Screening Assessment for the Challenge

Phosphoric Acid Tributyl Ester (Tributyl Phosphate)

Chemical Abstracts Service Registry Number
126-73-8

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 phosphoric acid tributyl ester, or tributyl phosphate (TBP), Chemical Abstracts Service Registry Number 126-73-8. This substance was identified in the categorization of the *Domestic Substances List* as a high priority for action under the Challenge. TBP 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. The substance met the ecological categorization criteria for persistence, but did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of TBP relates to human health risks.

According to the information submitted under section 71 of CEPA 1999, TBP was not manufactured in Canada in the calendar year of 2006 above the reporting threshold of 100 kg. Some importation activities were reported at a total quantity of approximately 260 000 kg in 2006.

TBP has been identified in indoor air and drinking water in Canada. Recent data are available on concentrations of TBP in other environmental media in other countries. In Canada, TBP is used primarily for industrial purposes. It is used in aviation and other hydraulic fluids, including as a flame retardant. It is also used as an extraction solvent for rare earth metals from ores, as an aid in the manufacture of uranium trioxide, as a defoamer, as a plasticizer and in industrial wood coatings. It is found in some paints and brake fluids to which the general population of Canada may be exposed during their use.

Based on consideration of relevant available information, including weight of evidence–based assessments by international and other national agencies, a critical effect for the characterization of risk to human health for TBP is carcinogenicity. Tumours in urinary bladder were observed in male and female rats following dietary exposure at the highest dose tested. Tumours in liver were also observed in male mice. TBP did not show any genotoxicity from bioassays in bacteria, cultured mammalian cells or animals. Mechanistic study and evaluations by international and other national agencies suggest that TBP is a non-genotoxic carcinogen and that tumours are associated with cytotoxicity and proliferative effects.

Based on comparison of the levels at which non-neoplastic effects (bladder hyperplasia) are observed with the upper-bounding estimates of exposure to TBP from environmental media and during the use of consumer products by the general population in Canada, and taking into account the uncertainties in the databases on exposure and effects, the resulting margins of exposure are considered to be adequately protective of human health.

On the basis of the consideration of the existence of a practical threshold for carcinogenicity of TBP in the animal studies, considering the magnitude of the margins

of exposure for non-cancer effects, it is concluded that TBP 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.

On the basis of ecological hazard and reported releases of TBP, it is concluded that TBP 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. TBP does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations*.

This substance will be included in the upcoming *Domestic Substances List* inventory update initiative. In addition and where relevant, research and monitoring will be undertaken to confirm assumptions used during the screening assessment.

Based on the information available, it is proposed to conclude that TBP does not meet any 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 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 TBP 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 TBP was determined to be a high priority for assessment with respect to human health, it did not meet the criteria for persistence, bioaccumulation potential 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. When available and relevant, information presented in hazard assessments from other jurisdictions was considered. 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 prioritization of 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.

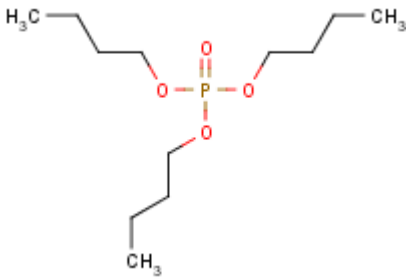
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and at Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external scientific review. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Dr. Lynne Haber (TERA), Dr. Michael Jayjock (The LifeLine Group) and Dr. Glenn Talaska (University of Cincinnati). While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Additionally, the draft of this assessment was subject to a 60-day public comment period.

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

Substance Identity

TBP is a non-flammable, non-explosive, colourless and odourless liquid, which behaves as a weak alkylating agent. It is thermally unstable and begins to decompose at temperatures below its boiling point (IPCS 1991). Additional information on the identity of TBP is summarized in Table 1.

Table 1. Substance identity of TBP

CAS RN	126-73-8
DSL name	Phosphoric acid tributyl ester
NCI names	Phosphoric acid tributyl ester (ASIA-PAC, NZIoC, PICCS, SWISS, TSCA); Phosphoric acid, tributyl ester (AICS); Tributyl phosphate (ECL, EINECS, ENCS, PICCS); Tributylphosphate (PICCS); Tri-*n*-butyl phosphate (PICCS)
Other names	Butyl phosphate ($(BuO)_3PO$); Calloway 6814; Celluphos 4; Disflamoll TB; NSC 8484; Phosflex 4; TBP; TBPA; Tributoxyphosphine oxide
Chemical group	Discrete organics
Chemical subgroup	Alkyl phosphate esters
Chemical formula	$C_{12}H_{27}O_4P$
Chemical structure	
SMILES	O=P(OCCCC)(OCCCC)OCCCC
Molecular mass	266.32 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; NZIoC, New Zealand Inventory of Chemicals; 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 summarizes key experimental and modelled physical and chemical properties of TBP that are relevant to its environmental fate.

