spray	1.8 * (dermal)	5.6×10^5 (based on a short-term oral NOAEL of 1015 mg/kg-bw/day)

*assumption that 40% TCPP absorbed based on doses considered most representative of exposure from dermal contact with foam (TNO Quality Life 2005).

9.3.3 Uncertainties in Evaluation of Risk to Human Health

Overall there is a moderate to high confidence in the estimated intake from environmental media. Canadian monitoring data for TDCPP and TCPP is available for surface water, ambient air and house dust. There is uncertainty in estimating exposure from indoor air, food and breast milk concentrations as the data used was from the United States or Europe. Although there is uncertainty on the basis of different environmental conditions in Europe or the US compared to Canada, the estimates of exposure from environmental media and food were based on conservative assumptions.

There were uncertainties in the parameters (e.g., dermal absorption, migration rate) used in modelling the estimate of exposure to TDCPP and TCPP from use of consumer products. For example, use of a passive migration rate may underestimate oral exposure from mouthing or sucking a foam object, an activity which is expected to be associated with a more active migration of the substance. However, this was the only data available and these estimates were based on conservative assumptions. While a conservative scenario was assessed for exposure to foam products based on a migration study of covered foam, direct exposure to uncovered foam cannot be precluded and is an uncertainty. There is moderate confidence in estimating exposure to TCPP from other DIY products based on the conservative assumptions used in the model, given the infrequent use and fact of not accounting for personal protective equipment.

The health effect database of TDCPP consists of a number of experimental animal studies for acute, repeated-dose, carcinogenicity, genotoxicity, reproductive and developmental toxicity studies. Repeated-dose toxicity studies were limited to the oral route and no female animal reproductive studies were identified. Biomonitoring studies and limited human epidemiological data were also identified.

The health effect database of TCPP consists of mostly experimental animal studies. Data were identified for acute, repeated-dose, reproductive and developmental toxicity studies. Repeated-dose toxicity studies were limited to the oral route. No chronic or carcinogenicity studies were available. US NTP is currently conducting two-year carcinogenicity studies in both rats and mice. Limited biomonitoring studies were

identified where TCPP has been detected in urine and human milk samples. No volunteer or epidemiological studies were identified.

There is uncertainty on the potential contribution of individual chain isomers to the overall toxicity of TCPP as well as levels of these isomers outside of this mixture, however given that they are not commercially available nor are they typically isolated in pure form, further characterization of risk was not considered in this assessment.

This draft screening assessment does not include a full analysis of the mode of action for tumours associated with exposure to TDCPP. The BMD calculations for TDCPP used only the incidences of adenoma for analysis, as the information on the incidences of combined adenoma and carcinoma was not available from the original study. For the two -year carcinogenicity study in rat for TDCPP (Stauffer Chemical Co. 1981a), there was a greater than 20% decrease in body weights observed in the high-dose animals compared to controls by the end of the study. There is uncertainty whether the high-dose level may have had an impact on the dose response curve for the derivation of the BMD and BMDL. Uncertainties also exist for the two TDCPP metabolites (3-MCPD, 1,3-DCP) that were classified as IARC 2B carcinogens and whether they contribute to the carcinogenic effect of TDCPP.

There is no chronic study available yet for TCPP. The selection of TCEP and TDCPP as read-across analogues for assessing the carcinogenic potential of TCPP is associated with uncertainty as there are similarities but also differences between these chemicals. Overall, based on a qualitative read-across from analogues as well as QSAR and structural alerts analyses, the information suggests that TCPP may be carcinogenic in rodents.

There is uncertainty for extrapolation of health effects from oral toxicity studies in animals to dermal route of exposure. Adjustment for dermal absorption percentage was applied for the exposure estimates but no other dermal toxicology studies were available to characterize possible differences in dermal metabolism or possible local effects.

10. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from TCPP and TDCPP. It is proposed to conclude that TCPP and TDCPP do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA 1999 as they are not entering the environment in a quantity or concentration or under conditions that have or may have an

immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Based on the available information on its potential to cause harm to human health, it is proposed to concluded that TDCPP does not meet the criteria under paragraph 64(*c*) as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. It is proposed to conclude that TCPP meets the criteria under paragraph 64(*c*) as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is proposed to conclude that TCPP meets one or more criteria as set out in section 64 of CEPA 1999. In addition, it is proposed that TCPP meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999.

It is proposed to conclude that TDCPP does not meet any of the criteria set out in section 64 of CEPA 1999.

Although present estimated levels of exposure of TDCPP are not indicative of harm to the environment or to human health, there may be concerns if import and use quantities were to increase in Canada.

11. References

ABC Laboratories. 1993. Aerobic aquatic biodegradation of Antiblaze 80 using a shake flask test system. Final Report #40822. Analytical Bio-Chemistry Laboratories, Inc.

[ACC] American Chemistry Council. 2012. Spray polyurethane foam ventilation research project – phase 2, American Chemistry Council's Center for the Polyurethanes Industry, Report dated December 19, 2012. Report submitted to Environment Canada on October 31, 2014.

ACD/pKaDB [Prediction Module]. c1997–2012. Version 9.04. Toronto (ON): Advanced Chemistry Development. [cited 2012]. Available from: http://www.acdlabs.com/products/phys_chem_lab/pka/. [restricted access]

Ahrens VD, Maylin GA, Henion JD. 1979. Fabric release, fish toxicity, and water stability of the flame retardant Fyrol FR-2. Bull Environ Contam Toxicol 21:409–412.

Akzo Nobel. 2001a. Final research report. Hydrolysis as a function of pH of TCPP.CGS-ENV F01047 T 01007 H.

Akzo Nobel. 2001b. Test plan for FYROL FR-2 (Tris[1,3-dichloro-20propyl] Phosphate). CAS No. 13674-87-8. High Production Volume Challenge Plan. Akzo Nobel Functional Chemicals LLC, 5 Livingstone Avenue, Dobbs Ferry, NY 10522.

Akzo Nobel. 2001c. Final research report. Evaluation of the removal of TCPP in an aqueous medium – semi-continuous activated sludge method. CGS-ENV F01049 T01007 SC.

Akzo Nobel. 2002. Biodegradability of FYROL PCF in the prolonged closed bottle test. Akzo Nobel Report F02101. [cited in EU RAR 2008a].

Ali N, Dirtu A, Van den Eede N, Goosey E, Harrad S, Neels H, Mannetje A, Coakley J, Douwes J, Covaci A. 2012. Occurrence of alternative flame retardants in indoor dust from New Zealand: Indoor sources and human exposure assessment. Chemosphere 88: 1276–1282

Ali N, Ali L, Medhi T, Dirtu A, Al-Shammari F, Neels H, Covaci A. 2013. Levels and profiles of organochlorines and flame retardants in car and house dust from Kuwait and Pakistan: Implication for human exposure via dust ingestion. Environment International 55:62–70

Alibaba. 2013. Product information sheet. TDCPP. CAS RN 13674-87-8. Available from: http://flame-retardant.en.alibaba.com.

Allen JG, Stapleton HM, Vallarino J, McNeely E, McClean MD, Harrad SJ, Rauert CB, Spengler JD. 2013. Exposure to flame retardant chemicals on commercial airplanes. Environ Health 12:17.

Andresen JA, Muir D, Ueno D, Darling C, Theobald N, Bester K. 2007. Emerging pollutants in the North Sea in comparison to Lake Ontario, Canada, data. Environmental Toxicology and Chemistry 26(6): 1081–1089.

Anon. 1980. An Ames Salmonella/mammalian microsome mutagenesis assay for determination of potential mutagenecity of tris (2-chloropropyl) phosphate (Report No. 471-80). [cited in IPCS 1998].

[AOPWIN] Atmospheric Oxidation Program for Windows [Estimation Model]. 2010. Version 1.92. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Arcadis EBRC. 2011. Identification and evaluation of data on flame retardants in consumer products. Contract for European Commission. Available from: http://ec.europa.eu/consumers/archive/safety/news/flame_retardant_substances_study_en.pdf

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci. 22(3):337–345.

Arnot JA, Mackay D, Parkerton TF, Bonnell M. 2008a. A database of fish biotransformation rates for organic chemicals. Environmental Toxicology and Chemistry 27(11): 2263–2270.

Arnot JA, Mackay D, Bonnell M. 2008b. Estimating metabolic biotransformation rates in fish from laboratory data. Environmental Toxicology and Chemistry 27: 341–351.

ASTreat Model [sewage treatment plant removal model]. 2006. Version 1.0. Cincinnati (US): Procter & Gamble Company. [cited 2014 March]. Available from Procter & Gamble Company, P.O. Box 538707, Cincinnati, OH 45253-8707, US.

[ATSDR] Agency for Toxic Substances and Disease Registry. 2012. Toxicological profile for Phosphate Ester Flame Retardants. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Available at http://www.atsdr.cdc.gov/ToxProfiles/tp202.pdf

Bayer.1991a. Biodegradation test on TCPP. Bayer AG. [cited in ECHA 2013, EU RAR 2008a and UNEP 1999].

Bayer. 1991b. Tris-chlorisopropyl phosphate: Mutagenicity test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro (Unpublished report). Bayer AG. [cited in EU RAR 2008a].

Bayer. 1991c. Tris-chloroisopropyl phosphate: Micronucleus test on the mouse (Unpublished report). Bayer AG. [cited in EU RAR 2008a].

Bayer. 1991d. 28-d study-full details needed. Bayer AG. [cited in EU RAR 2008a].

Bayer Healthcare. 2005. TCPP, Tris(2-chloro-1-methylethyl) phosphate Unscheduled DNA Synthesis test with rat liver cells in vivo (Unpublished report). Bayer AG. [cited in EU RAR 2008a].

[BCFBAF] Bioaccumulation Program for Windows [Estimation Model]. 2010. Version 3.01. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Bendz D, Paxeus N, Ginn TR, Loge FJ. 2005. Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Hoje River in Sweden. Journal Hazardous Materials 122: 195–204.

Bergh C, Torgrip R, Emenius G, Ostman C. 2011. Organophosphate and phthalate esters in air and settled dust – a multi-location indoor study. Indoor Air 21:67–76.

Beyer A, Mackay D, Matthies M, Wania F, Webster E. 2000. Assessing long-range transport potential of persistent organic pollutants. Environmental Science and Technology 34(4): 699–703.

[BIOWIN] Biodegradation Probability Program for Windows [Estimation Model]. 2010. Version 4.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Bloom SE. 1982. Detection of sister chromatid exchanges in vivo using avian embryos. Cytogenetic Assays of Environmental Mutagens 137–159. [cited in EU RAR 2008b].

Bloom SE. 1984. Sister chromatid exchange studies in the chick embryo and neonate: actions of mutagens in a developing system. Basic Life Sciences 29:509–533. [cited in EU RAR 2008b].

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. Chemosphere 30(4):741−752.

Bollmann U, Moller A, Xie Z, Ebinghaus R, Einax J. 2012. Occurrence and fate of organophosphorus flame retardants and plasticizers in coastal and marine surface waters. Water Research 46:531–538.

Bradman A, Gaspar F, Castorina R, Tong-Lin E, McKone T. 2012. Environmental exposures in early childhood education environments. For California Air Resources Board.

Brandsma S, de Boer J, van Velzen M, Leonards P. 2014. Organophosphorus flame retardants and plasticizers in house and car dust and the influence of electronic equipment. Chemosphere 116:3–9.

Brommer S, Harrad S, Van den Eede N, Covaci A. 2012. Concentrations of organophosphate esters and brominated flame retardants in German indoor dust samples. Journal of Environmental Monitoring 14: 2482.

Brusick D, Matheson D, Jagannath DR, Goode S, Lebowitz H, Reed M, Roy G, Benson S. 1980. A comparison of the genotoxic properties of tris(2,3-dibromopropyl)phosphate and tris(1,3-dichloro-2-propyl)phosphate in a battery of short-term bioassays. Journal of Environmental Pathology and Toxicology 3:207–226.

Butt C, Congleton J, Hoffman K, Fang M, Stapleton H. 2014. Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate (EH-TBB) in urine from paired mothers and toddlers. Environ Sci Technol 48:10432-10438.

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C., 1999, c. 33, Canada Gazette. Part III, vol. 22, no. 3. Available from: http://www.gazette.gc.ca/archives/p3/1999/g3-02203.pdf.

Canada. 2000. *Canadian Environmental Protection Act, 1999: Persistence and Bioaccumulation Regulations,* P.C. 2000-348, 23 March, 2000, SOR/2000-107, Canada Gazette, Part II, vol. 134, no. 7, p. 607−612. Available from: http://www.gazette.gc.ca/archives/p2/2000/2000-03-29/pdf/g2-13407.pdf.

Canada. 2013. CEPA 1999 section 71 Notice with respect to certain organic flame retardant substances. Canada Gazette, Part I: Vol. 147, No. 13. March 30, 2013.

Campone L, Piccinelli A, Ostman C, Rastrelli L. 2010. Determination of organophosphorus flame retardants in fish tissues by matrix solid-phase dispersion and gas chromatography. Anal Bioanal Chem 397:799–806.

Carignan C, McClean M, Cooper E, Watkins D, Fraser A, Heiger-Bernays W, Stapleton H, Webster T. 2013. Predictors of tris(1,3-dichloro-2-propyl) phosphate metabolite in the urine of office workers. Environmental International 55:56–61.

[CEH] Center for Environmental Health. 2013a. Playing on poisons: harmful flame retardants in children's furniture. Available from:http://www.ceh.org/wp-content/uploads/2013/11/Kids-Furniture-Report-Press.pdf.

