Screening Assessment for the Challenge

Ethanol, 2-chloro-, phosphate (3:1)
(Tris(2-chloroethyl) phosphate [TCEP])

Chemical Abstracts Service Registry Number
115-96-8

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of ethanol, 2-chloro-, phosphate (3:1) (tris(2-chloroethyl) phosphate or TCEP), Chemical Abstracts Service Registry Number 115-96-8. This substance was identified in the categorization of the *Domestic Substances List* as a high priority for action under the Ministerial Challenge. TCEP was identified as a high priority as it was considered to pose intermediate potential for exposure of individuals in Canada and had been classified by the European Commission on the basis of carcinogenicity. Although TCEP met the ecological categorization criteria for persistence, it did not meet the criteria for potential for bioaccumulation or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of TCEP relates to human health risks.

Based on empirical data for persistence in water, TCEP is expected to be persistent in the environment. However, experimental and modelled data indicate that this substance does not have a high potential to bioaccumulate in the environment. The substance therefore meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*.

According to information reported under section 71 of CEPA 1999, TCEP was imported into Canada in 2006 in a quantity ranging between 100 000 and 1 000 000 kg. TCEP is used as a plasticizer and viscosity regulator with flame-retardant properties in polyurethanes, polyester resins, polyacrylates and other polymers. These polymers may be used in furniture, building (e.g., roofing insulation) and textile industries (e.g., back-coatings for carpets and upholstery), in some electronic products and in the manufacture of cars.

TCEP has been identified in indoor and outdoor air, dust, drinking water, surface water and groundwater, as well as in various food products. It has also been detected in polyurethane foam that may be found in furniture or mattresses in Canadian homes.

Based on weight of evidence–based assessments of international and other national agencies and taking into consideration more recent data, the critical effects for the characterization of risks to human health for TCEP are carcinogenicity and impaired fertility. Carcinogenic effects included kidney tumours in rats and mice; thyroid tumours in rats; and liver, forestomach and Harderian gland tumours and leukemia in mice. Mixed results were obtained in the limited *in vivo* and *in vitro* genotoxicity assays in mammalian cells. However, based on the range of tumours observed in multiple species of experimental animals for which the modes of induction have not been elucidated, it cannot be precluded that TCEP induces tumours via a mode of action involving direct interaction with genetic material.

Non-neoplastic effects were also observed in the liver and kidneys of rats and mice in short-term repeated-dose and long-term studies. In addition, TCEP impaired fertility in mice and induced testicular toxicity in both mice and rats. Based on comparison of

estimated exposures to TCEP in Canada with the critical effect level for non-cancer effects, a dose that was also associated with increased incidences of tumours in a long-term study in rats, and taking into account the uncertainties in the databases on exposure and effects, it is considered that the resulting margins of exposure may not be adequately protective of human health.

On the basis of the carcinogenic potential of TCEP, for which there may be a probability of harm at any exposure level, as well as the potential inadequacy of the margins between estimated exposure and critical effect levels for non-cancer effects, it is concluded that TCEP is a substance that may be 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.

On the basis of ecological hazard and the potential for environmental exposure to TCEP, it is concluded that TCEP is 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. TCEP meets the criteria for persistence but does not meet the criteria for bioaccumulation set out in the *Persistence and Bioaccumulation Regulations*.

This substance will be included in the *Domestic Substances List* inventory update initiative. In addition, and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, it is concluded that TCEP meets one or more of the criteria set out in section 64 of CEPA 1999.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List for further assessment or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), which challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance ethanol, 2-chloro-, phosphate (3:1) (tris(2-chloroethyl) phosphate or TCEP) was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by another agency on the basis of carcinogenicity.

The Challenge for TCEP was published in the *Canada Gazette* on February 16, 2008 (Canada 2008). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although TCEP was determined to be a high priority for assessment with respect to human health and also met the ecological categorization criteria for persistence, it did not

meet the criteria for potential for bioaccumulation or inherent toxicity to aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as "toxic" as set out in section 64 of the Act, where

> 64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
> (*c*) constitute or may constitute a danger in Canada to human life or health.

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents and stakeholder research reports and from recent literature searches, up to May 2009. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritizing the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

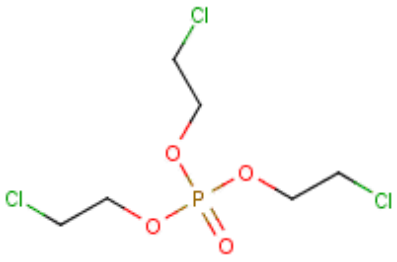
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment, including Harlee Strauss (H. Strauss Associates, Inc.), Michael Jayjock (The Lifeline Group) and Susan Griffin (US Environmental Protection Agency). Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Although external comments were taken into consideration, the final content and conclusions of the screening risk assessment remain the responsibility of Health Canada and Environment Canada.

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

Substance Identity

For the purposes of this document, this substance will be referred to as TCEP, which has been derived from the chemical name tris(2-chloroethyl) phosphate.

Table 1. Substance identity of TCEP

CAS RN	115-96-8
DSL name	Ethanol, 2-chloro-, phosphate (3:1)
NCI names	Ethanol, 2-chloro-, phosphate (PICCS) Ethanol, 2-chloro-, phosphate (3:1) (AICS, ASIA-PAC, DSL, ENCS, PICCS, SWISS, TSCA) Tris(2-chloroethyl) phosphate (EINECS, PICCS) Tri(2-chloroethyl)phosphate (ECL)
Other names	3CF; Amgard TCEP; CEF; Celluflex CEF; CLP; Disflamoll TCA; Fyrol CEF; Fyrol CF; Genomoll P; Niax 3CF; Niax Flame; NSC 3213; Retardant 3CF; TCEP; Tri(β-chloroethyl) phosphate; Tri(2-chloroethyl) phosphate; Tri(chloroethyl) phosphate; Tris(β-chloroethyl) phosphate; Tris(2-chloroethyl) orthophosphate; Tris(chloroethyl) phosphate
Chemical group	Discrete organics
Chemical subgroup	Alkyl phosphate esters
Chemical formula	$C_6H_{12}Cl_3O_4P$
Chemical structure	
SMILES	O=P(OCCCl)(OCCCl)OCCCl
Molecular mass	285.49 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SMILES, simplified molecular input line entry specification; SWISS, Swiss Giftliste 1 and Inventory of Notified New Substances; TSCA, Toxic Substances Control Act Chemical Substance Inventory.
Source: NCI 2006

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of TCEP that are relevant to its environmental fate.

Table 2. Physical and chemical properties of TCEP

Property	Type	Value	Temperature (°C)	Reference
Melting point (°C)	Experimental	−55 to −60		ECB 2000
Boiling point (°C)	Experimental	145–202 (at 66–1333 Pa)		ECB 2000
Density (kg/m^3)	Experimental	1420	20–25	ECB 2000
Vapour pressure (Pa)	Experimental	<10	20	ECB 2000
	Modelled	0.05	25	MPBPWIN 2000
Henry's Law constant (Pa·m^3/mol)	Modelled	0.33 (3.29×10^{-6} atm·m^3/mol)[1]		PhysProp 2008
	Modelled	2.58×10^{-3} (2.55×10^{-8} atm·m^3/mol)[1]	25	HENRYWIN 2000
Log K_{ow} (dimensionless)	Experimental	1.47–1.78	20	ECB 2000
	Modelled	1.63	25	KOWWIN 2000
Water solubility (mg/L)	Experimental	7820	20	ECB 2000
	Modelled	877.9	25	WSKOWWIN 2000
Log K_{oc} (dimensionless)	Modelled	2.408		PCKOCWIN 2000

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

[1] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.

Sources

TCEP does not occur naturally in the environment. This substance is produced by reacting phosphorus oxychloride with ethylene oxide and requires subsequent purification (IARC 1990; IPCS 1998).

Based on a survey conducted under section 71 of CEPA 1999, no Canadian companies reported manufacturing TCEP in a quantity greater than or equal to the 100 kg reporting threshold in 2006. However, results from the same survey and from voluntary data submitted by industry indicate that the total quantity of TCEP imported into Canada in 2006 was in the range of 100 000–1 000 000 kg (Environment Canada 2008a, b).

Uses

According to submissions made under section 71 of CEPA 1999, TCEP is used in Canada as a flame retardant in polyurethane foams, which are used in automotive applications, as a flame retardant in adhesives and in fire-resistant coatings (Environment Canada 2008a). TCEP was also reported as being used as a plasticizer in thermoplastic resins in Canada (Environment Canada 2008a).

Based on available scientific and technical literature, TCEP is used primarily as a plasticizer and viscosity regulator with flame-retardant properties for polyurethanes, polyester resins, polyacrylates, polyvinyl chloride, cellulose derivatives and other polymers (IARC 1990; EURAR 2006). Polymer products containing TCEP are used in furniture, building (e.g., roofing insulation) and textile industries (e.g., back-coatings for carpets and upholstery); in the manufacture of cars, railway cars and aircraft; in polyvinyl chloride compounds; in flame-resistant paints and varnishes and epoxy, phenolic and amino resins; and in wood resin composites, such as particleboards, adhesives and lacquers; and in some electronic products (IARC 1990; IPCS 1998; Malmgren-Hansen et al. 2003; EURAR 2006; OECD 2006).