Table 2. Physical and chemical properties of TBP

Property	Value[1]	Reference

Property	Value[1]	Reference
Melting point (°C)	−70	Bayer AG 1987
Boiling point (°C)	289 (with decomposition)	PhysProp 2003
Density (kg/m^3)	970[2]	Bayer AG 1987
	972.7	Lide 2005–2006
Vapour pressure (Pa)	3.46×10^{-4}	ABC Laboratories 1990a
	0.8 @ 20°C	Bayer AG 1987
	0.46 (modelled)	MPBPWIN 2000
	0.55 (modelled)	ACD 2008
Henry's Law constant (Pa·m^3/mol)	0.32 (modelled)[2] (Bond estimation method)	HENRYWIN 2000
	2.29×10^{-4} (modelled) (Group estimation method)	HENRYWIN 2000
Log K_{ow} (dimensionless)	4.00[2]	Saeger et al. 1979
	3.82 (modelled)	KOWWIN 2000
	4.27 (modelled)	ACD 2008
Log K_{oc} (dimensionless)	2.58 (sandy loam)[2]	FMC Study No. I90-1176[3]
	3.16 (silty loam)[2]	
	3.27 (modelled)[2]	PCKOCWIN 2000
	3.7 (modelled)[2]	ACD 2008
Water solubility (mg/L)	280	PhysProp 2003
	400 @ 20°C	Bayer AG 1987

Abbreviations: K_{oc}, organic carbon–water partition coefficient; K_{ow}, octanol–water partition coefficient.
[1] All experimental values were obtained at 25°C unless otherwise stated.
[2] Temperature not specified.
[3] Cited in OECD 2002.

Sources

TBP is an anthropogenic substance and does not occur naturally in the environment (IPCS 1991). It is produced by the reaction of phosphorus oxychloride with *n*-butanol (O'Neil 2001).

According to information submitted under section 71 of CEPA 1999, TBP was not manufactured in Canada in the calendar year of 2006 above the reporting threshold of 100 kg (Environment Canada 2008). Some importation activities were reported at a total quantity of approximately 260 000 kg in 2006 (Environment Canada 2008).

Uses

The major global uses of TBP in industry are as a flame retardant component of aircraft hydraulic fluid and as a solvent for rare earth extraction and purification from its ores (IPCS 1991; OECD 2002; Supresta 2008). These uses comprise over 80% of the total global production (OECD 2002). In Canada, TBP is used in aviation and other hydraulic fluids, including as a flame retardant. It is also used as an extraction solvent for rare earth

metals from ores and as an aid in the manufacture of uranium trioxide (Environment Canada 2008).

TBP is also utilized as an extreme pressure additive and anti-wear agent to prevent surface damage in hydraulic fluids, lubricants and transmission and motor oils (ATSDR 1997). Reported use of this type in Canada includes use as a brake fluid, as a corrosion inhibitor, as a vehicle transmission oil, to replenish aircraft hydraulic systems, and in industrial adhesives and lubricants (Environment Canada 2008).

Many of the applications of TBP utilize its physical and chemical properties. For example, it is a polar solvent, which makes it highly efficient and suitable for extraction and purification and for use as an antifoaming agent and as a plasticizer. As it is an odourless liquid, this property makes it an ideal defoamer in the textile and paper industries (Verschueren 2001; Supresta 2008), and its use as a defoamer has been reported in Canada (Environment Canada 2008). Addition of less than 1% by weight of TBP is usually sufficient to prevent undesirable foaming (Supresta 2008). TBP is also used as a primary plasticizer in the manufacture of plastics (Sandmeyer and Kirwin 1981). It has been used as a plasticizer for a polyacrylonitrile-based material for barcode printing. In this application, the polymer absorbs the infrared light radiation emitted or reflected from a pattern (Wypych 2004). However, the use of TBP for this specific application in Canada has not been confirmed. TBP has also been used in the dissolution process of nuclear fuel processing and in the preparation of purified phosphoric acid (IPCS 1991; Godfrey et al. 1996; OECD 2002).

TBP is an effective solvent in blending of materials that are difficult to dissolve (Supresta 2008). Because of this characteristic, it is an excellent solvent for lithographic inks and in the preparation of concentrates for agricultural herbicides and fungicides (Supresta 2008).

In Canada, TBP has been proposed for use in inks at levels of 0.102%, for use in paints at a maximum level of 1.10% and for use in defoamers at levels that would result in 0.03% of TBP being present in the paperboard materials. TBP has also been proposed for use in adhesives at levels of 20 mg/kg. However, as no submission has been completed for these specified uses in Canada, Health Canada has not cleared such use (2008 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). In the United States, TBP is listed under the indirect food additives section in US Food and Drug Administration (FDA) Code of Federal Regulations, Title 21: Section 175.105 for adhesives and components of coatings, substances for use only as components of adhesives; Section 176.180 for paper and paperboard components, components of paper and paperboard in contact with dry food; and Section 176.210 for paper and paperboard components, defoaming agents used in the manufacture of paper and paperboard (US FDA 2008).