[CEH] Center for Environmental Health. 2013b. Naptime nightmares: toxic flame retardants in child care nap mats. Available from: http://www.ceh.org/campaigns/flame-retardants/

Chen D, Letcher RJ, Chu S. 2012. Determination of non-halogenated, chlorinated and brominated organophosphate flame retardants in herring gull eggs based on liquid chromatography–tandem quadrupole mass spectrometry. Journal of Chromatography A 1220:169–174.

[CHRIP] Chemical Risk Information Platform [database on the Internet]. c2008. Tokyo (JP): National Institute of Technology and Evaluation, Chemical Management Centre (CMC). [cited 2013 March]. Available from: http://www.safe.nite.go.jp/english/db.html.

CIT. 2001. Skin sensitisation test in guinea pigs. Unpublished report [as cited in EU RAR 2008b].

CITI. 1992. Biodegradation and bioaccumulation data on existing chemicals based on the CSCL Japan. Compiled under the supervision of Chemical Products Division, Basic Industries Bureau MITI, Edited by

CITI October 1992. Published by Japan Chemical Industry Ecology Toxicology and Information Centre. Report Number: 2-1914. [cited in ECHA 2013, EU RAR 2008b, and HSDB 1983–].

[RIVM] ConsExpo Consumer Exposure Model [Internet]. 2012. Version 4.1. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment). Available from: www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840.

Cooper E, Covaci A, van Nuijs A, Webster T, Stapleton H. 2011. Analysis of the flame retardant metabolites bis(1,3-dichloro-2-propyl) phosphate (BDCPP) and diphenyl phosphate (DPP) in urine using liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 401: 2123–2132.

Covance Laboratories Inc. 2004. Chromosomal aberrations in chinese hamster ovary (CHO) cells. Unpublished report. [cited in EU RAR 2008b].

Covance Laboratories Inc. 2005a. In vivo/in vitro Unscheduled DNA Synthesis in rat primary hepatocyte cultures at two timepoints with a dose range finding assay. Unpublished report [cited in EU RAR 2008b].

Covance Laboratories Inc. 2005b. Tris (2-chloro-1-methylethyl) phosphate: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the MitrotitreÒ Fluctuation Technique (Unpublished report). [cited in EU RAR 2008a].

Covance Laboratories Inc. 2006. Detection of DNA damage in the liver of treated rats using the Comet assay (Unpublished report). [cited in EU RAR 2008a].

[CPOPs] Canadian Persistent Organic Pollutants Profiler Model. 2012. Version 1.1.18. Gatineau (QC): Environment Canada, Existing Substances Division; Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. [Model developed based on Mekenyan et al. 2005].

Crump D, Chiu S, Kennedy SW. 2012. Effect of TCPP and TDCPP on cytotoxicity and mRNA expression in primary cultures of avian hepatocytes and neuronal cells. Toxicological Sciences 126(1):140–148.

Davison JM, Noble MCB. 1981. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. British Journal of Obstetrics and Gynaecology 88:10–17.

Danish EPA [Environmental Protection Agency]. 2014. Survey, health and environmental assessment of flame retardants in textiles. Survey of chemical substances in consumer products No. 126. Miljøstyrelsen. Available from: http://mst.dk/service/publikationer/publikationsarkiv/2014/apr/survey,-health-and-environmental-assessment-of-flame-retardants-in-textiles/.

Diamond M, Goosey E, Saini A, Chaudhuri S. 2013. Assessment of the prevalence and exposure to the new flame retardants (NFRs) in Canadian indoor environments. Contract prepared for Health Canada. Diamond Environmental Research Group, University of Toronto.

Dirtu A, Ali N, Van den Eede N, Neels H, Covaci A. 2012. Country specific comparison for profile of chlorinated, brominated and phosphate organic contaminants in indoor dust. Case study for Eastern Romania, 2010. Environment International 49:1–8.

Dishaw LV, Hunter DL, Padnos B, Padilla S, Stapleton HM. 2014. Developmental exposure to organophosphate flame retardants elicits overt toxicity and alters behavior in early life stage zebrafish (*Danio rerio*). Toxicology Science 142(2): 445-454.

[DPD] Drug Product Database [database on the Internet]. 2013. Health Canada. [cited 2014 04 24]. Available from http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp.

Dodson RE, Perovich LJ, Covaci A, Van den Eede N, Ionas AC, Dirtu AC, Brody JG, Rudel RA. 2012. After the PBDE Phase-Out: A Broad Suite of Flame Retardants in Repeat House Dust Samples from California. Environ Sci Technol 46(24):13056–13066.

[ECHA] European Chemicals Agency. 2010. Guidance on information requirements and chemical safety assessment. Chapter R.16: Environmental exposure estimation. May 2010. Guidance for the implementation of REACH. Helsinki (FI): European Chemicals Agency.

[ECHA] European Chemicals Agency. 2013. Online database of registered substances. Available from: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances. Accessed 2013 October.

Eggen T, Heimstad ES, Stuanes AO, Norli HR. 2013. Uptake and translocation of organophosphates and other emerging contaminants in food and forage crops. Environmental Science Pollution Res. 20:4520–4531.

Eldefrawi AT, Mansour NA, Brattsten LB. 1977. Further toxicological studies with commercial and candidate flame retardant chemicals. Part II. Bulletin Environmental Contamination. Toxicol 17:720–726.

[Empack] Empack Spraytech Inc. 2014. Safe n Dry fire retardant and water repellent. Available from: www.empack.ca.

Environmental Affairs and Toxicology Department. 1981. A murine lymphoma mutagenesis assay, heterozygous at the thymidine kinase locus for the determination of the potential mutagenicity of Antiblaze 80 (Unpublished report). [cited in EU RAR 2008a].

Environment Canada, Health Canada. 2009. Screening assessment for the Challenge: ethanol, 2-chloro, phosphate (3:1) (tris(2-chloroethyl)phosphate [TCEP]): Chemical Abstract Service Registry Number 115-96-8 [Internet]. Ottawa (ON): Environment Canada, Health Canada. [cited 2014 Jun 18]. Available from: http://www.ec.gc.ca/ese-ees/default.asp?lang=En&xml=C378778A-D834-54E0-7F69-E6E2944A74FC

Environment Canada. 2007. Guidance for conducting ecological assessments under CEPA, 1999. Science Resource Technical Series, Technical Guidance Module: QSARs. Reviewed Draft Working Document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2013-2014. Data collected pursuant to section 71 (CEPA 1999) and in accordance with the published notice "*Notice with respect to certain organic flame retardant substances"* Canada Gazette, Vol. 147 no. 13". Data prepared by: Environment Canada, Health Canada, Existing Substances Program.

Environment Canada. 2013. Wise water use. Available from: https://www.ec.gc.ca/eau-water/default.asp?lang=En&n=F25C70EC-1.

Environment Canada and Health Canada. 2007. Chemical substances: Categorization [Internet]. Ottawa (ON): Government of Canada. [updated May 25, 2013; cited July 31, 2013]. Available from: http://www.chemicalsubstanceschimiques.gc.ca/about-apropos/categor/index-eng.phphttp://gazette.gc.ca/rp-pr/p1/2013/2013-03-30/html/notice-avis-eng.html#d119

Environment Canada, Health Canada. 2014. Supporting Document of the Screening Assessment on TCPP and TDCPP. Available upon request.

[EPI Suite] Estimation Programs Interface Suite for Microsoft Windows [Estimation Model]. 2000–2012. Version 4.1. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. [cited 2014 January]. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

[EQC] Equilibrium Criterion Model. 2011. Version 1.0 (Beta). Peterborough (ON): Trent University, Canadian Environmental Modelling Centre. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/NewEQCv100.html.

Eulaers I, Jaspers VLB, Halley DJ, Lepoint G, Nygard T, Pinxten R, Covaci A, Eens M. 2014. Brominated and phosphorus blame retardants in White-tailed Eagle *Haliaeetus albicilla* nestlings: Bioaccumulation and associations with dietary proxies. Science of the Total Environment 478:48–57.

EU RAR. 2008a. European Union Risk Assessment Report.Tris(2-chloro-1-methylethyl)phosphate (TCPP). Luxembourg: Office for Official Publications of the European Communities. [Internet]. [cited 2014 Jun 18]. Available at http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/tcppreport425.pdf

EU RAR. 2008b. European Union Risk Assessment Report.Tris[2-chloro-1-(chloromethyl)ethyl]phosphate (TDCP).Luxembourg: Office for Official Publications of the European Communities. Available at http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/tdcpreport426.pdf

EU RAR. 2009. European Union Risk Assessment report. TRIS (2-CHLOROETHYL) PHOSPHATE (TCEP). Luzembourg: Office for Official Publications of the European Communities. [Internet]. [cited 2016 Jan 12]. Available at http://echa.europa.eu/documents/10162/2663989d-1795-44a1-8f50-153a81133258

European Commission. 2003, Technical Guidance Document on Risk Assessment. Part II. European Chemicals Bureau.

European Commission. 2013. Details on Substances Classified in Annex VI to Regulation (EC) No 1272/2008.EC Number:237-159-2. [Internet]. [cited 2013 Nov 13]. http://esis.jrc.ec.europa.eu/clp-ghs/index.php?INDEXNO=615-005-00-9.

Evenset A, Leknes H, Christensen G, Waner N, Remberger M, Gabrielsen G. 2009. Screening of new contaminants in samples from the Norwegian arctic. Contract with Norwegian Pollution Control Authority.

Farhat A, Crump D, Chiu, S, Williams KL, Letcher RJ, Gauthier LT, Kennedy SW. 2013. *In ovo* effects of two organophosphate flame retardants – TCPP and TDCPP – on pipping success, development, mRNA expression, and thyroid hormone levels in chicken embryos. Toxicological Sciences 134(1):92–102.

Farhat A, Crump D, Porter E, Chiu S, Letcher RJ, Su G, Kennedy SW. 2014. Time-dependent effects of the flame retardant tris(1,3-dichloro-2-propyl) phosphate (TDCPP) on mRNA expression, *in vitro* and *in ovo,* reveal optimal sampling times for rapidly metabolized compounds. Environmental Toxicology and Chemistry 33(12):2842-2849.

Fernie KJ, Palace V, Peters LE, Basu N, Letcher RJ, Karouna-Renier NK, Schultz SL, Lazarus RS, Rattner BA. 2015. Investigating Endocrine and Physiological Parameters of Captive American Kestrels Exposed by Diet to Selected Organophosphate Flame Retardants. Environmental Science and Technology 49(12): 7448-7455.

Follmann W and Wober J. 2006. Investigation of cytotoxic, genotoxic, mutagenic, and estrogenic effects of the flame retardants tris-(2-chloroethyl) -phosphate (TCEP) and tris-(2- chloropropyl) -phosphate (TCPP) in vitro. Toxicology Letters 161(2):124–134.

Francis WJA. 1960. Disturbances of bladder function in relation to pregnancy. The Journal of Obstetrics and Gynaecology of the British Empire. LXVII(3):353–366.

Freudenthal RI and Henrich RT. 1999.A subchronic toxicity study of Fyrol PCF in Sprague-Dawley rats. International Journal of Toxicology 18:173–176.

Freudenthal RL and Henrich RT. 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.

Fries E, Mihajlovic I. 2011. Pollution of soils with organophosphorus flame retardants and plasticizers. J Environ Monit. 13: 2692.

Gobas F. 2007. Development and review of a generic water–sediment modelling framework for organic chemicals. Report prepared for Environment Canada. Burnaby (BC): Simon Fraser University, Faculty of Environment. March 26, 2007.

Gobas F. 2010. Comments on approach to sediment exposure approach. Report prepared for Environment Canada. Burnaby (BC): Simon Fraser University, Faculty of Environment. March 25, 2010.

Greaves AK and Letcher RJ. 2014. Comparative body compartment composition and *in ovo* transfer of OPFRs in North American Great Lakes Herring Gulls. Environmental Science and Technology. 48:7942–7950.

Green N, Schlaback M, Bakke T, Brevik E, Dye C, Herzke D, Huber S, Plosz B, Remberger M, Schoyen M, Uggerud H, Vogelsang C. 2008. Screening of selected metals and new organic contaminants 2007. Norwegian Pollution Control Authority. SPFO-report: 1014/2008.

Guerra P, Alaee M, Eljarrat E, Barcelo D. 2011. Introduction to Brominated Flame Retardants: Commercial Products, Applications, and Physicochemical Properties. In Eljarrat E, Barceló D. editors. 2011. Brominated Flame Retardants. Series: The Handbook of Environmental Chemistry. Volume 16. Heidelberg Berlin:Springer. 290 pp.

Hartmann P, Burgi D, Giger W. 2004. Organophosphate flame retardants and plasticizers in indoor air. Chemosphere 57:781–787

Hattori Y, Ishitani H, Kuge Y, Nakamoto M. 1981. Environmental fate of organic phosphate esters. Suishitsu Odaku Kenkyu, 4(3):137–141. [cited in WHO 1998].

Health Canada. 1995. Investigating human exposure to contaminants in the environment: A handbook for exposure calculations. Ottawa (ON): Great Lakes Health Effects Program, Health Protection Branch, Health Canada.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

Health Canada. 2013. List of Permitted Food Additives. Health Canada Food Directorate. [cited 2014 04 24]. Available from: http://www.hc-sc.gc.ca/fn-an/securit/addit/list/index-eng.php

Health Canada. 2014. CMP Survey 2014-2015: Determination of flame retardants in consumer products. Unpublished. Health Canada. Ottawa, Ontario.