TCEP was historically used in the production of rigid and flexible polyurethane foams and systems but has been substituted with other flame-retardant substances (IPCS 1998; EURAR 2006). TCEP is not recommended for use as a flame retardant in fabrics meant for apparel (IARC 1990; IPCS 1998).

Releases to the Environment

Information reported under section 71 of CEPA 1999 indicated that 7 kg of TCEP was released into sanitary sewers in 2006 (Environment Canada 2008a).

Releases of TCEP are not currently reportable under the National Pollutant Release Inventory (NPRI 2006) or to the US Toxics Release Inventory (TRI 2006).

TCEP may be released during formulation and processing mainly into wastewater and, to a lesser extent, exhaust gases (OECD 2006). It may also be released into the environment during use by consumers of products containing the substance and when disposed of in landfills. Significant leaching from landfills is possible as a result of TCEP's high water solubility (OECD 2006). TCEP has been found in various water systems and landfill leachate (Ishikawa et al. 1985; Yasuhara 1994; Scott et al. 1996; IPCS 1998; Yasuhara et al. 1999; Fries and Püttmann 2003; Andresen et al. 2004).

Environmental Fate

As indicated in Table 2, TCEP has a high water solubility (7820 mg/L), a moderate vapour pressure (0.05 Pa), a low to very low Henry's Law constant (2.58×10^{-3} to 0.33 $Pa \cdot m^3/mol$), a low log K_{ow} (1.47) and a low log K_{oc} (2.4). Based on its physical and chemical properties (Table 2) and the results of Level III fugacity modelling (Table 3), TCEP is expected to reside predominantly in water or soil, depending on the compartment of release. Entry into the environment would most likely be predominantly from wastewater, so TCEP would probably reside mostly in water.

Table 3. Results of Level III fugacity modelling (EQC 2003) for TCEP

Substance released to:	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air (100%)	0.6	26.1	73.3	0.1
Water (100%)	0.0	99.7	0.0	0.2
Soil (100%)	0.0	22.3	77.7	0.1

Persistence and Bioaccumulation Potential

Environmental Persistence

Empirical and modelled data concerning the persistence of TCEP in different environmental media are shown in Tables 4 and 5, respectively.

Table 4. Empirical data for persistence of TCEP

Medium	Fate process	Degradation value	Endpoint (units)	Reference
Water-	Biodegradation	4	BOD (%) 28 days	MITI 1992
Water	Biodegradation	<10	Biodegradation (%) 27 days	Hoechst AG 1985 (OECD TG 302 B)
Water	Biodegradation	15	Biodegradation (%) 21 days	Hoechst AG 1978 (OECD TG 302 B)
Water	Biodegradation	13 (10 mg/L) 4 (20 mg/L)	Biodegradation (%) 28 days	Akzo Chemicals 1990a (OECD TG 301 B)
Water	Hydrolysis	3980	Half-life (days) (pH 7)	Brown et al. 1975
Soil	Primary degradation	167	Half-life (days)	Römbke et al. 1995
Sewage sludge	Biodegradation (anaerobic)	0	Biodegradation (%) 58 days	Noack 1993

Abbreviations: BOD, biological oxygen demand; OECD TG, Organisation for Economic Co-operation and Development Test Guideline.

Table 5. Modelled data for degradation of TCEP

Fate process	Model and model basis	Model output	Expected half-life (days)
Air			
Atmospheric oxidation	AOPWIN 2000	$t_{½}$ = 5.8 h	<2
Ozone reaction	AOPWIN 2000	n/a[1]	n/a
Water			
Hydrolysis	HYDROWIN 2000	n/a[1]	n/a
Biodegradation (aerobic)	BIOWIN 2000 Submodel 3: Expert Survey (ultimate biodegradation)	2.20	>60

Biodegradation (aerobic)	BIOWIN 2000 Submodel 4: Expert Survey (primary biodegradation)	3.60	<182
Biodegradation (aerobic)	BIOWIN 2000 Submodel 5: MITI linear probability	0.32	<182
Biodegradation (aerobic)	BIOWIN 2000 Submodel 6: MITI non-linear probability	0.02	>182
Biodegradation (aerobic)	CATABOL ©2004–2008 % BOD	0.50	<182

Abbreviations: BOD, biological oxygen demand; MITI, Ministry of International Trade & Industry, Japan; $t_{½}$, half-life.
[1] Model does not provide an estimate for this type of structure.

Although experimental data on the degradation of TCEP are available, a quantitative structure–activity relationship (QSAR)-based weight of evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 5. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that TCEP is expected to be released to this compartment, biodegradation in water was examined primarily. The resulting model estimates are, however, equivocal, some indicating potential for persistence and others not.

The empirical results (Table 4), on the other hand, consistently indicate that the ultimate biodegradation half-life in water is longer than 182 days (6 months). Based mainly on these empirical data, TCEP is therefore likely to persist in water.

In air, a predicted atmospheric oxidation half-life value of 0.486 day (see Table 5) demonstrates that this substance is likely to be rapidly oxidized. The substance is not expected to react appreciably with other photo-oxidative species in the atmosphere, such as ozone, nor is it likely to degrade via direct photolysis. Therefore, it is expected that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for TCEP. With a half-life of 0.486 day via reactions with hydroxyl radicals, TCEP is considered not persistent in air.

Based mostly on the empirical and modelled data and using an extrapolation ratio of 1:1:4 for a water:soil:sediment biodegradation half-life (Boethling et al. 1995), the ultimate degradation half-life in soil is >182 days, and the half-life in sediments is >365 days. This indicates that TCEP is expected to be persistent in soil and sediment.

In summary, based on the empirical and modelled data (see Tables 4 and 5 above), TCEP meets the persistence criteria in water, soil and sediment (half-lives in soil and water ≥182 days and half-life in sediment ≥365 days), but does not meet the persistence criterion in air (half-life in air ≥2 days), as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

Experimental and modelled log K_{ow} values for TCEP (Table 2) indicate that this chemical has a low potential to bioaccumulate in the environment. The reported experimental bioconcentration factor (BCF) values in fish (Table 6) range from 0.7 to 3.16 L/kg.

Table 6. Empirical data for bioaccumulation of TCEP

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish (*Cyprinus carpio*)	BCF	0.7–3.16	MITI 1992
Fish (*Carassius auratus*)	BCF	0.7–0.9	Sasaki et al. 1981
Fish (*Oryzias latipes*)	BCF	2.19	Sasaki et al. 1981

QSAR modelled bioaccumulation factor (BAF) and BCF values agree quite well with the experimental values (Table 7). The modified Gobas BAF middle trophic level model produced a BAF of 1.16 L/kg, indicating that TCEP has a low potential to bioconcentrate and biomagnify in the environment. The four BCF models also provide a weight of evidence to support the low bioconcentration potential of this substance.

Table 7. Modelled data for bioaccumulation

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish	BAF	1.16	Arnot and Gobas 2003 (Gobas BAF T2MTL)
Fish	BCF	1.16	Arnot and Gobas 2003 (Gobas BCF T2LTL)
Fish	BCF	31.91	OASIS Forecast 2005
Fish	BCF	0.4486	BCFWIN 2000
Fish	BCF	1.37	ACD 2008

The modelled bioaccumulation values do not take into account the metabolism potential of the substance. However, both the experimental BCF values and the modelled values indicate that this substance has a low potential for bioaccumulation, and therefore the exclusion of metabolism in the models is not likely to change the bioaccumulation conclusions for this substance.

The weight of evidence indicates that TCEP does not meet the bioaccumulation criteria (BCF or BAF ≥5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

As indicated previously, TCEP meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Ecological Effects Assessment

There is experimental evidence that TCEP is not acutely lethal to aquatic organisms at concentrations below 1 mg/L (Table 8).

Table 8. Empirical data for aquatic toxicity of TCEP

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish (*Oryzias latipes*)	Acute (48 h)	LC_{50}	190	MITI 1992
Fish (*Oncorhynchus mykiss*)	Acute (96 h)	LC_{50}	249	Akzo Chemicals 1990b
Alga	Acute (48 h)	EC_{50}	5.0	Akzo Chemicals 1992

Abbreviations: EC_{50}, concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC_{50}, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

A range of aquatic toxicity predictions were also obtained from the various QSAR models considered. Table 9 lists those predictions that were considered reliable and were used in the QSAR weight of evidence approach for aquatic toxicity (Environment Canada 2007). These modelled and experimental results (acute LC_{50}s ranging from 3.17 to 1030 mg/L) indicate that the substance poses a low to moderate hazard to aquatic organisms.

Table 9. Modelled data for aquatic toxicity of TCEP

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 h)	LC_{50}	1030	OASIS Forecast 2005
Fish	Acute (96 h)	LC_{50}	3.17	AIES 2003–2005
Fish	Acute (96 h)	LC_{50}	68.2	ECOSAR 2004
Daphnia	Acute (48 h)	EC_{50}	493	ECOSAR 2004

Abbreviations: EC_{50}, concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC_{50}, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Ecological Exposure Assessment

Environmental releases reported by industry pursuant to section 71 of CEPA 1999, were very low in 2006.

Concentrations of TCEP in air, surface water and groundwater are presented in the Potential to Cause Harm to Human Health section under "Environmental Media."