TBP has been used as a constituent of cotton defoliants, which act by producing leaf scorching (IPCS 1991). Non-specific plant herbicides that contained TBP were reformulated in the mid-1980s and are no longer available for use (OECD 2002).

In Canada, although TBP is listed on the Pest Management Regulatory Agency list of formulants (Health Canada 2007a), it is not currently used in any pest control products registered for use in Canada as either an active ingredient or a formulant (2008 e-mail communication from Pest Management Regulatory Agency, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced).

Due to the surfactant and antifreeze characteristics of TBP, it is suitable as a coalescing agent for latex paints and lacquers in cold weather applications, enabling latex coating to flow evenly in cold climate and reducing brush marks (Wicks 2002; Supresta 2008). TBP is used in water-thinned exterior paints and tinting bases, including barn and roof paints (Scorecard 2005). TBP is also used as an anti-air entrainment additive for coatings and floor finishes and as a carrier for fluorescent dyes (Godfrey et al. 1996; OECD 2002). Canadian uses reported include paint additives, industrial wood coatings and pigment dispersant (Environment Canada 2008).

TBP is not currently prohibited in cosmetics in Canada (Health Canada 2007b), although it is prohibited in cosmetic products in the European Union (European Commission 1999).

Releases to the Environment

According to information submitted under section 71 of CEPA 1999, approximately 9000 kg of TBP were released into the Canadian environment in 2006; the majority of releases were to water (Environment Canada 2008). One of the companies in boxboard production reported a release of 7400 kg of TBP per year. This company indicated that the reported quantity was the production quantity, as the actual amount released from the facility into liquid effluent was unknown. This facility is now closed. Another facility reported the release of 1300 kg of TBP per year. In both cases, the reported quantities were for a worst-case release scenario, as they were based on the use/production quantities. One other company reported the release of approximately 300 kg of TBP per year.

The information submitted under section 71 of CEPA 1999 also indicated that 10 000–100 000 kg of TBP were transferred to hazardous waste facilities, whereas 100–1000 kg were transferred to non-hazardous waste facilities in 2006 (Environment Canada 2008). TBP is not included in the National Pollutant Release Inventory (NPRI 2008) or in the US Toxics Release Inventory Program (TRI 2008).

Environmental Fate

Based on the physical and chemical properties of TBP (Table 2), the results of Level III fugacity modelling (Table 3) suggest that the substance will reside predominantly in water or soil, depending on the compartment of release.

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

Substance released to:	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air (100%)	0.4	7.8	91.4	0.3
Water (100%)	0.0	96.2	0.0	3.8
Soil (100%)	0.0	0.1	99.9	0.0

If TBP is released to air, the Level III fugacity model indicates that a very small amount of the substance remains in air (Table 3). A vapour pressure of 3.46×10^{-4} Pa and a Henry's Law constant of up to 0.32 $Pa \cdot m^3/mol$ indicate that TBP is non-volatile to slightly volatile. Therefore, if TBP is released solely to air, soil will be the primary medium into which it is expected to partition, with some partitioning to water also being predicted.

If released into water, TBP is expected to have moderate sorption to suspended solids based upon its estimated log K_{oc} value of ~3 and its experimental log K_{ow} of ~4. Volatilization from water surfaces is expected to be a less important fate process based upon this compound's estimated Henry's Law constant. Thus, if water is a receiving medium, TBP is expected to remain mainly in water and to some extent partition into sediment (Table 3).

If released to soil, TBP is expected to have moderate sorption to soil based upon its estimated log K_{oc} and its experimental log K_{ow}. The moderate solubility of this substance in water (400 mg/L) also indicates that it may have slight mobility in soil. Volatilization from moist soil surfaces is not likely to be an important fate process based upon its estimated Henry's Law constant. Volatilization from dry soil surfaces, based upon its vapour pressure, is not expected to be an important fate process. Therefore, if released to soil, TBP will mainly remain in this environmental compartment, as illustrated by the results of the Level III fugacity modelling (Table 3).

For TBP, potential environmental releases are mainly to water, so the substance would be expected to reside mostly in water, with a small fraction partitioning to sediments.

Persistence and Bioaccumulation Potential

Environmental Persistence

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

Table 4. Empirical data for persistence of TBP

Medium	Fate process	Degradation value	Endpoint (units)	Reference
Water	Biodegradation	89	Biodegradation (%)	Bayer AG [date unknown]
		90.8		Saeger et al. 1979

Medium	Fate process	Degradation value	Endpoint (units)	Reference
Air	Atmospheric oxidation	85	Decrease after 1 h (%)	Ishikawa et al. 1985

Table 5. Modelled data for degradation of TBP

Fate process	Model and model basis	Model output	Expected half-life (days)
Air			
Atmospheric oxidation	AOPWIN 2000	$t_{½}$ = 1.63 h	<2
Ozone reaction		n/a[1]	n/a
Water			
Hydrolysis	HYDROWIN 2000	n/a[1]	n/a
Biodegradation (aerobic)	BIOWIN 2000, Submodel 3 Expert Survey (ultimate biodegradation)	3.6594	<182
	BIOWIN 2000, Submodel 4 Expert Survey (primary biodegradation)	4.7361	
	BIOWIN 2000, Submodel 5 MITI linear probability	0.5205	
	BIOWIN 2000, Submodel 6 MITI non-linear probability	0.4729	
	CATABOL ©2004–2008, % BOD	2	≥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 TBP 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 TBP is expected to be released to this compartment, biodegradation in water was examined primarily.