Health Canada. 2015. Supporting documentation: Carcinogenic potential information for 2-propanol, 1-chloro-, phosphate (3:1). Ottawa (ON): Health Canada. Available upon request from: substances@ec.gc.ca.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [Estimation Model]. 2011. Version 3.20. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. [cited 2014 January]. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. 1994.Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol. 171:984–989.

Hoffman K. Daniels J. Stapleton HM. 2014. Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. Environment International 63:169–172.

[HSDB] Hazardous Substances Data Bank [database on the Internet]. 1983–. Bethesda (MD): National Library of Medicine (US). Revised 2006 Apr 14; [cited 2013 December]. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Hughes MF, Edwards BC, Mitchell CT, Bhooshan B. 2001. In vitro dermal absorption of flame retardant chemicals. Food and Chemical Toxicology 39:1263–1270.

[IARC] International Agency for Research on Cancer. 2012a. IARC monographs on the evaluation of the carcinogenic risks to humans: Some chemicals present in industrial and consumer products, food and drinking-water. 3-monochloro-1,2-propanediol. IARC monograph 101:349–374. Available at http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-010.pdf [Accessed 19 Feb 2014].

[IARC] International Agency for Research on Cancer. 2012b. IARC monographs on the evaluation of the carcinogenic risks to humans: Some chemicals present in industrial and consumer products, food and drinking-water. 1,3-dichloro-2-propanol. IARC monograph 101:375–390. Available athttp://monographs.iarc.fr/ENG/Monographs/vol101/mono101-011.pdf [Accessed 19 Feb 2014].

[ICRP].International Commission on Radiological Protection. 2003. Basic anatomical and physiological data for use in radiological protection: Reference values. ICRP Publication 89. Ann. ICRP 32(3-4).

Inveresk Research International. 1985. TDCP LV: Mouse lymphoma mutation assay, (Unpublished report). [cited in EU RAR 2008b].

Ionas A, Dirtu A, Anthonissen T, Neels H, Covaci A. 2014. Downside of the recycling process: harmful organic chemicals in children's toys. Environment International 65:54–62.

[IPCS] The International Programme on Chemical Safety. 1998. Environmental Health Criteria 209: Flame retardants: tris(chloropropyl)phosphate and tris(2-chloroethyl)phosphate. World Health Organization, Geneva. [Internet]. [cited 2014 Jun 18]. Available at http://www.who.int/entity/ipcs/publications/ehc/who_ehc_209.pdf.

Ishidate M. 1983. Application of chromosomal aberration tests in vitro to the primary screening for chemicals with carcinogenic and/or genetic hazards. From: Short-term tests for Carcinogenesis: Montpellier, 1981, 58–79. [cited in EU RAR 2008b].

Jantunen LM, Gawor A, Wong F, Bidleman T, Wania F, Stern G, Hung H. 2013a. Flame retardants, plasticizers and pesticides in the Canadian Arctic. A poster at *Northern Contaminants Program 2013.*

Jantunen L, Struger J, Backus S, Kraft J, Brommer S. 2013b. Organophosphate flame retardants in Southern Ontario tributaries and precipitation. A poster at the Sixth International Symposium of Flame Retardants (BFR 2013).

Jantunen L. 2014. TDCPP and TCPP concentrations in water from the Great Lakes area. Unpublished report. Personal communication to Health Canada: Ottawa, ON

Juberg D, Alfano K, Coughlin R, Thompson K. 2001. An observational study of object mouthing behavior by young children. Pediatrics. 107: 135.

Kajiwara N, Noma Y, Takigami H. 2011. Brominated and organophosphate flame retardants in selected consumer products on the Japanese market in 2008. J Hazardous Materials 192:1250–1259.

Kamata E, Naito K, Nakaji Y, Ogawa Y, Suzuki S, Kaneko T, Takada K, Kurokawa Y, Tobe M. 1989. Acute and subacute toxicity studies of tris (1,3-dichloro-2-propyl) phosphate on mice. Eisei Shikenjo Hokoku 107:36–43 [abstract in English] [article in Japanese] [cited in IPCS 1998 and NRC 2000].

Keller AS, Raju NP, Webster TF, Stapleton HM. 2014. Flame retardant applications in camping tents and potential exposure. Environ Sci Technol Letters 1(2):152–155.

Kemmlein S, Hahn O, Jann O. 2003. Emissions of organophosphate and brominated flame retardants from selected consumer products and building materials. Atmospheric Environment 37:5485–5493.

Klasmeier, J, Matthies M, MacLeod M, Fenner K, Scheringer M, Stroebe M, Le Gall AC, McKone T, van de Meent D, and Wania F. 2006. Application of Multimedia Models for Screening Assessment of Long-Range Transport Potential and Overall Persistence. Environmental Science and Technology 40(1):53–60.

Klempner DR, Sendijarevic V, editors. 2004. Handbook of polymeric foams and foam technology. Portland (OR): Book News, Inc.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [Estimation Model].[2010] Version [1.10]. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm.

Kojima H, Takeuchi S, Itoh T, Iida M, Kobayashi S, Yoshida T. 2013. In vitro endocrine disruption potential of organophosphate flame retardants via human nuclear receptors. Toxicology. 314:76–83.

Lentner C, editor. 1981. Geigy scientific tables volume 1: Units of measurement, body fluids, composition of the body, nutrition. 8th ed. Basel (CH): Ciba-Geigy Ltd.

Leonards P, Steindal EH, van der Veen, I, Berg V, Bustnes JO, van Leeuwen S. 2011. Screening of organophosphorus flame retardants 2010.SPFO-Report 1091/2011.TA-2786/2011; 2011.[cited in Eulaers et al. 2014].

[LNHPD] Licensed Natural Health Product Database [database on the Internet]. 2013. Health Canada. [cited 2014 04 24]. Available from: http://webprod5.hc-sc.gc.ca/lnhpd-bdpsnh/index-eng.jsp

Life Science Research. 1990. FYROL FR-2: Assessment of its ready biodegradability. Modified sturm test. LSR Report No: 90/AKL029/0232. Life Science Research Limited, Eye, Suffolk IP23 7PX, England.

Liu X, Ji K, Chio K. 2012. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquatic Toxicology. 114-115:173–181.

Liu C, Wang Q, Liang K, Liu J, Zhou B, Zhang X, Liu H, Giesy JP, Yu H. 2013. Effects of tris(1,3-dichloro-2-propyl) phosphate and triphenyl phosphate on receptor-associated mRNA expression in zebrafish embryos/larvae. Aquatic Toxicology 128-129:147–157.

Liu Y, Liggio J, Harner T, Jantunen L, Shoeib M, Li S-M. 2014a. Heterogeneous OH initiated oxidation: A possible explanation for the persistence of organophosphate flame retardants in air. Environmental Science and Technology 48:1041–1048.

Liu Y, Huang L, Li S-M, Harner T, Liggio J. 2014b. OH initiated heterogeneous oxidation of

tris-2-butoxyethyl phosphate: implications for its fate in the atmosphere. Atmospheric Chemistry and Physics 14:19431–19468.

Lynn RK, Wong K, Dickinson RG, Gerber N, Kennish JM. 1980. Diester metabolites of the flame retardant chemicals tris(1,3-dichloro-2-propyl) phosphate and tris(2,3- dibromopropyl) phosphate in the rat: identification and quantification. Research Communications in Chemical Pathology and Pharmacology 28(2):351–360. [cited in EU RAR 2008b].

Lynn RK, Wong K, Garvie-Gould C, Kennish JM. 1981. Deposition of the flame retardant, tris(1,3-dichloro-2-propyl) phosphate, in the rat. Drug Metabolism and Disposition 9(5):434–41.

Mackay D. 2006. The OECD Persistence and Long Range Transport Potential Screening Tool, Paper prepared for distribution at an OECD workshop held in Ottawa, Canada, May 31 to June 2, 2006.

Marklund A, Andersson B, Haglund P. 2003. Screening of organophosphorus compounds and their distribution in various indoor environments. Chemosphere 53:1137–1146

Marklund A, Andersson B, Haglund P. 2005a. Traffic as a source of organophosphorus flame retardants and plasticizers in snow. Environ Sci Technol 39:3555–3562.

Marklund A, Andersson B, Haglund P. 2005b. Organophosphorus flame retardants and plasticizers in air from various indoor environments. J Environ Monit 7:814–819.

Martinez-Carballo E, Gonzalez-Barreiro C, Sitka A, Scharf S, Gans O. 2007.Dermination of selected organophosphate esters in the aquatic environment of Austria. Science of Total Environment 388: 290–299.

Matthews HB, Anderson MW. 1979. Disposition of tris-(1,3-dichloro-2-propyl) - phosphate in the rat. Toxicology and Applied Pharmacology. Abstracts Eighteenth Annual Meeting. A184. [cited in EU RAR 2008b].

McGoldrick DJ, Letcher RJ, Barresi E, Keir MJ, Small J, Clark MG, Sverko E, Backus SM. 2014.Organophosphate flame retardants and organosiloxanes in predatory freshwater fish from locations across Canada. Environ Pollut. Environmental Pollution 193:254–261.

Meeker JD and Stapleton HM. 2010. House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. Environmental Health Perspectives 118(3): 318–323.

Meeker J, Cooper E, Stapleton H, Hauser R. 2013. Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environmental Health Perspectives 121 (5):580.

Mekenyan G, Dimitrov SD, Pavlov TS, Veith GD. 2005. POPs: A QSAR system for creating PBT profiles of chemicals and their metabolites. SAR QSAR Environ Res 16(1–2):103−133.

Meyer J, Bester K. 2004.Organophosphate flame retardants and plasticizers in wastewater treatment plants. Journal of Environmental Monitoring 6:599–605.

Mihajlovic I, Miloradov MV, Fries E. 2011. Application to Twisselman extraction,SPME and GC-MS to assess input sources for organophosphate esters onto soil. Environmental Science and Technology 45:2264–2269.

Mihajlovic I, Fries E. 2012. Atmospheric deposition of chlorinated organophosphate flame retardants (OFR) onto soils. Atmospheric Environment 56:177–183.

Miller RC, Brindle E, Holman DJ, Shofer J, Klein NA, Soules MR, O'Connor KA. 2004. Comparison of specific gravity and creatinine for normalizing urinary reproductive hormone concentrations. Clinical Chemistry 50(5):924–932.

Minegishi KI, Kurebayashi H, Seiichi N, Morimoto K, Takahashi T, Yamaha T. 1988. Comparative studies on absorption, distribution, and excretion of flame retardants halogenated alkyl phosphate in rats. Eisei Kagaku 34(2):102–114 [cited in ATSDR 2012 and EU RAR 2008b].

MITI. 1992. Ministry of International Trade and Industry (Japan). Biodegradation in water: screening tests. Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan, Tokyo (Japan): Japan Chemical Industry Ecology-Toxicology and Information Centre. [cited in EU RAR 2008a and ECHA 2013].

Mobil. 1985. Static 96-hour acute toxicity of Antiblaze 80 to Fathead Minnows. Report of test number: 50593. Mobil Environmental Health Science Laboratory, Pennington, New Jersey 08534. [cited in EU RAR 2008a].

Mobil Environmental and Health Safety Laboratory. 1980a. An Ames Salmonella/Mammalian Microsome Mutagenesis Assay for Determination of Potential Mutagenicity of Tris (2-chloropropyl) phosphate (Unpublished report). [cited in EU RAR 2008a].

Moller A, Xie Z, Caba A, Sturm R, Ebinghaus R. 2011. Organophosphorus flame retardants and plasticizers in the atmosphere of the North Sea. Environmental Pollution 159:3660–3665.

Moller A, Sturm R, Xie Z, Cai M, He J, Ebinghaus R. 2012. Organophosphorus flame retardants and plasticizers in airborne particles over the Northern Pacific and Indian Ocean towards the polar regions: evidence for global occurrence. Envi Sci Tech 46(6):3127–3134.

Morales NM and Matthews HB. 1980. In vivo binding of the flame retardants tris(2,3-dibromopropyl)phosphate and tris(1,3-dichloro-2-propyl) phosphate to macromolecules of mouse liver, kidney and muscle. Bulletin of Environmental Contamination andToxicology 25(1):34–8.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B and Zeiger E. 1986.Salmonella mutagenicity tests. 2. results from the testing of 270 chemicals. Environmental Mutagen 8(suppl 7):1–119.

Nakamura A, Tateno N, Kojima S, Kaniwa M-A, Kawamura T. 1979. The mutagenicity of halogenated alkanols and their phosphoric acid esters for Salmonella typhimurium. Mutation Research.66:373–380. [cited in EU RAR 2008a,b].

[NCI] National Chemical Inventories [database on a CD-ROM]. 2013. Columbus (OH): American Chemical Society, Chemical Abstracts Service. [cited 2013 October]. Available from: http://www.cas.org/products/other-cas-products/nci-on-cd.

Neithardt AB, Dooley SL, Borensztajn J. 2002. Prediction of 24-hour protein excretion in pregnancy with a single voided urine protein-to-creatinine ratio. Am J Obstet Gynecol 186:883–886.

[NHPID] Natural Health Product Ingredients Database [database on the Internet]. 2013. Health Canada. [cited 2014 04 24]. Available from: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do?lang=eng

Nomeir AA, Kato S, Matthews HB. 1981. The metabolism and disposition of tris(1,3-dichloro-2-propyl) phosphate (Fyrol FR-2) in the rat. Toxicology and Applied Pharmacology. 57:401–413.

Norris and Smith 2002. Research into the mouthing behaviour of children up to 5 years old. London, England: Consumer and Competition Policy Directorate, Department of Trade and Industry. [cited in US EPA 2011 Exposure Factors Handbook. Available from: http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf].

[NPRI].National Pollutant Release Inventory. 1994–2009. Available from:http://ww.ec.gc.ca/pdb/npri.