The highest concentration reported for surface water is 1236 ng/L (1.236×10^{-3} mg/L) in the Oder River at Frankfurt, Germany, in July 2001 (Fries and Püttmann 2003). The highest concentration reported for TCEP in surface water in Canada is 9.4 ng/L (9.4×10^{-6} mg/L) in the Great Lakes Basin (Scott et al. 1996). The predicted environmental concentration (PEC) based on Canadian data is 9.4×10^{-6} mg/L.

EURAR (2006) estimated local water concentrations ranging from 0.006 to 0.037 mg/L, based on estimated releases from various industries and assuming a dilution factor of 10.

The highest estimate pertained to processing losses from the paints and varnishes industry.

Characterization of Ecological Risk

Based on the available information, TCEP is persistent in the environment and is not bioaccumulative, based on criteria defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000). The experimental and modelled ecotoxicological data indicate that TCEP poses a low to moderate hazard to aquatic organisms.

As presented above, the PEC based on Canadian data is 9.4×10^{-6} mg/L.

From the experimental aquatic toxicity data presented in Table 8 above, algae are the most sensitive organisms, with a 48-h EC_{50} of 5.0 mg/L. Dividing this value by an assessment factor of 100 to account for inter- and intraspecies variability in sensitivity and to derive a long-term no-effects concentration from a short-term toxicity test gives a predicted no-effects concentration (PNEC) of 0.05 mg/L.

The reasonable worst-case risk quotient based on Canadian exposure data is therefore PEC/PNEC = 9.4×10^{-6} mg/L / 0.05 mg/L = 0.000 19. Although it is possible that concentrations in Canadian surface waters are higher than 9.4×10^{-6} mg/L close to point industrial sources, based on the local water concentrations of up to 0.037 mg/L estimated in EURAR (2006), near-source concentrations are also likely to be below the PNEC.

Therefore, taking into consideration this risk quotient and information on TCEP's fate and potential for toxicity, TCEP is unlikely to cause harm to sensitive aquatic organisms in Canada.

Uncertainties in Evaluation of Ecological Risk

Regarding toxicity, the only effects data identified apply primarily to pelagic aquatic exposures. Wastewater is the most likey route of entry into the environment for TCEP, so the substance would be expected to reside mostly in water, based on fugacity modelling.

Although there is potential for relatively fast primary degradation, there is uncertainty associated with the model predictions, and the identity of the transformation products is unknown. The estimated potential for persistence of TCEP is conservatively based mostly on the empirical data for ultimate degradation. It is possible that TCEP can be degraded (primary) by oxidative dealkylation in soil organisms. This would limit the persistence of the substance in soil.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media

TCEP has been measured in various environmental media in Canada, Japan and Europe. Although no data on concentrations of TCEP in ambient or indoor air in Canada were identified, TCEP was measured in ambient air in Japan and Sweden. The maximum outdoor air concentration of TCEP identified was measured outside a home in Japan (58.4 ng/m^3; geometric mean concentration 14.3 ng/m^3) (Ohura et al. 2006), and this concentration was used to estimate upper-bounding estimates of intake of TCEP from ambient air (Appendix 1). However, the results of other studies indicated that concentrations of TCEP in outdoor air are generally lower (less than 1 ng/m^3) (Carlsson et al. 1997; Saito et al. 2007).

Concentrations of TCEP in indoor air have been measured in homes (not detected to 380 ng/m^3; detection limits not specified to 3.9 ng/m^3), offices (not detected to 870 ng/m^3; detection limits not specified to 3.9 ng/m^3), schools (18–6000 ng/m^3; detection limits not specified), day care facilities (2.5–144 ng/m^3; detection limits not specified to 3.9 ng/m^3), transport vehicles such as cars (not detected to 320 ng/m^3; detection limits 0.15–<1 ng/m^3) and various other settings in multiple studies from Japan, Sweden, Switzerland or Germany (Carlsson et al. 1997; Hansen et al. 2001; Ingerowski et al. 2001; Otake et al. 2001, 2004; Hartmann et al. 2004; Marklund et al. 2005; Staaf and Östman 2005; Ohura et al. 2006; Saito et al. 2007). The presence of TCEP appears to be primarily due to emissions from indoor sources. The maximum concentration of TCEP measured in homes was 380 ng/m^3 in Japan (mean concentration 20 ± 70 ng/m^3) (Otake et al. 2004). The maximum concentration of TCEP identified in the literature was 6000 ng/m^3 in a school in Germany (mean concentration from homes, schools and businesses was 52 ng/m^3), where an acoustic ceiling contained 68 000 mg TCEP/kg (Ingerowski et al. 2001). This value is not considered to represent a typical indoor air concentration, and therefore the maximum concentration from homes (380 ng/m^3) in Japan was used to estimate upper-bounding intakes of TCEP from indoor air (Appendix 1).

Concentrations of TCEP in drinking water in Canada were reported in three studies conducted in the early 1980s (LeBel et al. 1981; Williams and LeBel 1981; Williams et al. 1982). Concentrations of TCEP ranged from not detectable to 52 ng/L. The maximum value (52 ng/L) was used to estimate upper-bounding intakes of TCEP from drinking water (Appendix 1). TCEP has been detected in surface waters from Canada, Germany, Japan, Italy and the United States (Ishikawa et al. 1985; Guzella and Mingazzini 1994; Scott et al. 1996; Slobodník et al. 1997; Guzella and Sora 1998; Fries and Püttmann 2001, 2003; Kolpin et al. 2002; Andresen et al. 2004; Andresen and Bester 2006; Kim et

al. 2007; Quednow and Püttmann 2008). TCEP concentrations in Canadian surface waters ranged from 0.2 to 9.4 ng/L (Scott et al. 1996), and the maximum concentration of 1236 ng/L was measured in river water from Germany (Fries and Püttmann 2003).

TCEP was also measured in groundwater in Germany and Japan (Yasuhara 1994; Fries and Püttmann 2001, 2003). The concentrations ranged from not detectable to 754 ng/L. This substance has also been measured in rain (Scott et al. 1996; Laniewski et al. 1998; Fries and Püttmann 2001, 2003), with levels in Canada ranging from not detectable to 52.3 ng/L (Scott et al. 1996). In addition, TCEP was measured in sediment in Japan in the late 1970s at concentrations up to 0.07 mg/kg (Ishikawa et al. 1985; IPCS 1998).

TCEP has also been measured in dust in homes, schools, hospitals and various other locations in Sweden and Germany (Hansen et al. 2001; Ingerowski et al. 2001; Marklund et al. 2003). Concentrations range from less than 10 to 2200 mg/kg, with the highest concentration being found in schools (Hansen et al. 2001). The maximum concentration identified in a home was 44 mg/kg (Hansen et al. 2001). This value was used to estimate upper-bounding intakes of TCEP from dust (soil) via ingestion. Dermal exposure to household dust was also estimated (see Appendix 3).

There are no approved or cleared food uses for TCEP in Canada (2009 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced), and no Canadian-specific data on concentrations of TCEP in food items have been identified. However, TCEP was detected in various food items in a total diet study conducted by the US Food and Drug Administration (US FDA 2006a), as summarized in Appendix 2. TCEP was also measured in one composite fruit and fruit juice sample from infant foods at a concentration of 0.2 µg/kg in a food survey conducted on infant and toddler diets from October 1979 to September 1980 in the United States (Gartrell et al. 1985; IPCS 1998). TCEP was also measured in one sample of oils and fats from toddler foods sampled in 1980–1982 at a concentration of 38.5 µg/kg (Gartrell et al. 1986; IPCS 1998). Furthermore, TCEP has been identified in fish and shellfish in Japan, with concentrations ranging from not detected (detection limits not specified) to 90 µg/kg (Yasuhara and Morita 1987; IPCS 1998). Concentrations of TCEP in the various food items identified in the US total diet study varied from year to year. In light of the infrequent detection of TCEP (e.g., it was present in only 1 or 2 samples out of 44 examined, and representing samples of approximately 285 foods collected and analysed in 44 market baskets between 1991 and 2003), the mean concentrations were used to calculate upper-bounding estimates of food intake for the general population in Canada (Appendix 1). It was assumed that TCEP was present at the detection limit in items in which it was not detected; however, since the limits of detection were not available, the lowest detected concentration of TCEP in all of the foodstuffs examined was used as a surrogate for the detection limit in the calculation of the mean values. For all these reasons, dietary estimates based on the total diet samples from the United States are considered to be very conservative.

Analyses were conducted for TCEP in human adipose tissue in several Canadian cities; however, TCEP was not detected in any sample (detection limit of 1 ng/g) (LeBel et al.

1989). TCEP was measured in human adipose tissue in the United States, although actual levels detected were not specified (Phillips and Birchard 1991).

Upper-bounding estimates of intake of TCEP for each age group in the general population of Canada, based on the information listed above, are presented in Appendix 1. The upper-bounding estimate of daily intake for the general Canadian population ranges from 0.09 µg/kg body weight (kg-bw) per day for adults aged 60+ years to 0.5 µg/kg-bw per day for children aged 0.5–4 years. Dermal exposure to dust was also estimated, with values ranging from 0.4 to 0.5 µg/kg-bw per day (see Appendix 3). These values likely overestimate intake, however, as 100% dermal absorption was assumed due to the lack of chemical-specific data. Based on these estimates, exposures to indoor air and dust represent the predominant sources of exposure for the general population.