Table 5 summarizes the results of available QSAR models for degradation in various environmental media. In air, a predicted atmospheric oxidation half-life value of 1.63 hours 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 TBP. With an estimated half-life of 1.63 hours via reactions with hydroxyl radicals (BIOWIN 2000) and based on the rapid oxidation reported in one experimental study (Ishikawa et al. 1985), TBP is considered not persistent in air.

The BIOWIN (2000) model results suggest that the primary and ultimate biodegradation is relatively fast and that the half-life in water would be <182 days. Although these results are not consistent with that of CATABOL, they are consistent with the results of

two empirical tests that reported about 90% biodegradation in water over 28 days (Table 4).

In summary, the experimental and modelled data indicate that TBP has primary and ultimate biodegradation half-lives of <182 days, with the experimental data indicating that degradation half-lives are likely to be less than 28 days.

Based on these data and using an extrapolation ratio of 1:1:4 for a water:soil:sediment biodegradation half-life (Boethling et al. 1995), the half-life in soil is also <182 days and the half-life in sediments is <365 days. This indicates that TBP is not expected to be persistent in soil or sediment.

Based on the empirical persistence and modelled biodegradation data (see Tables 4 and 5), TBP does not meet the persistence criteria in air, water, soil or sediment (half-life in air ≥2 days, half-lives in water and soil ≥182 days and half-life in sediment ≥365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

Experimental and modelled log K_{ow} values for TBP (Table 2) indicate that this chemical has a low to moderate potential to bioaccumulate in the environment (Tables 6 and 7).

Table 6. Empirical data for bioaccumulation of TBP in fish

Test species	Endpoint	Value (L/kg wet weight)	Reference
Medaka, high-eyes	BCF	34.7	Sasaki et al. 1981
Goldfish		7.08	
Carp		13.5	MITI 1992

Abbreviation: BCF, bioconcentration factor.

Table 7. Modelled data for bioaccumulation of TBP in fish

Endpoint	Value (L/kg wet weight)	Reference
BAF	3.94	Arnot and Gobas 2003 (Gobas BAF T2MTL)
BCF	3.95	
	39.8	BCFWIN 2000
	1030	ACD 2008
	1406	OASIS Forecast 2005

Abbreviations: BAF, bioaccumulation factor; BCF, bioconcentration factor.

The reported experimental bioconcentration factors (BCFs) in fish range from 7.08 to 34.7 L/kg (Table 6).

QSAR modelled bioaccumulation factor (BAF) and BCF values (Table 7) agree with the experimental values (Table 6). The Modified Gobas BAF middle trophic level model for fish produced a BAF of 3.94 L/kg, indicating that TBP has a low potential to

bioconcentrate and biomagnify in the environment. The metabolic potential for this substance was calculated from experimental BCF data. This metabolic rate was then used to calculate the QSAR-based Gobas BAF and Gobas BCF values. The BCF models that do not consider metabolism also provide a weight of evidence to support the relatively low bioconcentration potential of this substance.

The weight of evidence indicates that TBP 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, TBP does not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Ecological Effects Assessment

Experimental data and modelled predictions indicate that TBP is not acutely lethal to aquatic organisms at concentrations below 1 mg/L (Tables 8 and 9, respectively).

Table 8. Empirical data for aquatic toxicity

Test organism	Type of test		End-point	Value (mg/L)	Reference
Alga (*Scenedesmus subspicatus*)	Acute	72 h	EC_{50}	2.8	ABC Laboratories 1990b
			EC_{10}	0.37	Kuhn and Pattard 1990
Alga (*Selenastrum capricornutum*)	Acute	96 h	EC_{50}	4.4	ABC Laboratories 1990c
Alga (*Chlorella vulgaris*)	Chronic	7 days	EC_{50}	5	Yoshioka and Ose 1993
Daphnia magna	Acute	24 h	EC_{50}	4.2–35	OECD 2002
		48 h		2.6–9	
		72 h	LC_{50}	2.1	Bringmann and Kuhn 1977
	Chronic	14 days	NOEC	3.1	Yoshioka and Ose 1993
		21 days		0.87	ABC Laboratories 1991a
		21 days	LOEC	2.1	
Gammarus pseudolimnaeus	Acute	96 h	EC_{50}	1.7	ABC Laboratories 1991b
Hyalella azteca	Acute	96 h	EC_{50}	2.4	ABC Laboratories 1990b
Goldfish (*Carassius auratus*)	Acute	96 h	EC_{50}	8.8	Sasaki et al. 1981
Fathead minnow (*Pimephales promelas*)	Acute	96 h	LC_{50}	6.4–11	Geiger et al. 1990
Zebrafish (*Brachydanio rerio*)	Acute	96 h	LC_{50}	~11.8	Bayer AG [date unknown]
		144 h		11.4	Dave et al. 1981
		10 days	NOEC	13.5	