[NRC] National Research Council. 2000. Toxicological Risks of Selected Flame-Retardant Chemicals. Washington, DC: The National Academies Press. (open book available at http://www.nap.edu/openbook/0309070473/html/370.html). [accessed 16 Jun 2014].

[NRC] National Research Council. 2006. Human Biomonitoring for Environmental Chemicals.

Washington, DC: The National Academies Press. (open book available at http://www.nap.edu/catalog/11700/human-biomonitoring-for-environmental-chemicals) [accessed 5 Dec 2014].

[NTP].National Toxicology Program.1998. NTP technical report on the toxicology and carcinogenesis studies of 1-chloro-2-propanol (technical grade) (CAS No. 127-00-4) in F344/N rats and B6C3F1 mice (drinking water studies).NTP TR 477.NIH publication No. 98-3967. NC (Research Triangle Park): US Department of Health and Human Services, Public Health Service, National Institutes of Health. [cited 2014 April 4]. Available from: http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr477.pdf

[NTP].National Toxicology Program. 2009. Link to data search for CAS RN 13674-84-5. Genetic toxicity studies. [cited 2014 Jan 6]. Available from http://tools.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.showStudiesForChemical&cas_no=13674-84-5

[NTP] National Toxicology Program. 2014. Link to data search for CAS RN 13674-84-5. 2 year and 90 days oral study (test on-going). [cited 2014 Dec 2]. Available from http://tools.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.showStudiesForChemical&cas_no=13674-84-5

[Nuco] Nuco Inc. 2011. UltraSeal PF-200 MSDS. Available from: http://sealants.sealantcentre.com/resources/technical-downloads

[OECD] The Organisation for Economic Co-operation and Development. 1995. Test No. 418. Delayed neurotoxicity of organophosphorus substances following acute exposure. [cited 2014 Jan 6]. Available from http://www.oecd-ilibrary.org/test-no-418-delayed-neurotoxicity-of-organophosphorus-substances-following-acute-exposure_5lmqcr2k7nf6.pdf?contentType=/ns/Book,/ns/OECDBook&itemId=/content/book/9789264070905-en&containerItemId=/content/serial/20745788&accessItemIds=&mimeType=application/pdf

[OECD] The Organisation for Economic Co-operation and Development. 2002. SIDS Initial Assessment Report for tris(1-chloro-2-propyl)phosphate; CAS RN 13674-84-5. SIDS Initial Assessment Meeting 4; May 1996. [cited 2014 Jun 18]. Available from http://webnet.oecd.org/Hpv/UI/handler.axd?id=2d21fd8a-1b05-4c2e-b698-7a45672c51af

[OECD] The Organisation for Economic Co-operation and Development. 2009. SIDS Initial Assessment Report for tris(1-chloro-2-propyl)phosphate; CAS RN 13674-84-5. SIDS Initial Assessment Meeting 28; April 2009. [cited 2014 Jun 18]. Available from http://webnet.oecd.org/Hpv/UI/handler.axd?id=2faccdae-0b90-474e-be47-aabb29217fef

Parboosingh J, Doig A. 1973. Studies of nocturia in normal pregnancy.Journal of Obstetrics and Gynaecology of the British Commonwealth 80:888–895.

Parmar AS. 1977. Activity of trichloropropylene phosphate in the Salmonella/microsomal assay for bacterial mutagenicity. Bethesda, Maryland, Microbiological Associates (Project No. T1108). [cited in IPCS 1998].

Perucca J, Bouby N, Valeix P, Bankir L. 2007. Sex difference in urine concentration across differing ages, sodium intake, and level of kidney disease. Am J Physiol Regul Integr Comp Physiol. 292:R700-R705.

Phytosafe. 2003a. Laboratory determination of the long term toxicity of TCPP to earthworms (*Eisenia fetida*) using artificial soil substrate. PHYTOSAFE s.a.r.l., 2, rue Marx Dormoy, 64000 PAU, France.

Phytosafe. 2003b. Laboratory assessment of the side-effects of TCPP on plant growth. Report of Phytosafe Study Number: 03-69-012-ES. PHYTOSAFE s.a.r.l., 2, rue Marx Dormoy, 64000 Pau, France. [cited in ECHA 2013 and EU RAR 2008a].

Phytosafe. 2004a. Laboratory determination of the long term toxicity of TDCP to earthworms (*Eisenia foetida*) using artificial soil. Study Number: 04-99-021-ES.PHYTOSAFE s.a.r.l. Pau, France. [cited in ECHA 2013 and EU RAR 2008b].

Phytosafe. 2004b. Laboratory assessment of the side-effects of TDCP on plant growth. Study Number: 04-99-022-ES. PHYTOSAFE s.a.r.l. Pau, France. [cited in ECHA 2013 and EU RAR 2008b].

[Red Devil] Red Devil Inc. 2004. Foam & Fill minimal expanding polyurethane sealant MSDS. Available from: http://www.reddevil.com/index.php?l=page_view&p=tech_docs#.VFJMeyLF81I

Revúsová V, Zvara V, Gratzlová J. 1971. Some Laboratory Findings in Patients with Urolithiasis. Int Urol Nephrol 3(3), 251-258.

SafePharm Laboratories Ltd. 1979. Determination of the contact sensitisation potential of Tris Mono Chloropropyl Phosphate (unpublished report). [cited in EU RAR 2008a].

SafePharm Laboratories Ltd. 1984. Tolgard TDCP. LV: Ames test (Unpublished report). [cited in EU RAR 2008b].

SafePharm Laboratories Ltd. 1985a. Tolgard TDCP. LV: Ames test (Unpublished report). [cited in EU RAR 2008b].

SafePharm Laboratories Ltd. 1985b. Tolgard TDCP. LV: OECD 474 micronucleus study in the mouse. (Unpublished report). [cited in EU RAR 2008b].

SafePharm Laboratories Ltd. 1992. TMCPP: Reverse mutation assay “Ames Test” using Salmonella typhimurium and Escherichia coli (Unpublished report). [cited in EU RAR 2008a].

SafePharm Laboratories. 1993. Amgard TDCP. Acute toxicity to Rainbow Trout. Report reference JWH/AQ71/272. SafePharm Laboratories Limited, Derby, UK. [cited in ECHA 2013 and EU RAR 2008b].

SafePharm. 1996. Inherent biodegradation test. SPL project number 0741457. [cited in EU RAR 2008a].

SafePharm Laboratories. 1996a. Assessment of inherent biodegradability.SPL Project Number 071/455.

SafePharm Laboratories. 1996b. Acute toxicity to earthworms. Report of SPL Project Number: 071/458.

SafePharm Laboratories Ltd., Derby. [cited in ECHA 2013 and EU RAR 2008a].

SafePharm Laboratories. 1996c. Amgard TDCP.Acute toxicity to earthworms (*Eisenia foetida*).Report of Project Number 071/456.SafePharm Laboratories Limited, Derby, UK.

SafePharm Laboratories. 2002a. TCPP: Determination of general physic-chemical properties. SPL Project Number: 1613/007. SafePharm Laboratories Limited, P.O. Box No. 45, Derby, DE1 2BT, UK.

SafePharm Laboratories. 2002b. TCPP: Determination of general physicochemical properties, Report 1613/001, SafePharm Laboratories, PO Box 45, Derby, UK. [cited in EU RAR 2008a].

SafePharm Laboratories. 2002c. TCPP: Determination of general physicochemical properties, Report 1613/002, SafePharm Laboratories, PO Box 45, Derby, UK. [cited in EU RAR 2008a].

SafePharm Laboratories. 2002d. TDCP: Determination of general physicochemical properties, Report 1613/008, SafePharm Laboratories, PO Box 45, Derby, UK.

SafePharm Laboratories. 2002e. TDCP: Determination of vapour pressure. Report 1613/003, SafePharm Laboratories, PO Box 45, Derby, UK.

SafePharm Laboratories. 2002f. TDCP: Determination of general physicochemical properties, Report 1613/004, SafePharm Laboratories, PO Box 45, Derby, UK.

SafePharm Laboratories 2005. TCPP: local lymph node assay in the mouse (unpublished report). [cited in EU RAR 2008a].

Salamova A, Ma Y, Venier M, Hites R. 2013. High levels of organophosphate flame retardants in the Great Lakes atmosphere. Environmental Science and Technology Letters September 2013.

Salamova A, Hermanson MH, Hites RA. 2014a. Organophosphate and halogenated flame retardants in atmospheric particles from a European Arctic site. Environmental Science and Technology 48(11):6133–6140.

Salamova A, Ma Y, Venier M, Hites RA. 2014b. High levels of organophosphate flame retardants in the Great Lakes atmosphere. Envi Sci Tech Letters 1(1):8–14.

Santa Cruz. 2010. Material Safety Data Sheet. TCPP.CAS RN 13674-84-5.Santa Cruz Biotechnology, Inc., 2145 Delaware Avenue, Santa Cruz, California 95060.

Sasaki K, Suzuki T, Takeda M. 1982. Bioconcentration and excretion of phosphoric-acid triesters by killifish Oryzias-latipes. Bulletin of Environmental Contamination and Toxicology 28(6):752–759.

Sasaki K, Suzuki T, Uchiyama M. 1984. Metabolism of phosphoric acid trimesters by rat liver homegenate. Bulletin of Environmental Contamination and Toxicology 33:281–288.

Sasaki K, Takeda M, Uchiyama M. 1981. Toxicity, absorption, and elimination of phosphoric acid triesters by killifish and goldfish. Bulletin of Environmental Contamination and Toxicology 27:775–782.

Scheringer M, MacLeod M, Wegmann F. 2006. The OECD P_{OV} and LRTP Screening Tool. Version 2.0. Organisation for Economic Cooperation and Development; Zurich (CH): Swiss Federal Institute of Technology. Distributed at OECD/UNEP Workshop on Application of Multimedia Models for Identification of Persistent Organic Pollutants, Ottawa, Canada, May 31–June 2, 2006. Available from: http://www.sust-chem.ethz.ch/downloads/Tool2_0_Manual.pdf.

Shoeib M, Jantunen L. 2013. Legacy and current use of flame retardants in Great Lakes atmosphere. A poster at the Sixth International Symposium of Flame Retardants (BFR 2013).

Shoeib M, Ahrens L, Jantunen L, Harner T. 2014. Concentrations in air of organobromine, organochlorine and organophosphate flame retardants in Toronto, Canada. Atmospheric Environment 99: 140-147.

Soderlund EJ, Dybing E, Holme JA, Hongslo JK, Rivedal E, Sanner T, Nelson SD. 1985. Comparative genotoxicity and nephrotoxicity and nephrotoxicity studies of the two halogenated flame retardants tris(1,3-dichloro-2-propyl) phosphate and tris(2,3- dibromopropyl) phosphate. Acta Pharmacology and Toxicology 56:20–29. [cited in EU RAR 2008b].

[SPIN] Substances in Preparations in Nordic Countries [database on the Internet]. 2013. Copenhagen (DK): Nordic Council of Ministers. [cited 2013 October]. Available from: http://195.215.202.233/DotNetNuke/default.aspx.

Sprague GL, Sandvik LL, Brookins-Hendricks MJ. 1981. Neurotoxicity of two organophosphorus ester flame retardants in hens. J Toxicol Environ Health 8(3):507–18.

Staaf T, Otsman C. 2005.Organophosphate trimesters in indoor environments. J Environ Monit. 7:883–887

Stapleton H, Klosterhaus S, Eagle S, Fuh J, Meeker J, Blum A, Webster T. 2009. Detection of organophosphate flame retardants in furniture foam and U.S. house dust. Environ Sci Technol. 43:7490–7495

Stapleton H, Klosterhaus S, Keller A, Ferguson P, van Bergen S, Cooper E, Webster T, Blum A. 2011. Identification of flame retardants in polyurethane foam collected from baby products. Envi Sci Technol 45:5323–5331.

Stapleton H, Sharma S, Gerzinger G, Ferguson P, Gabriel M, Webster T, Blum A. 2012. Novel and high volume use flame retardants in U.S. couches reflective of the 2005 PentaBDE phase out. Envi Sci Technol 46: 13432–13439.

Stapleton H, Misenheimer J, Hoffman K, Webster T. 2014. Flame retardant associations between children's handwipes and house dust. Chemosphere. 116:54-60.

Statistics Canada. 2014. Population by year, by province and territory. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm.

Stauffer Chemical Co. 1976. Mutagenicity evaluation of Fyrol PCF (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1977. Mutagenicity evaluation of Fyrol FR-2 in the mouse lymphoma multiple endpoint test (MET). (Unpublished report). [cited in EU RAR 2008b].

Stauffer Chemical Co. 1978a. Mutagenicity evaluation of Fyrol FR-2 in the mouse bone marrow cytogenetic analysis.(Unpublished report). [cited in EU RAR 2008b].

Stauffer Chemical Co. 1978b. Teratology study in rats: FR-2 (Fyrol). (Unpublished report). [cited in EU RAR 2008b].

Stauffer Chemical Co. 1978c. Toxicology reports on Fyrol FR-2. Vol I of II: Summary of in vitro delayed neurotoxicity evaluation. Report T-6303. USEPA TSCAT document OTS0204911.

Stauffer Chemical Co. 1978d. Mutagenicity evaluation of Fyrol PCF in the Ames Salmonella/microsome plate tests (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1978e. Mutagenicity evaluation of Fyrol PCF in the mouse lymphoma forward mutation assay (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1978f. Evaluation of Fyrol PCF in the unscheduled DNA synthesis in human WI-38 cells assay (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1978g. Mutagenicity evaluation of Fyrol PCF in the in vitro transformation of BALB/3T3 cells assay (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1978h. Mutagenicity evaluation of Fyrol PCF in the rat bone marrow cytogenetic analysis (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1979. A 90-day neurotoxicity study in hens. Unpublished Report. [cited in EU RAR 2008b and ECHA 2013].