Consumer Products

TCEP is used as a plasticizer and viscosity regulator with flame-retardant properties in several types of plastics, such as polyurethanes and polyester resins (EURAR 2006), and may therefore be present in various consumer products. Exposure to TCEP could potentially occur due to "blooming," which refers to the diffusion of an ingredient in rubber or plastic material to the outer surface after curing (NICNAS 2001). Various factors, such as size and shape of a molecule, temperature and volatility, affect the rate at which blooming occurs (NICNAS 2001). Trisphosphates in general are known to bloom from car interior plastics, televisions and computer monitors; however, it is difficult to derive actual estimates of blooming potential (NICNAS 2001).

TCEP was measured in various finished products in Germany (Ingerowski et al. 2001), as summarized in Table 10.

Table 10. Concentrations of TCEP in various products (Ingerowski et al. 2001)

Materials	Concentration in product (mg/kg)
Wood preservation coatings	10 000
Mattresses (polyurethane)	890
Wall paper (glass fibre)	2 400
Polyurethane soft foam	19 800
Foam fillers (polyurethane)	32 000
Acoustic ceiling (coating)	68 000

Migration rates from interior surfaces of a newly built house and from the surface of television sets and computer monitors were measured in Japan (Saito et al. 2007). TCEP was not detected in the floor, wall or ceiling of the newly built house or in emissions from computer monitors. It was, however, measured on the surface of eight television sets, with a mean migration rate of 1.4 µg/m^2 per hour (range of not detected [method detection limit 0.23 µg/m^2 per hour] to 13 µg/m^2 per hour) (Saito et al. 2007). TCEP was also measured in five samples of soft polyurethane foam samples, with levels ranging from not detected (detection limit of 0.6µg/g) to 3.1 µg/g (Nagase et al. 2003).

The Danish Environmental Protection Agency (EPA) of the Danish Ministry of Environment has published four studies containing information on concentrations of TCEP in consumer products. Eight different toys produced from foam plastic were analysed for TCEP; however, the substance was not detected above the 50 mg/kg detection limit (Borling et al. 2006). TCEP was measured in another Danish EPA study on toys and children's products. Four out of the five products sampled did not contain TCEP at levels above the detection limit (not specified). It was detected in a soft cube toy for children made of textile, plastic and foam rubber at levels ranging from 4900 to 6500 mg/kg; however, this product is no longer available in Denmark (Glensvig and Ports 2006). In a study on chemicals found in electrical and electronic products, TCEP was detected in emissions from television sets at rates of <0.01–0.3 µg/h per set (sample size of 10). It was also detected in emissions from video recorders at rates of <0.01–0.08 µg/h per unit (sample size of 10) (Malmgren-Hansen et al. 2003). In a Danish EPA investigation of chemical substances in baby products, TCEP was not detected above the detection limit of 1 µg/g in any of the six products sampled (Tønning et al. 2008).

Based on the information above, the general population of Canada is potentially exposed to TCEP from consumer products that contain polyurethane foam, such as furniture or mattresses, and from electronic equipment (mainly television sets). Emissions from upholstered furniture and from television sets may contribute to TCEP levels in indoor air. However, some of these products may also be sources of oral or dermal exposures to TCEP. Estimates of exposure to TCEP from children mouthing foam were derived and are presented in Appendix 4. The highest consumer product exposure estimates are for infants (0–6 months old) and toddlers (6 months to 4 years old) mouthing foam containing TCEP (0.04 mg/kg-bw per day for infants and 0.02 mg/kg-bw per day for toddlers) (based on the application of methodology developed for another flame retardant by the US Environmental Protection Agency's Voluntary Children's Chemical Evaluation Program; Environ 2003a, b).

Dermal contact while sitting on upholstered furniture containing TCEP could also contribute to exposures to the substance, although insufficient data are available with which to quantify exposure via this route. However, NRC (2000) has estimated dermal exposures of 0.003 mg/kg-bw per day and 1.5 mg/kg-bw per day for substances similar to TCEP, tris(1,3-dichloropropyl-2)phosphate and tris monochloropropyl phosphate, respectively, which suggests that dermal exposure from sitting on furniture containing TCEP may occur. Other scenarios, such as the use of video recorders and wood preservative coatings, may contribute to exposure to TCEP, although available information is insufficient to allow quantitative estimates to be derived.

Confidence in the exposure database for environmental media is considered to be moderate, as several studies were available for the various media; however, the majority of the information is not specific to Canada. However, confidence in the intake estimates from food would be considered low taking into account the low number of total diet samples in which TCEP was detected, using the mean of these few positive samples and assigning at least the detection limit to what were mostly non-detects in the total diet dataset. There is low confidence in the modelled estimates of exposure from consumer

products, as there is a lack of data on specific types of products containing TCEP found in Canada and on the various chemical-specific parameters needed to estimate exposures to consumer products. Dermal exposures to consumer products were not quantified owing to the lack of relevant data.

Health Effects Assessment

Appendix 5 contains a summary of the available health effects information for TCEP.

The European Commission has classified TCEP as Category 3 for carcinogenicity (*causes concern for humans owing to possible carcinogenic effects*) (European Commission 1996, 1999; ESIS [date unknown]), whereas the International Agency for Research on Cancer has classified it as Group 3 (*not classifiable as to its carcinogenicity to humans*) (IARC 1990, 1999).

TCEP induced tumours at multiple sites in both rats and mice. In 2-year studies in rats and mice dosed orally with TCEP, increased incidences of renal tubule adenomas (both sexes of rats, male mice), renal tubule carcinomas (male mice) and leukemia (female mice) were observed. In addition, increased incidences of thyroid follicular adenomas or carcinomas (females) were observed in rats, and increased incidences of hepatocellular adenoma and carcinoma (males), forestomach papilloma and squamous cell carcinoma (females) and Harderian gland adenomas and carcinomas (females) were observed in mice. In rats, the renal tubule tumours showed a dose-related increase at 44 and 88 mg/kg-bw per day: in mice, these tumours showed increases in incidence at doses of 300 and 1500 mg/kg-bw per day (Takada et al. 1989; NTP 1991; Matthews et al. 1993). The non-neoplastic effects included a dose-related increase in renal tubule hyperplasia in both sexes of rats. Also, gliosis, hemorrhage, hemosiderosis and mineralization in the cerebrum and brain stem were observed in female rats at the highest dose (88 mg/kg-bw per day). A dose-related increase in the occurrence of karyomegaly in the renal tubule epithelial cells was observed in mice in the NTP (1991) study. The lowest-observed-adverse-effect level (LOAEL) for non-neoplastic effects was 44 mg/kg-bw per day, based on renal tubule hyperplasia in the 2-year rat study (NTP 1991; Matthews et al. 1993). Non-neoplastic kidney lesions were also reported in the 18-month oral mouse study, but there was insufficient information in the report with which to derive a non-neoplastic LOAEL for these effects (Takada et al. 1989).

No significant increase in tumours was observed in carcinogenicity studies in mice dermally administered TCEP (Sala et al. 1982; Takada et al. 1991). Long-term inhalation studies using TCEP were not identified.

In a 16-day oral rat study, absolute and relative kidney weights were increased in males and serum cholinesterase activities were decreased in females at 175 and 350 mg TCEP/kg-bw per day. In 16- to 18-week oral studies in rats and mice, absolute and relative liver and kidney weights were increased in female rats, whereas absolute liver weights were increased and absolute kidney weights were decreased in female mice at doses of 44 mg TCEP/kg-bw per day and higher. Also, decreased serum cholinesterase

activity and neuronal necrosis in the hippocampus of the brain were observed in female rats at 175 and 350 mg/kg-bw per day. The lowest-observed-effect level (LOEL) was considered to be 44 mg/kg-bw per day, based on increased relative liver and kidney weights in females in the 16-week rat study (NTP 1991; Matthews et al. 1993).

TCEP was not mutagenic in most bacterial mutation assays using *Salmonella typhimurium* and one forward mutation assay in Chinese hamster cells (Simmon et al. 1977; Nakamura et al. 1979; Haworth et al. 1983; NTP 1991; Zeiger et al. 1992; Föllmann and Wober 2006). For clastogenicity, most results of in vitro assays were negative, except for the sister chromatid exchange assays in Chinese hamster cells, which were either positive or equivocal with and without activation; equivocal results were also obtained in an *in vivo* micronucleus assay with Chinese hamsters exposed intraperitoneally (Sala et al. 1982; Galloway et al. 1987; Föllmann and Wober 2006). TCEP did not induce somatic cell chromosomal damage in an *in vivo* assay in *Drosophila melanogaster* (Vogel and Nivard 1993).

Fully elucidated modes of action for induction of the observed tumours that have been accepted by other regulatory agencies or have undergone international review have not been identified. As stated by the European Commission (2004), "There is [*sic*] assumed that chronic cell injury may induce persistent cell proliferation that may be responsible for the development of neoplasia. However, a reasonable threshold mechanism could not be identified for all tumors and tumor sites." Although the European Commission (2004) suggested that non-genotoxic mechanisms may be responsible for the renal, liver and Harderian gland tumours, it was recognized that species-specific modes of action had not been identified. Based on observations of other non-neoplastic effects in some organs (kidney, liver) in short- and long-term studies with TCEP, a non-genotoxic mode of action for the induction of tumours in these tissues is plausible. However, the European Commission (2004) did not address the thyroid tumours observed in rats or the forestomach tumours or leukemia observed in mice.