Test organism	Type of test		End-point	Value (mg/L)	Reference
Golden orfe (*Leuciscus idus*)	Acute	96 h	EC_{50}	7.6	Juhnke and Ludemann 1978
Medaka (*Oryzias latipes*)	Acute	48 h	LC_{50}	18	Yoshioka 1986
		96 h	EC_{50}	9.6	Sasaki et al. 1981
			LC_{50}	4.5	Yoshioka and Ose 1993
Rainbow trout (*Oncorhynchus mykiss*)	Acute	96 h	LC_{50}	11	Sasaki et al. 1982
				4.2–11.8	OECD 2002
				13	ABC Laboratories 1990d
	Chronic	50 days	NOEC	8.3	Dave et al. 1981
		95 days	NOEC	0.82	ABC Laboratories 1991c
			LOEC	1.7	

Abbreviations: EC_{50} (EC_{10}), concentration of a substance that is estimated to cause some toxic sublethal effect on 50% (10%) of the test organisms; LC_{50}, concentration of a substance that is estimated to be lethal to 50% of the test organisms; LOEC, lowest-observed-effect concentration; NOEC, no-observed-effect concentration.

Table 9. Modelled data for aquatic toxicity in fish

Type of test	Endpoint	Value (mg/L)	Reference
Acute (96 h)	LC_{50}	4.28	ECOSAR 2004
		6.49	OASIS Forecast 2005
		6.29	AIES 2003–2005

Abbreviation: LC_{50}, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Experimental toxicity data in Table 8 indicate that the acute EC_{50} and LC_{50} values for TBP are in the range of 1.7–35 mg/L.

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 empirical and modelled results indicate that TBP has a toxicity potential ranging from moderate to bordering on highly hazardous to aquatic organisms (i.e., EC_{50} and LC_{50} values typically in the 1–100 mg/L range).

Ecological Exposure Assessment

As stated above, based on the information submitted under section 71 of CEPA 1999, the maximum quantity of TBP used at one facility was reported to be 1300 kg in 2006. Assuming that 100% of the substance was used and released over a 150-day period, the amount released to a sewage treatment plant would be 8.7 kg/day. Sewage treatment plant models indicate that at least 95% of TBP would be removed from water at a sewage treatment plant with primary and secondary treatment.[1] Assuming a removal rate of 95%,

[1] Determined by ASTreat 1.0, a computer program developed by The Procter & Gamble Company for sewage treatment plant removal predictions. Revised and released in 2006. Available from The Procter & Gamble Company, Cincinnati, OH, USA.

the amount of TBP released in sewage treatment plant effluents would be 0.43 kg/day. The 10th-percentile flow of the river receiving the effluent is 0.175 m^3/s, or 15 120 000 L/day. The estimated concentration in the receiving water from this facility is then:

$$(0.43 \text{ kg/day}) / (15\ 120\ 000 \text{ L/day}) = 3 \times 10^{-8} \text{ kg/L} = 0.03 \text{ mg/L}$$

A second company reported the release of about 300 kg of TBP per year. The concentration of TBP in the effluent averages about 1.3 mg/L, and the effluent is released through a submerged effluent diffuser designed to ensure an initial dilution of 100:1. The average concentration of TBP in the receiving water at the diffuser from this facility would therefore be 0.013 mg/L.

The predicted environmental concentration (PEC) is therefore 0.03 mg/L, which is the higher estimated concentration of TBP in receiving water from the two facilities.

Characterization of Ecological Risk

Based on the available information, TBP is not persistent in the environment and is not bioaccumulative based on criteria defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Although TBP is used in relatively large amounts and its uses may be dispersive, information on concentrations of TBP in the environment has not been identified at this time. The experimental and modelled ecotoxicological data indicate that TBP has the potential to be moderately harmful to aquatic organisms.

From the chronic aquatic toxicity data presented above, the most sensitive aquatic organism is the rainbow trout (*Oncorhynchus mykiss*), with a 95-day lowest-observed-effect concentration (LOEC) of 1.7 mg/L. Dividing this value by an assessment factor of 10 to account for inter- and intraspecies variability in sensitivity gives a predicted no-effect concentration (PNEC) of 0.17 mg/L. The risk quotient, PEC/PNEC, is then calculated to be 0.18 (0.03/0.17).

Taking into consideration this risk quotient, which is less than 1, and information on TBP's fate and potential for toxicity, it is concluded that TBP is unlikely to cause harm to sensitive aquatic organisms.