Stauffer Chemical Co. 1980a. Morphological transformation of BALB/3T3 cells (Unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1980b. Fyrol PCF: A two-week dietary acute toxicity range finding study in male and female Charles River Sprague-Dawley derived rats (Unpublished report). [cited in EURAR 2008a].

Stauffer Chemical Co. 1981a. A two-year oral toxicity/carcinogenicity study of Fyrol FR-2 in rats (volume I-IV) (final reports) with attachments, cover sheets and letter dated 093081. USEPA TSCAT document OTS0204911.

Stauffer Chemical Co. 1981b. Toxicology reports on Fyrol FR-2 (volume I - II) with attachments and cover letter dated 020381. EPA Doc No. 88-8100271. USEPA TSCAT document OTS0204911.

Stauffer Chemical Co. 1981c. Fyrol PCF 3-month dietary sub-chronic toxicity in rats (unpublished report). [cited in EU RAR 2008a].

Stauffer Chemical Co. 1983a. A mortality study of workers employed at a Fyrol FR-2 manufacturing plant. Report presented to TSCATS. EPA Doc No. 88-8400615 USEPA TSCAT document OTS0204911.

Stauffer Chemical Co. 1983b. Fyrol FR-2: Mutagenicity evaluation in Salmonella typhimurium. (Unpublished report). [cited in EU RAR2008b].

Stauffer Chemical Co. 1983c. Fyrol Fr-2 fertility study in male rabbits. Report presented to TSCATS. EPA Doc No. FYI-OTS-0183-0228 US EPA TSCAT document OTS0000228-0.

Stauffer Chemical Co. 1983d. A morbidity survey or workers employed at a Fyrol FR-2 manufacturing plant. Report presented to TSCATS. EPA Doc No. 88-8400602. US EPA TSCAT document OTS0204911.

Stauffer Chemical Co. 1984. Fyrol PCF metabolism/pharmacokinetic study in rats (Unpublished report). [cited in EU RAR 2008a].

Study Submission. 2013. Unpublished confidential studies submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division.

Su G, Greaves AK, Gauthier LT, Letcher RJ. 2014. Liquid chromatography-electrospray-tandem mass spectrometry method for determination of organophosphate diesters in biotic samples including Great Lakes herring gull plasma. Journal of Chromatography A 1374: 85-92.

Sundkvist A, Olofsoon U, Haglund P. 2010. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. J Envi Monit 12:943–951.

Tanaka S, Nakaura S, Kawashima K, Nagao S, Endo T, Onoda KI, Kasuya Y, Omori Y. 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. [cited in EU RAR 2008b].

[TaPL3] Long Range Transport and Persistence Level III model [Internet]. 2000. Version 2.10. Peterborough (ON): Trent University, Canadian Environmental Modelling Centre. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/TaPL3.html.

Tenneco Chemical Inc. 1977a. Activity of trichloropropylene phosphate in the Salmonella/microsomal assay for bacterial mutagenicity (Unpublished report). [cited in EU RAR 2008a].

Tenneco Chemicals Inc. 1977b. Activity of TCPP in a test for differential inhibition of repair deficient and repair competent strains of Escherichia coli: Repair test (Unpublished report). [cited in EU RAR 2008a].

Thorp JM, Norton PA, Lewis Wall L, Kuller JA, Eucker B, Wells E. 1999. Urinary incontinence in pregnancy and the puerperium: A prospective study. Am J Obstet Gynecol. 181:266–273.

TNO Quality of Life. 2005. *In vitro* percutaneous absorption of [14C]tris(2-chloro-1-methylethyl)phosphate (TCPP) through human skin membranes using flow-through diffusion cells (Unpublished report). [cited in EU RAR 2008a].

TNO Quality of Life. 2006a. *In vitro* percutaneous absorption of neat [1,3-14C]TDCP (Tris (1,3-chloro-2-propyl) phosphate) through human skin membranes using flow-through diffusion cells. Unpublished report [cited in EU RAR 2008b].

TNO Quality of Life. 2006b. *In vitro* percutaneous absorption of neat [14C]TCPP (Tris(2-chloro-1-methylethyl)phosphate) through human skin membranes using flow-through diffusion cells (Unpublished report). [cited in EU RAR 2008a].

TNO Quality of Life. 2007. Oral two-generation reproduction toxicity study (including a dose range finding study) with Tris(2-chloro-1-methylethyl) -phosphate in rats (Unpublished report). [cited in EU RAR 2008a].

UNEP. 1990. United Nations Environmental Program. OECD Screening Information Data Sets (SIDS).SIDS Initial Assessment Profile.CAS RN 13674-84-5.UNEP Publications.

[US California EPA] California Environmental Protection Agency. 2011. Evidence on the carcinogenicity of tris(1,3-dichloro-2-propyl)phosphate. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Branch. Available from: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf.

[US CPSC] US Consumer Product Safety Commission. 1998. Post-hearing comments of the Upholstered Furniture Action Council on the toxicity of flame retardants chemical treatments for upholstery fabrics. Washington (DC). Available from: http://www.cpsc.gov/PageFiles/80024/uphlsfn2.pdf.

[US CPSC] US Consumer Product Safety Commission. 2005a. Analysis of FR Chemicals Added to Foams, Fabrics, Batting, Loose Fill, and Barriers. Washington (DC): Directorate for Laboratory Sciences, US CPSC. (uff6) Available from: http://www.cpsc.gov/PageFiles/103738/uff6.pdf.

[US CPSC] US Consumer Product Safety Commission, 2005b. Migration of Flame Retardant Chemicals in Upholstered Furniture Foam. Washington (DC): Division of Chemistry, US CPSC. (uhff2) Available from: http://www.cpsc.gov/PageFiles/88167/uhff2.pdf.

[US CPSC] US Consumer Product Safety Commission. 2006. CPSC Staff Preliminary risk assessment of flame retardant chemicals in upholstered furniture foam. US Consumer Product Safety Commission. Available from: https://www.cpsc.gov//PageFiles/87655/ufurn2.pdf.

[US EPA] US Environmental Protection Agency. 2003. Exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds, Part I: Estimating exposure to dioxin-like compounds, Volume 3: Site-specific assessment procedures, Chapter 4: Estimating exposure media concentrations," EPA/600/P-00/001Cb, U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC, December 2003.

[US EPA] US Environmental Protection Agency. 2008. High Production Volume Information System (HPVIS): Unpublished study obtained from US EPA HPV Challenge Program. Neurotoxicity studies on CAS No. 13674-87-8. Available from: http://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?SECTION=1&epcount=2&v_rs_list=24952643, 24952627 [Accessed 17 Jun 2014].

[US EPA] United States Environmental Protection Agency. 2011. Exposure Factors Handbook 2011. National Center for Environmental Assessment. Office of Research and Development. U.S. Environmental Protection Agency, Washington, DC 20460.

[US EPA] US Environmental Protection Agency. 2012. Chemical Data Access Tool (CDAT). Available from: http://java.epa.gov/oppt_chemical_search.

[US EPA] US Environmental Protection Agency. 2014. Benchmark dose software (BMDS). Available at http://www.epa.gov/ncea/bmds/about.html [accessed 20 Feb 2014].

[US EPA} US Environmental Protection Agency. 2015. Steps to Control Exposure. Available at http://www.epa.gov/dfe/pubs/projects/spf/steps_to_control_exposure.html#diyers [accessed 22 Jan 2015].

Ulsamer AG, Osterberg RE, McLaughlin J. 1980. Flame-retardant chemicals in textiles. Clinical Toxicology 17(1):101–131.

Van den Eede N, Dirtu A, Neels H, Covaci A. 2011. Analytical developments and preliminary assessment of human exposure to organophosphate flame retardants from indoor dust. Environ Int. 37:454–461.

Van den Eede N, Dirtu A, Ali N, Neels H, Covaci A. 2012. Multi-residue method for the determination of brominated and organophosphate flame retardants in indoor dust. Talanta 89:292–300.

Van den Eede N, Maho W, Erratico C, Neels H, Covaci A. 2013. First insights in the metabolism of phosphate flame retardants and plasticizers using human liver fractions. Toxicology Letters 223(1):9–15.

Van den Eede N, Heffernan AL, Alyward LL, Hobson P, Neels H, Mueller JF, Covaci A. 2015. Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. Environment International 74:1-8.

Van der Veen I, de Boer J. 2012. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88:1119–1153.

van Ginkel CG. 2005. Attempt to demonstrate anaerobic biodegradation of TDCP. Memorandum summarising the test. Reference number CER M05044, Akzo Nobel Research and Technology Chemicals, 28th November 2005. [cited in EU RAR 2008b].

Van Haarst EP, Heldeweg EA, Newling DW, Schlatmann TJ. The 24-h frequency-volume chart in adults reporting no voiding complaints: defining reference vales and analysing variables. BJU International. 93:1257–1261.

Venier M, Dove A, Romanak K, Backus S, Hites R. 2014. Flame retardants and legacy chemicals in Great Lakes' water. Environmental Science and Technology 48: 9563–9572.

Versar Inc. 1986. Standard Scenarios for Estimating Exposure to Chemical Substances During Use of Consumer Products. Prepared for the U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C.

Wang Q, Liang K, Liu J, Yang L, Guo Y, Liu C, Zhou B. 2013. Exposure of zebrafish embryos/larvae to TDCPP alters concentrations of thyroid hormones and transcriptions of genes involved in the hypothalamic–pituitary–thyroid axis. Aquatic Toxicology 126: 207–213.

Wang Q, Lai NL-S, Wang X, Guo Y, Lam PK-S, Lam JW-H, Zhou B. 2015a. Bioconcentration and transfer of the organophorous flame retardant 1,3-dichloro-2-propyl phosphate causes thyroid endocrine disruption and developmental neurotoxicity in zebrafish larvae. Environmental Science and Technology 49: 5123-5132.

Wang Q, Lam JCW, Han J, Wang X, Guo Y, Lam PKS, Zhou B. 2015b. Developmental exposure to the organophosphorus flame retardant tris(1,3-dichloro-2-propyl) phosphate: Estrogenic activity, endocrine disruption and reproductive effects on zebrafish. Aquatic toxicology 160: 163-171.

Wang Q, Lam JW-H, Man Y-C, Lai NL-S, Kwok KY, Guo Y, Lam PK-S, Zhou B. 2015c. Bioconcentration, metabolism and neurotoxicity of theorganophorous flame retardant 1,3-dichloro 2-propyl phosphate(TDCPP) to zebrafish. Aquatic Toxicology 158: 108-115.

Webster T. Watkins D, Walker C. Fraser A, Heiger-Bernays W, Stapleton H, McClean M. 2010. PentaBDE alternatives in homes, offices and cars. *Dioxin 2010: 30th International Symposium on Halogenated Persistent Organic Pollutants* (San Antonio, Texas 12-17 September 2010).

Weiner ML and Jortner BS. 1999. Organophosphate-induced delayed neurotoxicity of triarylphosphates. Neurotoxicology 20(4):653–673.

WHO. 1998. Flame retardants: Tris(chloropropyl) phosphate and tris(2-chloroethyl) phosphate. Environmental Health Criteria 209. World Health Organization, Geneva.

Wildlife International. 2005a. TDCP aerobic transformation in soil. Project No.: 497E-106. Wildlife International, Ltd., 8589 Commerce Drive, Easton, Maryland 21601.

Wildlife International. 2005b. TCPP: A 72-hour toxicity test with the freshwater alga (*Pseudokirchneriella subcapitata*). Project number: 583A-101. Wildlife International, Ltd., 8589 Commerce Drive, Easton, Maryland 21601.

Wildlife International. 2005c. TDCP: A 72-hour toxicity test with the freshwater alga (*Pseudokirchneriella subcapitata*). Project number: 583A-102. Wildlife International, Ltd., 8589 Commerce Drive, Easton, Maryland 21601.

Wildlife International. 2006a. Tris[2-chloro-1-chloromethyl)ethyl]-phosphate (TDCP): Adsorption/desorption characteristics in representative soils, sediment, and sludge solids in accordance with OECD Guideline for Testing of Chemicals, 106: Adsorption – Desorption Using a Batch Equilibrium Method. Wildlife International, Ltd. project no.: 584E-101. Draft report 2nd June 2006. [cited in EU RAR 2006b].

Wildlife International. 2006b. TDCP: A 28-day sediment toxicity test with Chironomus riparius using spiked sediment. Project number: 583A-104.

Wildlife International. 2006c. TDCP: A Prolonged Sediment Toxicity Test with *Hyalella azteca* Using Spiked Sediment. Project Number: 583A-105. Wildlife International, Ltd., Easton, Maryland 21601.

Wildlife International. 2006d. Tris[2-chloro-1-(chloromethyl)ethyl]-phosphate (TDCP):

A Prolonged Sediment Toxicity Test with *Lumbriculus variegatus* using Spiked Sediment. Final Report Project Number: 583A-106. Wildlife International, Ltd., Easton, Maryland 21601, U.S.A. [cited in EU RAR 2008b].

Williams GM, Mori H, McQueen CA. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutation Research 221:263–286. [cited in EU RAR 2008a].

Wilson R, Jones-Otazo H, Petrovic S, Mitchell I, Bonvalot Y, Williams D, Richardson GM. 2013. Revisiting dust and soil ingestion rates based on hand-to-mouth transfer. Human and Ecological Risk Assessment 19(1): 158–188. Available from: http://www.tandfonline.com/doi/full/10.1080/10807039.2012.685807.