In 2005, the European Union classification and labelling working group (human health) classified TCEP as a reproductive toxicant Category 2 with the following risk phrase: R60 (*may impair fertility*) (EURAR 2006; European Commission 2006). The rationale for this conclusion was based on the reproductive toxicity studies in mice, including crossover mating trials and evaluation of reproductive organs and sperm parameters in subchronic studies (European Commission 2004). These studies, as well as evaluation of rat reproductive parameters, are described below.

In an oral reproductive study in mice using the continuous breeding protocol, decreased numbers of live pups per litter (F_0 and F_1 generations) and decreased numbers of litters per pair (F_0 generation) were observed at 350 and 700 mg TCEP/kg-bw per day. This protocol included crossover mating trials in both sexes at the top dose (700 mg/kg-bw per day), which resulted in adverse effects on sperm in males (decreased numbers, decreased motility and increased percentage of abnormal sperm) but no effects on female estrous parameters (Gulati et al. 1991; Chapin et al. 1997). In 18-week studies on rats and mice, testicular toxicity was observed in both species (decreased relative testes weight and

increased number of abnormal sperm in mice; decreased sperm motility in rats). The LOAEL for reproductive effects was considered to be 700 mg/kg-bw per day in the mouse. Although Gulati and Russell (1985) stated that there was no reproductive or testicular toxicity in the 18-week study in rats orally administered TCEP at levels of 0, 22, 88 or 175 mg/kg-bw per day, a subsequent analysis of this study by Morrissey et al. (1988), showed decreased sperm motility, although they did not indicate the doses at which this effect was observed. Thus, a reproductive LO(A)EL cannot be determined for the rat. However, it is noteworthy that the critical effect level for repeated-dose administration in the rat (44 mg/kg-bw per day), as described above, lies between the low and middle doses tested in this study.

Testicular toxicity (decreased sperm counts and motility, increased number of abnormal sperm) was also observed in male mice exposed to TCEP by inhalation at concentrations of 0.5 and 1.5 mg/m^3 for 4 months. When exposed males were mated with unexposed females, pre- and post-implantation loss was increased and litter size was decreased at 1.5 mg/m^3 (Shepel'skaya and Dyshinevich 1981).

Developmental toxicity or teratogenicity was not observed in pregnant rats and mice dosed orally with TCEP during gestation (Kawashima et al. 1983a, b; Hardin 1987; Hardin et al. 1987). Maternal toxicity in these studies was observed at 200 mg/kg-bw per day in rats (general weakness and death) and at 940 mg/kg-bw per day in mice (decreased body weight gain and mortality).

In an acute oral neurotoxicity study in rats, a single dose of 275 mg/kg-bw resulted in convulsions, damage to the hippocampus of the brain and learning impairment (Tilson et al. 1990). Acute delayed neurotoxicity and repeated-dose neurotoxicity were not observed in oral studies conducted in hens (Bullock and Kamienski 1972; Sprague et al. 1981).

For many of the effects observed in the majority of the toxicity studies, female rats were more susceptible than male rats; although similar effects were observed in rats and mice, they occurred at higher doses in mice. These sex and species differences may be related to differing rates of metabolism and elimination. Matthews et al. (1990) showed that mice excreted more than 70% of a single oral dose in an 8-hour period compared with 40% in rats and that serum levels in female rats were higher than those in male rats during the first 30 minutes after receiving a single oral dose of TCEP.

The confidence in the toxicity database for TCEP is considered to be moderate, as adequate information is available to address effects that may be of concern and identify critical endpoints based on oral exposures. However, there were only limited data for effects induced via dermal contact and inhalation. Except for a possible acute study, no inhalation data were identified for the rat, the apparently more sensitive species. Also, no clinical human toxicity or epidemiological studies were identified.

Characterization of Risk to Human Health

Based principally on the weight of evidence–based assessment of the European Commission, an important effect of TCEP exposure is carcinogenicity (European Commission 1996, 1999). As shown under the "Health Effects Assessment" section, increased incidences of renal tubule tumours were observed in 2-year oral rat and mouse studies, whereas increased incidences of thyroid follicular tumours were observed in rats and increased incidences of hepatocellular tumours, forestomach and Harderian gland tumours and leukemia were observed in mice. Although TCEP does not appear to be mutagenic based on *in vitro* studies in bacterial and mammalian cells, no *in vivo* mutagenicity study was identified. Also, there is some evidence for clastogenicity based on the equivocal results in an *in vivo* micronucleus test in Chinese hamsters and *in vitro* sister chromatid exchange assays in Chinese hamster cells. Due to the mixed results in the limited *in vivo* and *in vitro* genotoxicity assays in mammalian cells and the range of tumours observed in multiple species of experimental animals for which the modes of induction have not been elucidated, it cannot be precluded that TCEP induces tumours via a mode of action involving direct interaction with genetic material.

With respect to non-cancer effects, the lowest LO(A)EL for short-term and subchronic exposures was 44 mg TCEP/kg-bw per day, based on increased relative liver and kidney weights in a 16-week oral rat study. Renal tubular hyperplasia along with renal tubule and thyroid tumours were also observed at 44 mg/kg-bw per day, the lowest dose tested, in the 2-year study in rats.

Reproductive toxicity has also been observed in several oral studies in rats and mice and in inhalation studies in mice. The oral LOAEL for reproductive effects was 700 mg/kg-bw per day in mice; however, the oral reproductive LOAEL for rats could not be determined due to insufficient information to enable characterization of dose–response in the critical analyses (rats were administered TCEP levels of 0, 22, 88 or 175 mg/kg-bw per day). In the only study in which the toxicity of repeated inhalation exposure to TCEP was examined, testicular toxicity was noted in mice at 0.5 mg/m^3 or more for 4 months.

Comparison of the critical effect level for repeated dosing via the oral route (i.e., 44 mg/kg-bw per day, at which non-cancer effects and significant increases in tumours were observed) and the upper-bounding estimate of daily intake of TCEP by the general population via environmental media in Canada (0.5 µg/kg-bw per day) results in a large margin of exposure of approximately 88 000. If the upper-bounding estimate of dermal exposure to household dust is considered, the resulting margin of exposure would be in the same order of magnitude. Comparison of the only identified effect level for reproductive effects via inhalation (0.5 mg/m^3) and the conservative upper-bounding exposure estimate via inhalation for TCEP in indoor air in private dwellings (0.38 µg/m^3) results in a margin of exposure of approximately 1300, whereas comparison with the average indoor air concentration in these homes (0.02 µg/m^3) results in a margin of exposure of 25 000. However, based on available data, general population exposures via inhalation of indoor air from schools, day care centres, offices, transportation vehicles and other locations may be higher and would result in lower margins of exposure than

those presented for residential settings. Exposure to TCEP may also occur through use of consumer products. Based on product scenario modelling, the highest consumer product exposure estimates were based on infants (0–6 months) and toddlers (6 months to 4 years old) mouthing foam containing TCEP at a concentration equivalent to TCEP's water solubility and resulted in a daily estimated exposure of 0.04 mg/kg-bw per day for infants and 0.02 mg/kg-bw per day for toddlers. Comparison of these conservative estimates with the critical effect level for oral exposure (44 mg/kg-bw per day) results in margins of exposure of 1100 for infants and 2200 for toddlers (who are expected to have greater accessibility than infants).

In light of the uncertainties in the databases on exposure and effects, including the fact that increased incidences of tumours were also observed at the critical effect level for non-cancer effects in oral studies in the more sensitive of two rodent species (44 mg/kg-bw per day in rats), which was the lowest dose tested (i.e., a lower bound on exposure levels associated with effects was not established), it is considered that estimated margins of exposure may not be adequately protective of human health.

Uncertainties in Evaluation of Risk to Human Health

This screening assessment does not include a full analysis of the mode of induction of effects, including cancer, of TCEP, nor does it take into account possible differences between humans and experimental species in sensitivity to effects induced by this substance. Also, as noted above, insufficient information is available with which to adequately characterize oral reproductive toxicity in rats. Similarly, a lower bound on oral exposures associated with toxic effects was not determined in the long-term study in rats, as effects were noted at the lowest dose tested in this species, which was also associated with an increased incidence of tumours. Therefore, margins of exposure between critical effect levels and exposures could be smaller (e.g., if the LOEL for reproductive toxicity in rats would be considered to be the lowest dose tested, the margin of exposure for predicted exposures from some consumer products would be twofold lower). In addition, only limited information is available concerning the potential toxicity of TCEP following inhalation and dermal exposures, routes of relevance to population exposure. In particular, data on the toxicity of inhaled TCEP to rats, the apparently more sensitive species, are lacking.