Uncertainties in Evaluation of Ecological Risk

Regarding toxicity, the only effects data identified apply primarily to pelagic aquatic exposures. Nonetheless, since TBP is most likely to enter the environment through wastewater, in which case it would be expected to reside in water, the lack of ecotoxicty data for other compartments is not considered to be critical.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Food

Multimedia intake estimates were derived primarily from international data, as insufficient recent Canadian data were available. Upper-bounding daily intake estimates for TBP are summarized in Appendix 1a. The total estimates ranged from 0.05 µg/kg body weight (kg-bw) per day for breast milk–fed infants (0–6 months old) to 0.40 µg/kg-bw per day for non-formula-fed infants (0–6 months old). Indoor air and food were estimated to contribute the most to the total estimated daily intake. Indoor air contributed predominantly to the total estimated daily intake for breast milk– and formula-fed infants (0–6 months old), whereas food was estimated to be the predominant contribution for non-formula-fed infants (0–6 months old) and children (6 months to 4 years old). For the rest of the age groups (5 years old and higher), indoor air and food contributed almost equally to the estimated total daily intake. Contributions from the other environmental media (ambient air, water and soil) were minimal compared with the contributions from indoor air and food.

There was no Canadian or North American study reporting TBP concentrations in ambient air. Elsewhere, the highest concentration of TBP in ambient air was reported in a Japanese study (Ohura et al. 2006) in which air samples of various organic pollutants were analysed in summer (in 25 houses) and winter (in 21 houses). The 90th-percentile TBP concentration in ambient air was 33.0 ng/m^3 in summer, with a geometric mean concentration of 13.7 ± 1.92 ng/m^3. In winter, the 90th-percentile TBP concentration in ambient air was 24.1 ng/m^3, with a geometric mean concentration of 9.27 ± 2.15 ng/m^3. The higher concentration of 33.0 ng/m^3 was used to estimate the total daily intake. Concentrations of TBP measured in other studies (Carlsson et al. 1997; Toda et al. 2004; Marklund et al. 2005a; Saito et al. 2007) were at least one order of magnitude lower than the value obtained in this study, indicating that the use of 33.0 ng/m^3 is conservative.

Indoor air was determined to be one of the two predominant contributors to the total multimedia intake. One Canadian study was identified reporting concentrations of TBP in indoor air from 1986 (Otson and Benoit 1986). In this study, two complementary sampling techniques were used concurrently for long-term monitoring of 100 target organic compounds in 10 Canadian homes during late summer and winter of 1983–1984. Sampling was carried out for three consecutive periods of 20 days in Montreal. The maximum concentration of 130 ng/m^3 was measured in winter.

There were also a number of studies reporting indoor air concentrations of TBP in recent years from Japan, Sweden and Switzerland. Among the identified studies, the highest concentration of TBP was the 90th percentile of 178 ng/m^3 measured in winter in the same Japanese study, where the highest concentration of TBP was also measured in ambient air (Ohura et al. 2006). This value was also the highest value in indoor air in residential homes among the identified studies (Otake et al. 2001, 2004; Toda et al. 2004; Marklund et al. 2005b; Staaf and Östman 2005a; Ohura et al. 2006; Saito et al. 2007).

Similar levels of TBP in indoor air were measured in other studies in various indoor environments other than residential homes, as presented in Table 10 (Carlsson et al. 1997; Sanchez et al. 2002; Hartmann et al. 2004; Toda et al. 2004; Marklund et al. 2005b; Staaf and Östman 2005a, b; Saito et al. 2007). The highest TBP concentration among the identified studies (178 ng/m^3) (Ohura et al. 2006) was used for exposure estimates, even though this was not the Canadian value, because a comparable level of TBP was measured in the Canadian study from 1986 (130 ng/m^3) (Otson and Benoit 1986).

Table 10. Summary of published data on indoor air concentrations of TBP

N	Description	Mean [range] (ng/m^3)	Reference	Country
Residential homes				
10	Winter	[Maximum: 130]	Otson and Benoit 1986	Canada
18		4.0	Saito et al. 2007	Japan
25	Summer	34.6 ± 2.01 79.0 (90th percentile)	Ohura et al. 2006	
21	Winter	41.1 ± 3.07 178 (90th percentile)		
4	Newly built "clean" rooms	[ND – 40]	Toda et al. 2004	
27		0.01 ± 0.03 [ND – 100]	Otake et al. 2004	
6		[ND – 100]	Otake et al. 2001	
2		[14 – 120]	Marklund et al. 2005b	Sweden
10		[5 – 80]	Staaf and Östman 2005a	
Offices				
14	Office buildings	6.6	Saito et al. 2007	Japan
3	Office rooms	[100 – 320]	Toda et al. 2004	
3		[3 –7]	Staaf and Östman 2005a	Sweden
1		18	Carlsson et al. 1997	
3		[ND – 8.1]	Hartmann et al. 2004	Switzerland
Transport vehicles				
7	Various	[2 – 15]	Staaf and Östman 2005a	Sweden
4	Cars	[2.5 – 14]	Hartmann et al. 2004	Switzerland
Public spaces				
3	Shops	[3.6 – 68]	Marklund et al. 2005b	Sweden
7	Public spaces	[<0.2 – 12]		
1	Lecture hall	5 (RSD 9%)	Staaf and Östman 2005b	
1	Lecture hall (with computer)	ND		
1	Lecture hall	1.93 ± 0.14	Sanchez et al. 2002	
1	Above the computer monitor	54.9 ± 2.7		
3	Workshops	[1 – 24]	Staaf and Östman 2005a	
4	Shops	[5 – 172]		
3	Health care facilities	[1 – 2]		
3	Schools	[9.8 – 64]	Carlsson et al. 1997	
1	Day care	13		