Wu AHB. 2006. Tietz clinical guide to laboratory tests. 4th ed. St. Louis (MO): Saunders Elsevier. p. 1102–1104.

Yang F, Ding J, Huang W, Xie W, Liu W. 2014. Particle size-specific distributions and preliminary exposure assessments of organophosphate flame retardants in office air particulate matter. Environmental Science and Technology 48(1):63–70.

Yoon Y, Ryu J, Oh J, Choi B-G, Snyder S. 2010. Occurrence of endocrine disrupting compounds, pharmaceuticals and personal products in the Han River (Seoul, South Korea). Science of Total Environment 408:636–643.

Zeiger et al. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environmental and Molecular Mutagenesis 19 (supplement 21):2-141. [cited in EU RAR 2008a].

Appendix A: Environmental Monitoring Data for the Indoor Atmospheric Compartment

There have been a few studies reporting environmental levels of flame retardants in Canada and other countries, including TCPP and TDCPP. Data for the atmospheric compartment (indoor air and dust) are summarized in the following tables, while information for the other compartments is presented in the supporting document (Environment Canada, Health Canada 2014).

A1. Environmental Monitoring Data for Dust Compartment in Canada

Table A1.1. Concentrations of TCPP in indoor dust in Canada

Location	Sample type	Sampling year	Sample size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
Canada	Vacuum	2007–2010	134	1.1	9.6	personal communication from Environmental Health Science and Research Bureau, Health Canada August 2014
Canada	Fresh	2007–2010	134	1.4	13.0	personal communication from Environmental Health Science and Research Bureau, Health Canada August 2014
Canada	NS	2007–2010	818	1.62	18.2	personal communication from Environmental Health Science

Location	Sample type	Sampling year	Sample size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
						and Research Bureau, Health Canada August 2014

Abbreviations: P95 = 95th percentile; NS = not specified

Table A1.2. Concentrations of TDCPP in indoor dust in Canada

Location	Sample Type	Sampling Year	Sample Size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
Toronto, ON, Canada (TI)	Vacuum	2010 (fall) and 2011(summer)	28	0.32 (mean)	0.89	Diamond et al. 2013
Toronto, ON, Canada	Vacuum	2012	20	2.5 (mean)	46 (max)	Diamond et al. 2013
Canada	Vacuum	2007–2010	134	2.0	12	personal communication from Environmental Health Science and Research Bureau, Health Canada August 2014
Canada	Fresh	2007–2010	134	2.7	9	personal communication from Environmental Health Science and Research Bureau, Health Canada

Location	Sample Type	Sampling Year	Sample Size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
						August 2014
Canada	NS	2007–2010	818	3.08	12.7	personal communication from Environmental Health Science and Research Bureau, Health Canada August 2014

Abbreviations: P95 = 95th percentile; ON = Ontario; NS = not specified; TI = Toronto Intensive pilot study

A2. Environmental Monitoring Data for the Atmospheric Compartment in Other Jurisdictions

Table A2.1. Concentration of TCPP and TDCPP in indoor air

Location (Sampling Year)	Area	Sample size	TCPP concentration (pg/m^3)	TDCPP concentration (pg/m^3)	Reference
Urban area, Sweden (NS)	Home	2	[38000–210000]	<500	Marklund et al. 2005b
Stockholm, Sweden (NS)	Home	10	[7000–160000]	<DL (1 ng/m^3)	Staaf and Otsman 2005
Stockholm, Sweden (2009)	Home	10	15000 [2400–64000]	3100 [ND – 17000]	Bergh et al. 2011
Urban area, Sweden (NS)	Office	7	[10000–160000]	[200–150000]	Marklund et al. 2005b
Stockholm, Sweden (NS)	Office	3	[41000–120000]	NM	Staaf and Otsman 2005
Norway (2007)	Office	2	[10000–21000]	[<40–7100]	Green et al. 2007
Stockholm, Sweden	Office	10	110000 [16000–240000]	24000 [NS – 73000]	Bergh et al. 2011

(2009)					
Zurich, Switzerland (NS)	Office	3	[ND – 130000]	ND	Hartmann et al. 2004
Stockholm, Sweden (NS)	public and personal vehicle	4	[5000–2300000]	NM	Staaf and Otsman 2005
Zurich, Switzerland (NS)	Personal vehicle	4	[ND – 260000]	ND	Hartmann et al. 2004

Abbreviations: NM = not measured; NS = not specified; ND = not detected; DL = detection limit

Table A2.2. Concentrations of TCPP in household dust.

Location	Sample type	Sampling year	Sample size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
USA	Living area surfaces	2006	16	2.1	120 (max)	Dodson et al. 2012
USA	Living area surfaces	2011	16	2.2 (Max)	2.2	Dodson et al. 2012
USA	NS	2002–2007	50	1.04	5.49	Stapleton et al. 2009
Germany	Vacuum	2010	6	0.74 (mean)	0.96 (max)	Brommer et al. 2012
Germany	Cars	2010–2011	12	3.1 [1.4–4.3]	NS	Brommer et al. 2012
Germany	Homes	2010–2011	6	0.74 [0.37–0.96]	NS	Brommer et al. 2012
Germany	Offices	2010–2011	10	3 [0.18–9.4]	NS	Brommer et al. 2012
Romania	NS	2010	47	0.86 (max)	3.72 (75^{th}%)	Dirtu et al. 2012
Belgium	NS	2006–2010	41	[0.45–1.38]	14.5	Van den Eede et al. 2012
Spain	NS	2006	1	0.185	0.185	Van den Eede et al. 2012

Location	Sample type	Sampling year	Sample size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
Stockholm, Sweden	NS	2009	10	3.1 [0.7–11]	NS	Bergh et al. 2011
Netherlands	Near electronics	NS	8	1.3 [0.48–3.8]	NS	Brandsma et al. 2014
Netherlands	On electronics	NS	8	1.3 [0.58–4.5]	NS	Brandsma et al. 2014
New Zealand	Floor measurements	2008	38	0.35 (max)	2.93	Ali et al. 2012
New Zealand	Mattress measurements	2008	16	0.250 (max)	1.34	Ali et al. 2012
Pakistan	NS	2011	15	<0.020	0.085	Ali et al. 2013
Kuwait	NS	2011	15	1.46 (max)	7.06	Ali et al. 2013
Kuwait	House dust	2011	15	1.46 [0.12–7.065]	NS	Ali et al. 2013
Kuwait	Car	2011	15	30.73 [2.49–134]	NS	Ali et al. 2013
Pakistan	House dust	2011	15	<0.02 [<0.02–0.085]	NS	Ali et al. 2013
Pakistan	Car	2011	15	0.1 [<0.02–2.615]	NS	Ali et al. 2013

Abbreviations: P95 = 95th percentile; NS = not specified

Table A2.3. Concentrations of TDCPP in household dust.

Location	Sample Type	Sampling Year	Sample Size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
USA	Preschool, vacuum	2010–2011	49	2.26 [0.76–70.9]	36.9	Bradman et al. 2012
USA	Living area surfaces	2006	16	2.8 (max)	24	Dodson et al. 2012
USA	Living area surfaces	2011	16	2.1	2.1	Dodson et al. 2012
USA	NS	2002–2007	50	1.88 (max)	56.1	Stapleton et al. 2009

Location	Sample Type	Sampling Year	Sample Size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
USA	NS	2009	30	6.3 (mean)	NS	Webster et al. 2010
Germany	Vacuum	2010	6	<0.08 (mean)	0.11	Brommer et al. 2012
Germany	Cars	2010–2011	12	130 [<0.08–620]	NS	Brommer et al. 2012
Germany	Homes	2010–2011	6	<0.08 [<0.08–0.11]	NS	Brommer et al. 2012
Germany	Offices	2010–2011	10	0.15 [<0.08–0.29]	NS	Brommer et al. 2012
Romania	NS	2010	47	0.060	0.13 (75^{th}%)	Dirtu et al. 2012
Belgium	NS	2006–2010	41	[0.162–0.36]	0.99	Van den Eede et al. 2012
Spain	NS	2006	1	0.124	0.124	Van den Eede et al. 2012
Stockholm, Sweden	NS	2009	10	12 [2.2–27]	NS	Bergh et al. 2011
Netherlands	Near electronics	NS	8	0.28 [0.07–3.2]	NS	Brandsma et al. 2014
Netherlands	On electronics	NS	8	0.68 [0.1–7.4]	NS	Brandsma et al. 2014
New Zealand	Floor measurements	2008	38	0.23	1.89	Ali et al. 2012
New Zealand	Mattress measurements	2008	16	0.103	0.303	Ali et al. 2012
Pakistan	NS	2011	15	<0.005	0.25	Ali et al. 2013
Kuwait	NS	2011	15	0.36	1.56	Ali et al. 2013
Kuwait	House dust	2011	15	0.36 [0.06–1.56]	NS	Ali et al. 2013
Kuwait	Car	2011	15	7.63 [0.6–166]	NS	Ali et al. 2013
Pakistan	House dust	2011	15	<0.005 [<0.005–0.255]	NS	Ali et al. 2013

Location	Sample Type	Sampling Year	Sample Size	Median [range] (mg/kg)	P95 (mg/kg)	Reference
Pakistan	Car	2011	15	0.029 [<0.005–1.24]	NS	Ali et al. 2013

Appendix B: Weight of Evidence in the Ecological Risk Assessment

Table B1. Major lines of evidence and weight assigned in the ecological risk assessment on TCPP and TDCPP

Evidence	Data uncertainty[a]	Strength of evidence/ inference[b]	Relevancy or impact[c]	Weight assigned[d]	Implication in proposing the conclusion
Water solubility	Low	High	High	Moderate to High (++++)	Used as a predictor of aquatic exposure
Persistence	Low	High	High	High (+++++)	Meet the persistence criteria
Rapid metabolism and BCFs	Low	High	High	High (+++++)	Not meet the bioaccumulation criteria
Potential increase of the import quantity	Moderate	Moderate	Moderate	Moderate (+++)	A significant increase of tonnage not expected
Monitoring data	Low	Moderate	High	Moderate to High (++++)	Evidence of environmental exposure
Release scenarios for the industrial activities	Moderate	Moderate	High	Moderate to High (++++)	Conservative PECs
Releases from the products	Moderate	Moderate	High	Moderate to High	Conservative PECs

Evidence	**Data uncertainty[a]**	**Strength of evidence/ inference[b]**	**Relevancy or impact[c]**	**Weight assigned[d]**	**Implication in proposing the conclusion**
				(++++)	
Risk quotient analysis for TCPP and TDCPP for water < 1	Moderate	High	High	High (+++++)	Not support meeting 64 (a) or (b)
Risk quotient analysis for TDCPP for sediment and soil < 1	Moderate	High	High	High (+++++)	Not support meeting 64 (a) or (b)

[a] Considers data quality, quantity and consistency.

[b] Ability to infer truth from the data given the level of uncertainty and power of the data

[c] Describes how relevant the data are scientifically and to this regulatory assessment

[d] Final weight assigned to a line of evidence which is a function of the outcomes assigned to the strength of inference and relevancy

Appendix C: Upper-bounding Estimates of Daily Intake by Various Age Groups within the General Population of Canada

Table C1. Upper-bounding estimates of daily intake (µg/kg bw/d) of TDCPP

Route of exposure	0–6 mo[a] (breast milk-fed)[b]	0–6 mo (formula fed)[c]	0–6 mo (not formula fed)[d]	0.5–4 yr[e]	5–11 yr[f]	12–19 yr[g]	20–59 yr[h]	⩾60 yr[i]
Ambient air[j]	5.3E-06	5.3E-06	5.3E-06	1.1E-05	8.8E-06	5.0E-06	4.3E-06	3.7E-06
Indoor air[k]	4.2E-03	4.2E-03	4.2E-03	8.9E-03	7.0E-03	4.0E-03	3.4E-03	3.0E-03
Drinking water[l]	N/A	1.5E-01	5.8E-02	6.5E-02	5.1E-02	2.9E-02	3.0E-02	3.2E-02
Food[m]	1.8E-02	NI	0.0E+00	2.9E-02	2.4E-02	1.3E-02	1.3E-02	8.2E-03
Dust[n]	1.9E-01	1.9E-0	1.9E-01	9.8E-02	3.7E-02	1.4E-03	4.5E-04	4.4E-04
Soil[o]	N/A	N/A	N/A	8.1E-08	6.1E-08	2.1E-09	2.0E-09	1.9E-09
Total intake	2.1E-01	3.5E-01	2.5E-01	2.0E-01	1.2E-01	4.8E-02	4.7E-02	4.4E-02

Abbreviations: N/A, not applicable; NI, data not identified in the literature; mo, months; yr, years.

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day (Health Canada 1998), and to ingest 38 and 0 mg of dust and soil per day, respectively (Wilson et al. 2013).

[b] Exclusively for breast milk-fed infants, assumed to consume 0.742 L of breast milk per day (Health Canada 1998), and breast milk is assumed to be the only dietary source. The concentration for whole (breast) milk of 0.186 µg/L was based on a reported TCPP of 5.3 ng/g lipid x 3.4% (lipid content of breast milk) x 1.03 g/mL (density of breast milk) identified in 90 samples of human breast milk collected in 2006 from subjects from Sweden (Sundkvist et al. 2010).

[c] Exclusively for formula-fed infants, assumed to drink 0.8 L of water per day (Health Canada 1998), where water is used to reconstitute formula. See footnote on drinking water for details.