There is uncertainty regarding the estimation of population exposures because of the use of modelling and the lack of Canadian data. Several studies were available for the various media; however, the majority of the information was not Canadian specific. Indoor air exposures to TCEP may be underestimated, as air concentrations measured in schools and offices were higher in some studies than those measured in private dwellings, and the general population may spend significant amounts of time during the day in these areas. There is uncertainty regarding the estimates of population exposure to TCEP in food, although confidence is high that these estimated intakes are conservative in light of the low frequency of detection of TCEP in very few foodstuffs analysed over a period of more than 10 years. There is uncertainty associated with the potential presence of TCEP in products available in Canada as well as the assumptions incorporated into the consumer product scenario models, such as the quantity and frequency of use in Canada.

Exposures of infants and toddlers to TCEP from mouthing of foam are considered overestimates, as the assumptions incorporated are conservative. In addition, there is some uncertainty regarding how estimates of dermal exposure to household dust relate to overall exposures, although it is likely that actual exposures do not exceed these estimates, as 100% dermal absorption was assumed. Furthermore, there is some uncertainty regarding dermal exposures to consumer products containing TCEP, as insufficient information was available with which to quantify exposures.

Conclusion

Based on the information presented in this screening assessment, it is concluded that TCEP is 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.

On the basis of the carcinogenicity of TCEP, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margins between estimated exposures to TCEP and critical effect levels, it is concluded that TCEP is a substance that may be 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 therefore concluded that TCEP does not meet the criteria in paragraphs 64(a) and 64(b) of CEPA 1999, but it does meet the criterion in paragraph 64(c) of CEPA 1999. Additionally, TCEP meets the criteria for persistence but does not meet the criteria for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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Appendix 1. Upper-bounding estimates of daily intake of TCEP by the general population of Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of TCEP by various age groups							
	0–6 months[1, 2, 3]			0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	Breast milk fed	Formula fed	Not formula fed					
Ambient air[9]	0.002	0.002	0.002	0.004	0.003	0.002	0.002	0.001
Indoor air[10]	0.09	0.09	0.09	0.2	0.2	0.09	0.08	0.07
Drinking water[11]	0.000	0.006	0.002	0.002	0.002	0.001	0.001	0.001
Food and beverages[12]	0.000	0.000	0.01	0.009	0.004	0.002	0.002	0.002
Dust/soil[13]	0.2	0.2	0.2	0.3	0.09	0.02	0.02	0.02
Total intake	**0.3**	**0.3**	**0.3**	**0.5**	**0.3**	**0.1**	**0.1**	**0.09**

1 No data were identified on concentrations of TCEP in breast milk.

2 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (Health Canada 1998).

3 For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of TCEP in water (52 ng/L) used to reconstitute formula was based on a Canadian drinking water study (Williams and LeBel 1981). No data were identified on concentrations of TCEP in formula in Canada or elsewhere. Approximately 50% of non–formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).

4 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 and to ingest 100 mg of soil per day (Health Canada 1998).

5 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 and to ingest 65 mg of soil per day (Health Canada 1998).

6 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 and to ingest 30 mg of soil per day (Health Canada 1998).

7 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 and to ingest 30 mg of soil per day (Health Canada 1998).

8 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 and to ingest 30 mg of soil per day (Health Canada 1998).

9 No Canadian-specific data on concentrations of TCEP in ambient air were identified. The maximum concentration of TCEP identified near homes was 0.0584 µg/m^3 from a Japanese study in which the air outside homes in the summer (25 samples) and winter (21 samples) was sampled (Ohura et al. 2006). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

10 No Canadian-specific data on concentrations of TCEP in indoor air were identified. Concentrations of TCEP were measured in indoor air in various studies from Japan, Germany and Sweden. The maximum concentration of TCEP identified was 0.38 µg/m^3 in a Japanese study in which 27 houses in the Tokyo metropolitan area were sampled (Otake et al. 2004). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

11 The maximum concentration of TCEP identified in Canadian drinking water was 0.052 µg/L from a study in which drinking water from 29 municipalities across Canada was examined (Williams and LeBel 1981). Several other studies on concentrations of TCEP in drinking water and surface water in Canada and elsewhere were identified.

12 No Canadian-specific data on concentrations of TCEP in food items have been identified. Estimates of intake from food are based upon concentrations in foods identified in a total diet study conducted in the United States from 1991–1993 through to 2003–2004 and are shown in Appendix 2 (US FDA 2006a). TCEP was identified in peas, broccoli, green beans, eggplant, sweet cucumber pickles, oatmeal, cream of wheat, rolls, bread, oriental noodle soup, hard candy and various baby foods (peas, turkey and rice, teething biscuits, pears and pineapple) (US FDA 2006a). Samples of the various food

items were analysed 4–44 times, depending on the food item (see reference for details). TCEP was generally detected in only one or two of these samples (for each food category); therefore, a mean was calculated using 0.0006 mg/kg (the lowest detected concentration of TCEP) to represent non-detect values (refer to Appendix 2). Amounts of foods consumed on a daily basis by each age group are described by Health Canada (1998), except for values for eggplant, which were derived from US FDA (2006b). The maximum concentration of TCEP was used for each of the various food items, and total TCEP consumption was calculated for each age group (values in the intake table).

[13] No Canadian-specific data on concentrations of TCEP in soil or dust were identified. No measured concentrations of TCEP were identified in soil; however, concentrations of TCEP were measured in indoor dust in several studies in Germany and Sweden.. The maximum concentration of TCEP measured in dust from homes was 44 000 µg/kg. This value is from a German study of dust in 31 homes (Hansen et al. 2001).

Appendix 2. Concentration of TCEP in various food items (US FDA 2006a) and calculated means[1]

Food item	Maximum (µg/kg)	Minimum (µg/kg)	Mean[2] (µg/kg)	Number of analyses	Number of results ≥ LOQ	Number of traces[3]
Peas, green, frozen, boiled	80	80	1.82	44	1	0
Broccoli, fresh/frozen, boiled	6	6	0.14	44	1	0
Green beans, fresh/frozen, boiled	70	70	1.59	44	1	0
Eggplant, fresh, peeled, boiled	77	77	1.75	44	1	0
Sweet cucumber pickles	2	2	0.05	40	0	1
Oatmeal, plain, cooked	1	1	0.02	44	0	1
Cream of wheat (farina), enriched, cooked	11.4	11.4	2.59	44	1	0
Rolls, white, soft, enriched	3	3	0.08	40	0	1
Bread, cracked wheat	1	1	0.02	44	0	1
Soup, oriental noodles (ramen noodles), prepared with water	29	29	7.25	4	1	0
Baby food, turkey and rice	21	21	0.48	44	1	0
Baby food, peas	1	1	0.02	44	1	0
Baby food, teething biscuits	2	0.6	0.06	44	0	2
Baby food, pears and pineapple	1	1	0.02	44	0	1
Candy, hard, any flavour	1	1	0.02	44	0	1

Abbreviation: LOQ, limit of quantification.

[1] These data represent samples of approximately 285 foods collected and analysed in 44 market baskets between 1991 and 2003

[2] Mean values calculated assuming 0.0006 mg/kg (lowest concentration of TCEP detected in any of the food items) to represent non-detect values.

[3] Traces: number of results that were greater than or equal to the limit of detection but less than the LOQ.

Appendix 3. Upper-bounding estimate of dermal exposure to dust using method from Environ (2003a, b)

Route of exposure	Estimated intake (µg/kg-bw per day) of TCEP by various age groups					
	0–6 months[1]	**0.5–4 years[2]**	**5–11 years[3]**	**12–19 years[4]**	**20–59 years[5]**	**60+ years[6]**
Dermal exposure to dust/soil[7]	0.36	0.27	0.25	0.23	0.25	0.24

[1] Assumed to weigh 7.5 kg (Health Canada 1998), total body surface area of 3680 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor of 0.337 (Environ 2003a, b), adherence rate of dust to skin of 0.05 mg/cm^2 per day and exposure frequency of 24 h/day (Environ 2003a, b). Absorption factor is unknown for TCEP: therefore, it is set to 1.

[2] Assumed to weigh 15.5 kg (Health Canada 1998), total body surface area of 5780 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor of 0.361 (average of 1- to 2-year-olds and 3- to 5-year-olds) (Environ 2003a, b), adherence rate of dust to skin of 0.05 mg/cm^2 per day and exposure frequency of 22 h/day (average of 1- to 2-year-olds and 3- to 5-year-olds) (Environ 2003a, b). Absorption factor is unknown for TCEP: therefore, it is set to 1.

[3] Assumed to weigh 31.0 kg (Health Canada 1998), total body surface area of 9660 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor of 0.368 (average of 6- to 8-year-olds and 9- to 11-year-olds) (Environ 2003a, b), adherence rate of dust to skin of 0.07 mg/cm^2 per day (average of 3- to 5-year-olds, 6- to 8-year-olds and 9- to 11-year-olds) and exposure frequency of 17 h/day (frequency for 6- to 8-year-olds and 9- to 11-year-olds) (Environ 2003a, b). Absorption factor is unknown for TCEP: therefore, it is set to 1.

[4] Assumed to weigh 59.4 kg (Health Canada 1998), total body surface area of 16 200 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor of 0.393 (average of 12- to 14-year-olds and 15- to 18-year-olds) (Environ 2003a, b), adherence rate of dust to skin of 0.07 mg/cm^2 per day and exposure frequency of 17 h/day (Environ 2003a, b). Absorption factor is unknown for TCEP: therefore, it is set to 1.