N	Description	Mean [range] (ng/m^3)	Reference	Country
1	Theatre	29	Hartmann et al. 2004	Switzerland
3	Electronic stores	[1.7– 17]		
2	Furniture stores	[14 – 17]		
Factory				
2	Plastics factory	[3.8 – 7.8]	Marklund et al. 2005b	Sweden

Abbreviations: N, number of samples; ND, not detected; RSD, relative standard deviation.

Canadian data were available for concentrations of TBP in drinking water in three studies reported in 1981–1982 (LeBel et al. 1981; Williams and LeBel 1981; Williams et al. 1982). The maximum concentration of TBP was reported to be 62 ng/L among 60 drinking water samples analysed in 29 municipalities across Canada to represent the total Canadian population exposure (Williams and LeBel 1981). The concentration of TBP was also reported in surface water and rain in other Canadian studies (Williams and LeBel 1981; Scott et al. 1996).

Food was determined to be another predominant contributor to the total multimedia intake. The upper-bounding daily intake estimates of TBP from food ranged up to 0.35 µg/kg-bw per day for non-formula-fed infants (0–6 months old).

While no information on TBP concentrations in foods was identified in Canada, various food items were reported to contain TBP in a recent US Total Diet Study in which data were collected between September 1991 and October 2003 (US FDA 2006a), as summarized in Appendix 1b. Due to lack of Canadian data, it was considered reasonable to use these data from the United States as the possible worst-case scenario for exposure to TBP from food for the general population of Canada. For a conservative estimate, the maximum concentrations of TBP in each food item were used to calculate the upper-bounding daily intake. For a few food items for which Canadian food consumption data were not available, the food consumption rates from US FDA (2006b) were used after adjustment to Canadian age groups. In addition, where Canadian consumption data covered more than one food item, the maximum concentration was used (see footnote 12 in Appendix 1a).

Two other non-Canadian studies reported the presence of TBP in food. One study reported residual pesticide analysis in food in Japan (Tomizawa et al. 2004), and the other study reported migration of TBP from food packaging laminates used for heat-and-eat meals in the United Kingdom (Lawson et al. 1996). Although both studies may indicate potential sources of TBP in various food items, neither qualitative nor quantitative extrapolation from these studies to the Canadian-specific situation was performed.

No studies were identified that reported data on TBP concentrations in soil. TBP concentrations in house dust were used as a surrogate for the concentration of TBP in soil, because indoor air was identified as the greatest contributor to human exposure from environmental media. The maximum TBP concentration of 610 µg/kg in house dust measured in Swedish houses was used to derive the total exposure estimates (Marklund et al. 2003).

Confidence in the exposure estimates for environmental media and food is moderate. Although there were limited available Canadian data on TBP concentrations in water and indoor air from the 1980s, more recent international data on concentrations of TBP in indoor and ambient air (Ohura et al. 2006) as well as in food (US FDA 2006a) were available and were considered appropriate for the derivation of conservative exposure estimates. Based on the submitted information, it is likely that the derived values overestimate actual exposures of the general population in Canada to TBP.

Consumer Products

TBP is used mainly in industrial settings, and limited information on consumer products in Canada is available. Based on the available information, consumer products that may result in exposure to TBP during their use by the general population in Canada are paints and brake fluid. Exposure estimates were calculated, and key information is summarized in Table 11. TBP contained in these products represents less than 1% of the total reporting quantity of TBP (Environment Canada 2008). Details of scenarios are summarized in Appendix 2, where both external and internal exposure estimates during use of these products are presented. Dermal exposure during the use of paints resulted in the predominant contribution to the overall exposure estimates. Internal dose estimates were derived using a dermal absorption rate of 4%, which was based on results from a study conducted in minipigs (BG Chemie 2000). Other absorption data were available from a study conducted in rats (MRI 1992a, b); however, the interspecies difference between humans and rats is considered larger than that between humans and minipigs, and therefore the rat data were not used to estimate dermal exposure.