[d] Exclusively for not formula-fed infants, assumed to drink 0.7 L of water per day (Health Canada 1998), with approximately 50% of non-formula-fed infants introduced to solid foods by 4 months of age, and 90% by 6 months of age (NHW 1990).

[e] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day, to consume 54.7 g of fish per day (Health Canada 1998), and to ingest 41 and 14 mg of dust and soil per day, respectively (Wilson et al. 2013).

[f] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day, to consume 89.8 g of fish per day (Health Canada 1998), and to ingest 31 and 21 mg of dust and soil per day, respectively (Wilson et al. 2013).

[g] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day, to consume 97.3 g of fish per day (Health Canada 1998), and to ingest 2.2 and 1.4 mg of dust and soil per day, respectively (Wilson et al. 2013).

[h] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day, to consume 111.7 g of fish per day (Health Canada 1998), and to ingest 2.5 and 1.6 mg of dust and soil per day, respectively (Wilson et al. 2013).

[i] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day, to consume 72.9 g of fish per day (Health Canada 1998), and to ingest 2.5 and 1.5 mg of dust and soil per day, respectively (Wilson et al. 2013).

[j] The highest mean concentration of TDCPP in outdoor air, (0.15 ng/m^3, from Toronto, ON (Shoeib et al. 2014) was used for deriving upper-bounding estimates of daily intake for ambient air exposure. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[k] No monitoring data of indoor air in North America were identified. An indoor air concentration from Stockholm, Sweden of 17 ng/m^3 (Bergh et al. 2011) was selected for deriving upper-bounding estimates of daily intake for ambient air exposure. Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[l] The maximum concentration of TDCPP (1437 ng/L) in water from tributaries of urban and rural areas to Lake Ontario (Jantunen et al. 2013b) was selected for deriving upper-bounding estimates of daily intake for drinking water exposure.

[m] No monitoring data on marketed foods in Canada were identified; however environmental fish data in Europe were available. The TDCPP concentration for whole fish of 8.1 µg/kg wet weight (based on a reported maximum TDCPP concentration of 192 µg/kg lipid x 5.73% lipid content) (n= 23) of Atlantic cod, Polar cod and Arctic char collected in 2008 in Norway (Evenset et al. 2009) was selected for deriving upper-bounding estimates of daily intake for exposure to all fish-related food items in the fish food group. Amounts of foods consumed on a daily basis by each age group over 12 food groups were obtained from the 1970–1972 Nutrition Canada Survey (Health Canada 1998).

[n] For all age groups below 20 years (i.e. children and adolescents), the 95th percentile concentration of 37 mg/kg measured in dust from early childhood education centres in California (Bradman et al. 2012) was selected for deriving upper-bounding estimates of daily intake for dust exposure. This is considered a conservative upper bound to account for higher levels indoors where children may spend several hours outside the home. For all other age groups, the 95th percentile concentration of TDCPP (12.7 mg/kg) in the Canadian baseline study (Canadian House Dust Study preliminary data; Kubwabo et al., manuscripts in preparation, Environmental Health Science and Research Bureau, Health Canada; unreferenced, dated December 13, 2013), measured in various Canadian cities, was selected for deriving upper-bounding estimates of daily intake for dust exposure.

[o] No monitoring data of soil in North America were identified. The detection limit (LOD) (9 x10^{-5} mg/kg) from a German soil study was selected for deriving upper-bounding estimates of daily intake for soil

exposure. This is considered a conservative upper bound to account for the reported samples all being below the LOD.

Table C2. Upper-bounding estimates of daily intake (µg/kg bw/d) of TCPP

Route of exposure	0–6 mo[a] (breast milk-fed)[b]	0–6 mo[a] (formula fed)[c]	0–6 mo[a] (not formula fed)[d]	0.5–4 yr[e]	5–11 yr[f]	12–19 yr[g]	20–59 yr[h]	⩾60 yr[i]
Ambient air[j]	2.4E-05	2.4E-05	2.4E-05	5.0E-05	3.9E-05	2.2E-05	1.9E-05	1.7E-05
Indoor air[k]	3.9E-02	3.9E-02	3.9E-02	8.4E-02	6.6E-02	3.7E-02	3.2E-02	2.8E-02
Drinking water[l]	N/A	2.0E-01	7.4E-02	8.3E-02	6.5E-02	3.7E-02	3.9E-02	4.1E-02
Food[m]	2.0E-01	NI	1.7E-02	6.8E-02	5.3E-02	2.9E-02	2.8E-02	1.9E-02
Dust[n]	9.2E-02	9.2E-02	9.2E-02	4.8E-02	1.8E-02	6.7E-04	6.4E-04	6.3E-04
Soil[o]	N/A	N/A	N/A	1.1E-06	8.3E-07	2.9E-08	2.8E-08	2.6E-08
Total intake	3.3E-01	3.5E-01	2.2E-01	2.8E-01	2.0E-01	1.0E-01	9.9E-02	8.8E-02

Abbreviations: N/A, not applicable; NI, data not identified in the literature; mo, months; yr, years.

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day (Health Canada 1998), and to ingest 38 and 0 mg of dust and soil per day, respectively (Wilson et al. 2013).

[b] Exclusively for breast milk-fed infants, assumed to consume 0.742 L of breast milk per day (Health Canada 1998), and breast milk is assumed to be the only dietary source. The concentration for whole (breast) milk of 1.99 µg/L was based on a reported TCPP of 57 ng/g lipid x 3.4% (lipid content of breast milk) x 1.03 g/mL (density of breast milk) identified in 50 samples of human breast milk collected in 2006 from subjects from Sweden (Sundkvist et al. 2010).

[c] Exclusively for formula-fed infants, assumed to drink 0.8 L of water per day (Health Canada 1998), where water is used to reconstitute formula. No monitoring data on TCPP in formula were identified; therefore dietary intakes are only those from water. See footnote on drinking water for details.

[d] Exclusively for not formula-fed infants, assumed to drink 0.7 L of water per day (Health Canada 1998), with approximately 50% of non-formula-fed infants introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).

[e] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day, to consume 54.7 g of fish and 249.7 g of fruit and fruit products per day (Health Canada 1998), and to ingest 41 and 14 mg of dust and soil per day, respectively (Wilson et al. 2013).

[f] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day, to consume 89.8 g of fish and 276 g of fruit and fruit products per day (Health Canada 1998), and to ingest 31 and 21 mg of dust and soil per day, respectively (Wilson et al. 2013).

[g] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day, to consume 97.3 g of fish and 251.6 g of fruit and fruit products per day (Health Canada 1998), and to ingest 2.2 and 1.4 mg of dust and soil per day, respectively (Wilson et al. 2013).

[h] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day, to consume 111.7 g of fish and 281.2 g of fruit and fruit products per day (Health Canada 1998), and to ingest 2.5 and 1.6 mg of dust and soil per day, respectively (Wilson et al. 2013).

[i] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day, to consume 72.9 g of fish and 242.9 g of fruit and fruit products per day (Health Canada 1998), and to ingest 2.5 and 1.5 mg of dust and soil per day, respectively (Wilson et al. 2013).

[j] An outdoor air vapour phase mean concentration of 0.67 ng/m^3 from Toronto (Jantunen 2014) was selected for deriving upper-bounding estimates of daily intake for ambient air exposure. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[k] No data was identified for indoor air exposure to TCPP in North America. A maximum indoor air concentration of 160 ng/m^3 from homes in Stockholm, Sweden (Staaf and Otsman 2005) was selected for deriving upper-bounding estimates of daily intake for indoor air exposure. Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[l] The TCPP maximum concentration of 1839 ng/L in water from tributaries of an urban area to Lake Ontario (Jantunen et al. 2013b) was selected for deriving upper-bounding estimates of daily intake for drinking water exposure.

[m] No monitoring data on marketed foods in Canada were identified; however environmental fish and shellfish data were available. The TCPP concentration of 15.6 µg/kg (based on a reported maximum TCPP concentration of 1300 µg/kg lipid x 0.44 % lipid content in mussel) in mussels (n=30) collected in 2007 in Sweden (Sundkvist et al. 2010) was selected for deriving upper-bounding estimates of daily intake for exposure to all fish-related food items in the Fish food group. The maximum concentration in fruits with peels (0.82 µg/kg) reported in the US EPA food basket studies (ATSDR 2012) was selected for deriving upper-bounding estimates of daily intake for exposure to all fruit-related food items in the Fruits and Fruit Products food group. Amounts of foods consumed on a daily basis by each age group over 12 food groups were obtained from the 1970–1972 Nutrition Canada Survey (Health Canada 1998).

[n] For all other age groups, the 95th percentile concentration of TDCPP (18.2 mg/kg) in the Canadian baseline study (Canadian House Dust Study preliminary data; Kubwabo et al., manuscripts in preparation, Environmental Health Science and Research Bureau, Health Canada; unreferenced, dated December 13, 2013), measured in various Canadian cities, was selected for deriving upper-bounding estimates of daily intake for dust exposure.

[o] No monitoring data of soil in North America were identified. A mean concentration from a German soil study of 1.23×10^{-3} mg/kg was selected for deriving upper-bounding estimates of daily intake for soil exposure.

Appendix D: Exposure Estimates of TCPP and TDCPP from Manufactured items

Based on the available information, dermal exposure intakes were estimated for direct contact with foam-containing mattresses and related manufactured items for young children and adults. Oral exposure estimates were also derived for young children mouthing (sucking) on foam manufactured items intended for children. The exposure parameters and values used to estimate exposures are presented in Tables D1 and D2, and are based on conservative assumptions.

Uptake = [SA × SCF × M × ED × DA] / BW

Table D1. Parameters for TCPP and TDCPP dermal uptake estimates for mattress polyurethane foam exposure

Symbol	Description	Value
SA[a]	Surface area of skin contact	215 +330 cm^2 (Infant) 357+435 cm^2 (Toddler) 1395+638 cm^2 (Adult)
SCF[b]	Skin contact factor	0.13
M[c]	Migration rate	4.6×10^{-3} $mg/cm^2/hr$ (TCPP) 5.6×10^{-5} $mg/cm^2/hr$ (TDCPP)
ED[d]	Exposure duration	12 hr/d (Infant) 12 hr/d (Toddler) 8 hr/d (Adult)
DA	Dermal absorption	40% (TCPP)[e] 30% (TDCPP)[f]
BW[g]	Body weight	7.5 kg (Infant) 15.5 kg (Toddler) 70.9 kg (Adult)
Uptake	TCPP Uptake (mg/kg-bw/d)	5.5×10^{-2} (Infant)

Symbol	Description	Value
		0.15 (Toddler) 0.21 (Adult)
Uptake	TDCPP Uptake (mg/kg-bw/d)	1.9×10^{-3} (Infant) 1.3×10^{-3} (Toddler) 5.0×10^{-4} (Adult)

[a] For this scenario, it is assumed that an individual is wearing shorts and a t-shirt. The surface area of exposure is based on exposure to a fraction of the lower limbs and the back of the head. The surface area of the lower limbs (Health Canada 1995) was multiplied by one third to account for the triangular shape of limbs, where only one side is directly in contact with the mattress (CPSC 2006b). The surface area of the head (Health Canada 1995) was multiplied by a factor of 0.5 to represent exposure to the back of the head only.

[b] No TCPP- or TDCPP-specific skin contact factor, i.e. the fraction of substance on a surface adhering to skin, was identified in the literature. As such, a value of 0.13, an average of multiple substances (i.e. malathion, glyphosate, permethrin and TRIS [tris-(2,3-dibromopropyl) phosphate]) in various textiles in wet and dry simulations (US CPSC 2006), was selected.

[c] The migration rates of 4.6×10^{-3} mg/cm^2/hr for TCPP and 5.6×10^{-5} mg/cm^2/hr for TDCPP used to estimate dermal exposures are based on migration studies of treated furniture foam by TNO Quality of Life (EU RAR 2008a) and the U.S. CPSC (US CPSC 2005b), respectively. The TNO Quality of Life (2005) study wetted filter papers with artificial sweat placed on top of a foam block containing 10% TCPP and compressed the foam, resulting in a migration rate of 4.6×10^{-3} mg/cm^2/hr. The US CPSC study built a furniture miniseat mock-up consisting of a block of foam covered with cotton fabric and attached to plywood. The miniseat was wetted with a saline solution, to mimic sweat, and pressure was applied to imitate the action of sitting. The migration rate of 5.6×10^{-5} mg/cm^2/hr for TDCPP was determined based on the reported maximum daily amount extracted (8 µg) onto the filter (5-cm diameter) over the course of the migration testing period (6 hours) (US CPSC 2005b).

[d] Exposure duration for sleeping was adjusted from durations reported in US CPSC (2006) for leisure sitting to account for longer sleeping durations relative to sitting.

[e] EU RAR 2008a.

[f] EU RAR 2008b.

[g] Health Canada (1998).

Intake = [SA × M × ED] / BW

Table D2. Parameters for TCPP and TDCPP oral intake (mouthing) estimates for polyurethane foam exposure

Symbol	Description	Value
SA[a]	Surface area of direct mouthing	20 cm^2
M[b]	Migration rate	4.6×10^{-3} mg/cm^2/hr (TCPP) 5.6×10^{-5} mg/cm^2/hr (TDCPP)
ED[c]	Exposure duration	24.5 min/d
BW	Body weight	15.5 kg (Toddler)

Symbol	Description	Value
Intake	Intake calculated in mg/kg-bw/d	2.4×10^{-3} (TCPP) 3.0×10^{-5} (TDCPP)

[a] Surface area based on professional judgment reflecting twice the surface area of the opening of a toddler's mouth.