[5] Assumed to weigh 70.9 kg (Health Canada 1998), total body surface area of 18 200 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor of 0.312 (average of adult male and female), adherence rate of dust to skin of 0.07 mg/cm^2 per day and exposure frequency of 24 h/day (Environ 2003a, b). Absorption factor is unknown for TCEP: therefore, it is set to 1.

[6] Assumed to weigh 72.0 kg (Health Canada 1998), total body surface area of 18 200 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor of 0.312 (average of adult male and female), adherence rate of dust to skin of 0.07 mg/cm^2 per day and exposure frequency of 24 h/day (Environ 2003a, b). Absorption factor is unknown for TCEP: therefore, it is set to 1.

[7] Concentrations of TCEP were measured in indoor dust in several studies in Germany and Sweden. The maximum concentration of TCEP measured in dust from homes was 44 000 µg/kg. This value is from a German study of dust in 31 homes (Hansen et al. 2001). See below for an example calculation.

Example Calculation

Scenario	**Assumptions**	**Estimated exposure**
Exposure to dust	**Dermal** – Child 0.5–4 years of age Suggested by Environ (2003a, b) for a child less than 1 year old: Concentration of TCEP in house dust (C_{dust}) is 44 000 ng/g (Hansen et al. 2001). Conversion factor (CF_1) of 1×10^{-9}, adherence rate of dust to skin (AR_{dust}) of 0.05 mg/cm^2 per day, total body surface area (S_{at}) of 5780 cm^2 (Health Canada 1995), fraction of skin surface area exposed to floor (FSA_f)of 0.361, exposure frequency at home (EF_h) of 22 h/day , conversion factor (CF_2) of 0.0417 day/h (Environ 2003a, b), body weight (BW) of 15.5 kg,(Health Canada 1995) and unknown absorption factor for the dermal route (AF_d), therefore assume 1. Dose rate	0.27 µg/kg-bw per day

Scenario	Assumptions	Estimated exposure
	$= \frac{C_{dust} \times CF_1 \times AR_{dust} \times S_{at} \times FSA_f \times AF_d \times EF_h \times CF_2}{BW}$ $= 44\ 000\ ng/g \times 1 \times 10^{-9}\ g/ng \times 0.05\ mg/cm^2\ per\ day \times 5780\ cm^2 \times 0.361 \times 1 \times 22\ h/day \times 0.0417\ day/h / 15.5\ kg$ $= 0.000\ 27\ mg/kg\text{-}bw\ per\ day$	

Appendix 4. Upper-bounding estimates of oral exposure to TCEP from mouthing foam[1]

Consumer product scenario	Assumptions	Estimated exposure
Mouthing foam (e.g, cushion or upholstered furniture)	**Infants 0–6 months old** Default values from Environ (2003a, b) for ingestion from mouthing. Water solubility (WS) of TCEP is 7820 mg/L, salivary flow rate in child's mouth (V_s) is 0.22 ml/min, convert L to mL (CF), fractional rate of extraction by saliva (FR) is 0.038, absorption factor by the oral route (AF_o) is 0.5, exposure frequency mouthing behaviour (EF_{mouth}) is 9 min/day (Environ 2003a, b), and body weight (BW) is 7.5 kg (Health Canda 1998). Dose rate $= \frac{WS \times V_s \times CF \times FR \times AF_o \times EF_{mouth} \times 1}{BW}$ = 7820 mg/L × 0.22 ml/min × 0.001 L/ml × 0.038 × 0.5 × 9 min/day × 1 / 7.5 kg = 0.039 mg/kg-bw per day	39 µg/kg-bw per day
Mouthing foam (e.g, cushion or upholstered furniture)	**Toddlers 6 months to 4 years old** Default values from Environ (2003a, b) for ingestion from mouthing. Water solubility (WS) of TCEP is 7820 mg/L, salivary flow rate in child's mouth (V_s) is 0.22 ml/min, convert L to mL (CF), fractional rate of extraction by saliva (FR) is 0.038, absorption factor by the oral route (AF_o) is 0.5, exposure frequency mouthing behaviour (EF_{mouth}) is 9 min/day (Environ 2003a, b), and body weight (BW) is 15.5 kg (Health Canada 1998). Dose rate $= \frac{WS \times V_s \times CF \times FR \times AF_o \times EF_{mouth} \times 1}{BW}$ = 7820 mg/L × 0.22 ml/min × 0.001 L/ml × 0.038 × 0.5 × 9 min/day × 1 / 15.5 kg = 0.019 mg/kg-bw per day	19 µg/kg-bw per day

[1] The method used to calculate oral exposure via mouthing of foam containing TCEP was derived from a Voluntary Children's Chemical Evaluation Program (VCCEP) assessment on penta- and octabrominated flame retardants (Environ 2003a, b). The VCCEP method uses a water solubility of TCEP of 7820 mg/L (ECB 2000), a salivary flow rate in a child's mouth of 0.22 mL/min and an absorption factor for the oral route of 0.5 and 9 min/day spent by a child sucking on foam (Environ 2003a, b).

Appendix 5. Summary of health effects information for TCEP

Endpoints	Lowest effect levels[1]/Results
Acute toxicity	**Oral LD_{50}** (rat) = 1150 mg/kg-bw (conducted according to OECD guidelines) (Kynoch and Denton 1990) **Other oral LD_{50}** (rat) = 0.43–3.6 g/kg-bw (Smyth et al. 1951; Ulsamer et al. 1980; Gardner 1987) **Inhalation LC_{50}** (possibly rat) = 5.0 mg/L (BRMA 1990) **Dermal LD_{50}** (rabbit) = >5 g/kg-bw (BRMA 1990)
Short-term repeated-dose toxicity	**Lowest oral LOAEL:** 175 mg/kg-bw per day was identified based on increased mean absolute and relative kidney weights in male F-344/N rats and reduced serum cholinesterase activity in female rats exposed to 0, 22, 44, 88, 175 or 350 mg/kg-bw per day, 5 days/week, for 16 days by gavage (NTP 1991; Matthews et al. 1993) No inhalation or dermal studies identified
Subchronic toxicity	**Lowest oral LOEL:** 44 mg/kg-bw per day based on increased absolute and relative weights of liver and kidney in female F-344/N rats exposed to 0, 22, 44, 88, 175 or 350 mg TCEP/kg-bw per day by gavage, 5 days/week, for 16 weeks. Decreased serum cholinesterase activity and neuronal necrosis in the hippocampus were observed in females at 175 and 350 mg/kg bw per day (NTP 1991). **Other oral studies:** LOEL of 175 mg/kg-bw per day was observed in B6C3F1 mice administered 0, 44, 88, 175, 350 or 700 mg TCEP/kg-bw per day by gavage, 5 days/week, for 16 weeks (female) or 18 weeks (male) based on increased absolute liver weights and reduced absolute kidney weights in females. Renal tubule epithelial cells with enlarged nuclei observed in both sexes at 700 mg/kg-bw per day (NTP 1991). No dermal studies identified
Chronic toxicity/ carcinogenicity	**Oral carcinogenicity in rats:** Groups of 50 male and 50 female F344/N rats were treated with 0, 44 or 88 mg TCEP/kg-bw per day in corn oil by gavage, 5 days/week for 103 weeks. A dose-related significant increase in the incidence of renal tubule adenomas was observed in both male rats (1/50, 5/50 and 24/50, respectively) and female rats (0/50, 2/50 and 5/50, respectively). The incidence of thyroid follicular cell neoplasms (adenoma or carcinoma) increased significantly in female rats (0/50, 3/50 and 4/50, respectively), but not significantly in male rats (1/50, 2/50 and 5/50, respectively), but were within the historical control range for adenoma or carcinoma (0–10%: European Commission 2004). Mononuclear cell leukemias were increased in both sexes (5/50, 14/50 and 13/50, respectively, in males; 14/50, 16/50 and 20/50, respectively, in females), but were within the historical control range (2–44%). The non-neoplastic effects included a dose-related increase in renal tubule hyperplasia in both sexes. Also, gliosis, hemorrhage, hemosiderosis and mineralization in the cerebrum and brain stem were observed in female rats at the top dose (88 mg/kg-bw per day) (NTP 1991; Matthews et al. 1993). **Oral carcinogenicity in mice:** Groups of 50 male and 50 female B6C3F1 mice were treated with 0, 175 or 350 mg TCEP/kg-bw per day in corn oil by gavage, 5 days/week for 103 weeks. A marginally increased incidence of renal tubule adenomas or carcinomas was observed in male mice (1/50, 1/50 and 4/50, respectively), and a marginally increased incidence of Harderian gland adenomas or carcinomas was observed in female mice (3/50, 8/50 and 7/50, respectively).

Endpoints	Lowest effect levels[1]/Results
	The non-neoplastic effects included a dose-related increase in the incidence of karyomegaly in renal tubule epithelial cells in both sexes (2/50, 16/50 and 39/50, respectively, in males; 0/50, 5/50 and 44/50, respectively, in females) (NTP 1991; Matthews et al. 1993). **Other oral carcinogenicity in mice:** Groups of 50 male and 50 female Slc:ddy mice received approximately 0, 12, 60, 300 or 1500 mg TCEP/kg-bw per day via diet (assuming 30 g body weight and 3 g/day food consumption)[2] for 18 months. In male mice, an increased incidence of renal cell carcinoma and adenoma was observed (2/50, 0/49, 2/49, 5/47 and 41/50, respectively), with a significant difference ($p < 0.01$) at the highest dose; and the incidences of hepatocellular adenoma and carcinoma were increased significantly at the doses of 300 and 1500 mg/kg-bw per day (4/50, 5/49, 7/49, 12/47 and 19/50, respectively). In female mice, a significantly increased incidence of forestomach papilloma and squamous cell carcinoma was observed at the highest dose (0/49, 0/49, 0/50, 1/49 and 7/50, respectively); and the incidence of leukemia was increased significantly at the doses of 300 and 1500 mg/kg-bw per day (1/49, 3/49, 6/50, 9/49 and 9/50, respectively). The non-neoplastic lesions, hyperplasia, hypertrophy and karyomegaly were observed in the kidney of all exposed animals, but the incidence and severity of these effects in the kidneys were not stated (as cited in IPCS 1998). Thus, a non-neoplastic LOEL could not be derived (Takada et al. 1989). **Dermal carcinogenicity in mice:** No significant increase in tumours in female Slc:ddy mice whose shaved skin was treated twice weekly for 79 weeks at a concentration of 5% or 50% of TCEP in ethanol solution. However, the amount of solution applied to skin was not reported (Takada et al. 1991). **Other dermal carcinogenicity:** TCEP showed no significant complete carcinogenic or promoting activity on mouse skin (Sala et al. 1982). **The lowest oral non-neoplastic effect levels:** 44 mg/kg-bw per day based on renal tubule hyperplasia in male and female rats. In mice, karyomegaly of tubule epithelial cells of the kidney was observed at 175 and 350 mg/kg-bw per day in both sexes (NTP 1991; Matthews et al. 1993). No inhalation studies identified
Developmental toxicity	**Oral developmental toxicity in mice:** No significant adverse effects on development (maternal mortality, pup survival, litter size, weight gain of pups or birth weight of pups) were observed in pregnant CD-1 mice administered 0 or 940 mg TCEP/kg-bw per day on gestation days 6–15. Decreased maternal body weight gain was observed in exposed animals (Hardin 1987; Hardin et al. 1987). **Oral developmental toxicity in rats:** No abnormalities on morphological examination or in functional behaviour tests were observed in Wistar rats administered 0, 50, 100 or 200 mg TCEP/kg-bw per day by gavage on gestation days 7–17. In the high dose group, reduced food consumption, general weakness and death (7/30) of dams were observed (Kawashima et al. 1983a, b). No inhalation or dermal studies identified

Endpoints	Lowest effect levels[1]/Results
Reproductive toxicity	**Oral reproductive toxicity in mice:** The fertility and reproductive toxicity of TCEP were examined in Swiss CD-1 mice according to the Reproductive Assessment by Continuous Breeding protocol with a crossover mating trial for high-dose males and females. The LOAEL of 350 mg/kg-bw per day was identified in Swiss CD-1 mice administered 0, 175, 350 or 700 mg TCEP/kg-bw per day by gavage, based on reduced number of litters per pair (F_0 generation), decreased numbers of live pups per litter (both F_0 and F_1 generations) and maternal toxicity. In the crossover mating trials conducted at 700 mg/kg-bw per day, decreased numbers of sperm, decreased sperm motility and increased percentages of abnormal sperm were observed in males; in females, no effects on estrous cycle or cyclicity were observed (Gulati et al. 1991; Chapin et al. 1997). **Other studies:** At 700 mg/kg-bw per day, decreased absolute epididymis weight and absolute and relative testes weight, decreased sperm count and increased numbers of sperm with abnormal morphology were observed in B6C3F1 mice administered 0, 44, 175 or 700 mg TCEP/kg-bw per day for approximately 18 weeks (Gulati and Russell 1985; Morrissey et al. 1988). **Oral reproductive toxicity in rats:** Decreased sperm motility was observed in F-344 rats administered 0, 22, 88 or 175 mg TCEP/kg bw per day for approximately 18 weeks (the doses at which this effect was statistically significant were not reported in the available references)[3] (Gulati and Russell 1985; Morrissey et al. 1988). **Inhalation reproductive toxicity in rats:** Testicular toxicity was observed in both exposed groups in an inhalation study of male mice exposed whole body to 0, 0.5 or 1.5 mg TCEP/m^3 continuously for 4 months, with the most severe effects at the high dose (LOEC = 0.5 mg/m^3). The effects included decreased sperm counts, decreased sperm mobility and abnormal sperm morphology. When the exposed males were mated, decreased fertility was observed at 1.5 mg/m^3, based on increased pre- and post-implantation loss and decreased litter size (Shepel'skaya and Dyshinevich 1981). No dermal studies identified
Genotoxicity and related endpoints: *in vivo*	**Micronuclei tests:** **Equivocal (positive but no clear dose-responses)**: in bone marrow cells from male and female Chinese hamsters intraperitoneally administered single doses at 0, 62.5, 125 or 250 mg TCEP/kg-bw (Sala et al. 1982) **Negative:** in bone marrow cells from NMRI mice orally administered single doses at 1000 mg TCEP/kg-bw (Otto 1984; FhG 1984) **Negative:** in bone marrow cells from CD-1 mice intraperitoneally administered single doses at 175–700 mg/kg-bw (IRI 1993) **Somatic cell damage:** **Negative:** in the w/w+ bioassay for somatic cell chromosome damage (recombination) in *Drosophila melanogaster* (white/white$^+$ eye mosaic assay) (Vogel and Nivard 1993)
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity in bacteria:** **Negative:** *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 (up to 5 mg/plate) with or without induced rat liver S9 (Simmon et al. 1977) **Negative:** *Salmonella typhimurium* TA100, TA1535, TA1538 (up to 10 mg/plate) with or without induced rat liver S9 (Prival et al. 1977) **Negative:** *S. typhimurium* TA98, TA100, TA1535, TA1537 (up to 333 µg/plate)

Endpoints	Lowest effect levels[1]/Results
	with or without induced rat or hamster liver S9 (Haworth et al. 1983; NTP 1991; Zeiger et al. 1992) **Negative:** *S. typhimurium* TA97a, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538 (up to 1 mmol/L) with or without induced rat liver S9 (Föllmann and Wober 2006) **Positive:** *S. typhimurium* TA1535 at the concentration of 2850 µg/plate in the presence of induced rat liver S9 (Nakamura et al. 1979) Negative: *Saccharomyces cerevisiae* D4 (concentrations not stated) with and without metabolic activation (Ulsamer et al. 1980) **HGPRT forward mutation assay:** **Negative:** in the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay in Chinese hamster V79 cells (Sala et al. 1982) **TK locus mutation assay:** **Negative:** in mouse lymphoma L5178Y cells with and without S9 mix (Stauffer Chemical Company 1978; Ulsamer et al. 1980) **Sister chromatid exchange (SCE):** **Positive:** in Chinese hamster V79 cells with and without rat liver S9 (Sala et al. 1982) **Equivocal:** negative in Chinese hamster ovary (CHO) cells without rat liver S9 metabolic activation; positive/negative with S9 (Galloway et al. 1987) **Chromosomal aberrations:** **Negative:** CHO cells with and without rat liver S9 metabolic activation (Galloway et al. 1987) **DNA damage (comet assay):** **Negative:** in Chinese hamster V79 cells by alkaline single cell gel electrophoresis (comet assay) (Föllmann and Wober 2006) **Cell transformation:** negative in C3H10T1/2 cells, but positive in Syrian hamster embryo cells (Sala et al. 1982)
Neurotoxicity	**LOAEL:** 275 mg/kg-bw, based on observed convulsions 60–90 min after dosing, hippocampal damage (loss of CA1 hippocampal pyramidal cells 7 days after dosing) and learning impairment (in a second study, impaired acquisition of a reference memory task in a water maze observed when rats tested 3 weeks after exposure) in female F-344 rats administered a single oral gavage dose of 275 mg/kg-bw (Tilson et al. 1990) **Other acute neurotoxicity studies:** Brain neuropathy target esterase inhibited by 30% and plasma cholinesterase inhibited by 87% 24 h after first dose in White Leghorn hens orally administered TCEP at 14 200 mg/kg-bw and at the same dose 3 weeks later. Other effects after the first dose included decreased body weight, feather loss and cessation of egg production, and 4 of 18 treated hens died within 6 weeks of the first dose. No delayed neurotoxicity was observed (Sprague et al. 1981). White Leghorn hens exposed orally to 420 mg TCEP/kg bw per day for 5 days showed no neurotoxicity after 21 days of observation (Bullock and Kamienski 1972).
Human studies	
Toxicity	No data available

[1] LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEL, lowest-observed-adverse-effect level; LOEL, lowest-observed-effect level.
[2] Doses estimated in IPCS (1998), as Takada et al. (1989) reported them only as percentages in diet.
[3] Although Gulati and Russell (1985) stated that there was no reproductive or testicular toxicity in the 18-week rat study, the analysis by Morrissey et al. (1988) of the same study showed decreased sperm motility, but the authors did not indicate the dose(s) at which this effect was observed. Morrissey et al. (1988) is a primary reference, but Gulati and Russell (1985) was cited in European Commission (2004).