[b] The migration rates of 4.6×10^{-3} mg/cm^2/hr for TCPP and 5.6×10^{-5} mg/cm^2/hr for TDCPP as presented in the dermal scenario were also used to estimate oral exposure.

[c] The mouthing duration for children's foam products such as nap mats, car seats and small furniture was based on the duration for "other objects" in Norris and Smith (2002) [cited in US EPA (2011)].

[d] Health Canada (1998).

Appendix E: Exposure Estimates of TCPP from Products

Exposure from polyurethane spray foam (PUF) products

Direct skin contact with PUF can result in dermal exposure to TCPP used in insulation spray and sealants. Inhalation exposure may also occur during application of the product from TCPP adhering to dust particles in the air. Both small-scale (sealants) and large-scale (insulation) products were considered based on confirmation of this use in Canada (ECCC 2013-2014). The exposure event for an adult using PUF products is not expected to occur frequently (likely every 5 years), and thus was estimated on a per event and acute or short-term basis. The exposure estimates presented below are based on conservative assumptions.

Intake = [SA × FT × ρ × WF × DA] / BW

Table E1. Dermal exposure factors for polyurethane spray foam – small scale (i.e. sealants)

Symbol	Description	Value	Reference
SA	Surface area of finger tips (cm^2)	10	Versar handbook thin film, instant application scenario (Westat 1987)
FT	Thickness of oil film on hand (cm)	1.59×10^{-2}	Versar handbook thin film, instant application scenario (Westat 1987)
ρ	Density of product (g/cm^3)	0.027	Versar handbook thin film, instant application scenario (Westat 1987)
WF	TCPP Weight fraction	0.12	Red Devil 2004
DA	Dermal absorption	40%	EU RAR 2008a
BW	Body weight	70.9 kg (Adult)	Health Canada 1998
Uptake	Uptake (µg/kg-bw/d)	2.7	--

Intake = SA × PA × WF × DA / BW

Table E2. Dermal exposure factors for polyurethane spray foam – large scale (i.e. insulation)

Symbol	Description	Value	Reference
SA	Surface area of back of hands and forearms (cm^2)	2185	Health Canada 1998

PA	Product amount on skin (g)	0.25	RIVM 2012
WF	TCPP Weight fraction	0.45	ECCC 2013-2014
DA	Dermal absorption	40%	EU RAR 2008a
BW	Body weight	70.9 kg (Adult)	Health Canada 1998
Uptake	Uptake (µg/kg-bw/d)	630	--

Table E3. Inhalation exposure factors for polyurethane spray foam – small scale (i.e. sealants)

Description	Value	Reference
Room volume (m^3)	20	RIVM 2012
Air exchange rate (/hr)	0.6	RIVM 2012
Exposure duration (min)	30	RIVM 2012
TCPP Weight fraction	0.12	Red Devil 2004
Product amount (g)	90	Red Devil 2004, RIVM 2012
Inhalation rate (m^3/day)	16.2	Health Canada 1998
Intake (µg/m^3)	185	--

Table E4. Inhalation exposure factors for polyurethane spray foam – large scale (i.e. full wall spraying)

Description	Value	Reference
Measured Air Concentration (Range; ug/m^3)	477 to 2,940	ACC 2012
Exposure duration (min)	30	RIVM 2012
Body Weight (Adult; kg)	70.9	Health Canada 1998
Inhalation rate (m^3/day)	16.2	Health Canada 1998

Exposure from waterproofing spray

The exposure event for an adult using a waterproofing spray is not expected to occur frequently (likely once a year), and thus was estimated on a per event and acute or short term basis. The inhalation scenario is based on spraying tent fabric from a can directed away from the applicator outdoors (Empack 2014). The large air exchange rate would result in negligible inhalation exposure. Direct skin contact with waterproofing spray can result in dermal exposure to TCPP. The dermal exposure estimates presented below are based on conservative assumptions.

Intake = [SA × PA × WF × DA] / BW

Table E5. Dermal exposure factors for waterproofing spray

Symbol	Description	Value	Reference
SA	Surface area of back of hands (cm^2)	455	Health Canada 1998
PA	Product amount on skin (g)	0.25	RIVM 2012
WF	TCPP Weight fraction	0.13	Empack 2014
DA	Dermal absorption	40%	EU RAR 2008a
BW	Body weight	70.9 kg (Adult)	Health Canada 1998
Uptake	Uptake (µg/kg bw/d)	1.8	--

Appendix F: TDCPP Intake Estimate from Urinary BDCPP Biomonitoring Reverse Dosimetry

Reverse dosimetry was used to derive estimates of daily intakes from urine concentrations for adult men and women, pregnant women and toddlers (aged 1–5 yrs). All urine concentrations in the literature were corrected for specific gravity and presented in Section 9.1.3, with the maximum concentrations for each age group shown in table F1. All other parameters have been previously discussed and are also presented below. Daily intakes are calculated for reverse dosimetry as shown in the equation below.

Daily Intake = $[[Urine]_{SG} \times V_{urine} \times MWR] / [BW \times FUE]$

Table F1. Reverse dosimetry parameters for TDCPP metabolite, BDCPP

Symbol	Description	Value
$[Urine]_{SG}$	Maximum urinary concentrations of metabolite corrected for specific gravity (ng/mL)	19.4 (Adult men/ women) [a] 34.3 (Pregnant women) [b] 251 (Toddlers)[c]
V_{urine}	Total daily urine volume (L/d)	2.03 (Adult men/women) [d] 2.7 (Pregnant women) [e] 0.7 (Toddlers)[f]
BW[g]	Body weight (kg)	70.9 (Adult) 15.5 (Toddlers)
FUE[h]	Fractional urine excretion (based on rat toxicokinetic study)	21% (common to all age groups)
MWR	Molecular weight ratio between parent and metabolite, i.e. TDCPP and BDCPP	1.34 (common to all age groups)
Intake	Intake (µg/kg bw/d)	3.5 (Adult men/women) 8.3 (Pregnant women) 72 (Toddlers)

[a] Males (n=45) in this study were from Boston, MA, U.S. (Meeker et al. 2013)

[b] Pregnant females (n=8) in this study were from Chapel Hill, North Carolina, U.S. (Hoffman et al. 2014)

[c] Toddlers (n=23) in this study were from New Jersey, U.S., and were between 1–5 years of age (Butt et al. 2014).

[d] Mean total daily urinary void volumes were reported to range from 0.6–2.03 L/d for men and women (Davison and Nobel 1981; Francis 1960; ICRP 2003; Lakind and Naiman 2008; Lentner 1981; Parboosingh and Doig 1973; Perucca et al. 2007; Revúsová 1971; Van Haarst et al. 2004; Wu 2006). The upper bound value of 2.03 L/d was selected for conservatism for reverse dosimetry.

[e] Mean total daily urinary void volumes were reported to range from 0.8–2.7 L/d for pregnant women (Davison and Nobel 1981; Francis 1960; Higby et al. 1994; Neithardt et al. 2002; Parboosingh and Doig 1973; Thorp et al. 1999). The upper bound value of 2.7 L/d was selected for conservatism for reverse dosimetry.

[f] Mean total daily urinary void volumes were reported to ranged from 0.45–0.7 L/d for toddlers (3–5 yrs) (ICRP 2003; Lentner 1981; Wu 2006). The upper bound value of 0.7 L/d was selected for conservatism for reverse dosimetry.

[g] Health Canada 1998.

[h] Following the oral administration of TDCPP in a rat study, 35% of radioactivity was excreted in urine, of which 60% was the metabolite, BDCPP. The FUE was calculated by determining the % BDCPP in urine to the original TDCPP dose, i.e., (0.35 moles total radiolabel in urine/ mole TDCPP administered radiolabel) × (0.6 moles of BDCPP in urine/moles total radiolabel in urine) (Minegishi et al. 1988; Nomeir et al. 1981; Lynn et al. 1980, 1981).

Appendix G: A Summary of Reproductive and Developmental Effects of Experimental Animals Treated with TCPP, TCEP and TDCPP

Detailed information on TCPP and TDCPP is presented in other sections of this screening assessment report. Information on TCEP was obtained from the screening assessment for the Challenge report on TCEP (Environment Canada, Health Canada 2009).

TCPP

The major effects observed were decrease in uterus weights and effects on oestrus cycle in parental females and decrease in organ weights and terminal body weights in parental males. No other reproductive effects were observed. There was a significant increase in the number of runts born in both F1 and F2 generations, with no other abnormalities observed.

TCEP

Testicular toxicity was observed in male mice and rats in a number of studies via the oral route and the inhalation route. Decreased number of live pups per litter and decreased numbers of litters were observed in mice. In female mice, no effects on estrous cycle or cyclicity were observed. When pregnant rats and mice were treated with TCEP during gestation, no development toxicity or teratogenicity was observed.

TDCPP

No male reproductive effects were observed in rabbits. There is a data gap for the female reproductive health endpoint as no studies were identified. No developmental toxicity effect or neurodevelopmental toxicity effects were observed in pups at dose levels below which maternal toxicity was observed in pregnant rats that were treated with TDCPP during gestation.

Based on animal toxicity studies, it was found that treatment of TCPP, TCEP and TDCPP do not exhibit similar reproductive and developmental health effects.

Appendix H: Benchmark Dose (BMD) Modelling and Identification of a Point of Departure for TDCPP Cancer Risk Characterization

General Methodology

The US EPA Benchmark Dose Software (BMDS2.4) (US EPA 2014) was used to calculate the benchmark dose (BMD) and the corresponding lower limit of a one-sided 95% confidence interval (BMDL) for characterization of the cancer risk associated with chronic exposure to TDCPP. The BMD approach, which includes dose-response modelling, provides a quantitative alternative to the dose-response assessment which first defines the point of departure (POD), and then extrapolates the POD for relevance to human exposure. A dichotomous restricted model type is chosen for the BMD and BMDL analysis. A benchmark response of 10% extra risk above predicted background response for dichotomous data is chosen because 10% is at or near the limit of sensitivity in most cancer bioassays. In animal cancer studies, BMD_{10} refers to a dose of a substance that produces a 10% increase in the response rate of tumour relative to the background response rate of this tumour. $BMDL_{10}$ refers to a lower one-sided 95% confidence limit on the corresponding benchmark dose (BMD_{10}). BMD_{10} and $BMDL_{10}$ levels are calculated for each tumour dataset from the nine models and a model is selected on the basis of best fit (see details in model section). The parameter of “restrict slope >=1” is applied. Then, the lowest $BMDL_{10}/BMD_{10}$ from various tumour types is chosen as a reasonable conservative estimate for subsequent risk characterization. For derivation of a BMD and BMDL for TDCPP, nine models were applied for analysis of each tumour type (described in Table H1) reported in the Stauffer Chemical Co. (1981a) study. These models included Gamma, Logistic, LogLogistic, LogProbit, Multistage, Multistage-Cancer, Probit, Weibull and Quantal-Linear (see Table H2)

Model Selection

The best-fit model is selected from nine models for each tumour type generally based on the highest P-value of goodness of fit; and the lowest Akaike's Information Criterion (AIC) value (a measure of information loss from a dose-response model that can be used to compare a set of models). A fit was judged adequate based on the goodness-of-fit P-value, scaled residual closest to the BMR (10% extra risk) and visual inspection of the model fit. A goodness-of-fit P-value > 0.1 and an absolute value of scaled residual of interest (SRI); represents observed minus predicted response divided by standard errors) <2, is considered to be indicative of an acceptable fit. If the models for a given tumour type were not accepted (e.g., P-values < 0.1), then the results from the high - dose group were omitted and remodelled.

The results for BMD_{10} and $BMDL_{10}$ estimation (mg/kg-bw/d) for tumours induced by TDCPP in the Stauffer Chemical Co. (1981a) study are shown in Table H2.

Table H1. Tumour incidences in Sprague Dawley rats exposed to TDCPP via diet for 2 years (Stauffer Chemical Co. 1981a)

Treatment dose (mg/kg-bw/d)	0	5	20	80
Renal cortical adenoma, male	1/45	3/49	9/48*	32/46*
Testes interstitial cell tumour, male	7/43	8/48	23/47*	36/45*
Hepatocellular adenomas, male	2/45	7/48	1/48	13/46*
Renal cortical adenoma, female	0/49	1/48	8/48*	29/50*
Adrenal cortical adenomas, female	8/48	5/27	2/33	19/49*
Hepatocellular adenomas, female	1/49	1/47	4/46	8/50*

*Statistically significantly different from control animals ($p<0.05$)

Table H2. BMD_{10} and $BMDL_{10}$ calculations (mg/kg-bw/day) for tumours induced by TDCPP in Sprague Dawley rats

Tumours	Model	Number of groups	AIC	P-value	SRI	BMR	BMD_{10} (mg/kg-bw/day)	$BMDL_{10}$ (mg/kg-bw/day)
Renal cortical adenoma, male	Multistage 2	4	141.65	0.98	0.019	0.1	12.24	6.84
Testes interstitial cell tumour, male	LogProbit	4	197.24	0.436	-0.364	0.1	9.07	6.74
Hepatocellular adenomas, male	Multistage 3	4	131.24	0.037	0.048	0.1	59.64	33.87
Renal cortical adenoma, female	LogLogistic	4	125.06	0.972	0.149	0.1	13.87	8.29
Adrenal cortical adenomas, female	Gamma	4	156.47	0.289	0	0.1	66.45	27.89
Hepatocellular adenomas, female	LogLogistic	4	95.21	0.724	0.66	0.1	47.95	26.52

Abbreviations: AIC, Akaike's Information Criterion; BMR, benchmark response; bw/d, body weight per day; SRI, scaled residual of interest