Table 11. Summary of estimated inhalation and dermal exposures to TBP during use of consumer products (refer to Appendix 2 for details)

Type of consumer products		Maximum concentration of TBP (%)	Exposure estimates (mg/kg-bw per event)[1]		
			Inhalation	Dermal	Integrated
Brake fluid		5[2]	N/A	0.006	0.006
Paint	Aerosol	0.0345[3]	0.0004	0.0003	0.001[4]
	Solvent-rich	0.5953[5]	**0.01**	0.01	0.02
	Waterborne	1.1[3]	0.002	**0.02**	0.02
	Waterborne wall	1.1[3]	0.006	**0.02**	**0.03**

[1] The highest estimates for each route of exposure (inhalation, dermal and integrated) are in bold.
[2] Radiator Specialty Co. of Canada 2007.
[3] 2008 personal communication from Canadian Paints and Coating Association to Risk Management Bureau, Health Canada; unreferenced.
[4] Integrated exposure estimate includes oral non-respirable exposure of 0.0004 mg/kg-bw per event.
[5] 2008 personal communication from Valspar Inc. to Risk Management Bureau, Health Canada; unreferenced.

Although information on Canadian consumer products containing TBP was very limited, various consumer products in Denmark and Japan have been reported to contain TBP. Products found to contain TBP in Denmark are fabric dye (63 mg/kg; Hansen 2005), glass and porcelain colour components (lemon yellow; 160–170 mg/kg; Mikkelsen et al. 2005), soft vinyl vibrator (0.14 g/kg; Nilsson et al. 2006) and television sets (three

monitors) (TBP used as a flame retardant; <10–18 ng/m^3; Malmgren-Hansen et al. 2003). TBP was used as a flame retardant in carpets (<47.07 µg/g), socks (2.57 µg/g) and curtains (trace amounts) in one Japanese study (Nakashima et al. 1994) and in a soft polyurethane cushion foam (<0.7 µg/g) in another Japanese study (Nagase et al. 2003). The presence of TBP in the products listed above has not been confirmed in Canada (Environment Canada 2008).

Confidence in the modelled estimates of exposure from paints and brake fluid is moderate to high, as the concentrations of TBP in these products are Canadian-specific information. However, there is uncertainty in the use of default values that are not Canadian specific in the consumer exposure model. Uncertainty is also recognized in use of the absorption rate from a minipig study to estimate dermal exposure.

Health Effects Assessment

Appendix 3 contains a summary of the available health effects information for TBP.

The European Commission has classified TBP as a Carcinogenicity Category 3 substance with risk phrase R40 ("limited evidence of carcinogenic effects from experimental animal studies") (European Commission 2002, 2004; ESIS 2009).

TBP was carcinogenic in the urinary bladder of male and female rats. Groups of 50 Sprague-Dawley rats per sex received diets containing 0, 200, 700 or 3000 mg TBP/kg (equivalent to 0, 9, 33 and 143 mg/kg-bw per day for males and 0, 12, 42 and 182 mg/kg-bw per day for females) for 24 months. The incidence of papillomas of the urinary bladder was increased in male rats (0/50, 0/50, 2/49, 23/49) and female rats (0/50, 0/50, 1/49, 11/49), with a significant increase at the highest dose ($p < 0.01$). In addition, transitional cell carcinomas were present in the bladder of males (6/49 compared with 0/50 in the control, $p < 0.01$) and females (2/50) at the highest dose. A dose-related increase in the incidence and severity of urinary bladder hyperplasia was also observed in male and female rats (Auletta et al. 1998a).

TBP showed carcinogenicity in the liver of male but not female mice. In an 18-month mouse study, groups of 50 CD-1 mice per sex received diets containing 0, 150, 1000 or 3500 mg TBP/kg (equivalent to 0, 24, 169 and 585 mg/kg-bw per day for males and 0, 29, 206 and 711 mg/kg-bw per day for females). An increase in the incidence of hepatocellular adenomas was observed in male mice (3/50, 6/50, 7/50, 10/50), with significance at the highest dose ($p < 0.03$) compared with the concurrent control; however, the incidence was only slightly above the historical control range (2/59 to 10/60). No significantly increased incidence of liver tumours was observed in female mice. In contrast with the observed carcinogenicity in the bladder in rats, no treatment-related preneoplastic or neoplastic lesions were seen in the urinary bladder in mice (Auletta et al. 1998b).

TBP was not mutagenic in most of the bacterial mutation assays. In the Ames test, negative results were observed in *Salmonella typhimurium* TA97, TA98, TA100, TA102,

TA1530, TA1535, TA1537, TA1538 and TA2638 from at least eight assays (see Appendix 3) in the presence or absence of metabolic activation by induced rat or hamster liver S9 (Hanna and Dyer 1975; Microbiological Associates, Inc. 1978; Bayer AG 1985; Pancorbo et al. 1987; Zeiger et al. 1992; Watabe et al. 1993; Abe and Urano 1994; Watanabe et al. 1996); only one assay gave a positive result in *S. typhimurium* TA1535 and TA1538 without S9 and a weakly positive result in the presence of S9 (Gafieva and Chudin 1986). Negative mutagenicity results were also reported in tests on *E. coli* strains WP2/pKM101 and WP2uvrA/pKM101 at the concentration of 5000 µg/plate without metabolic activation (Watanabe et al. 1996) or on other *E. coli* strains (Hanna and Dyer 1975). In mammalian cells, negative results were observed in *in vitro* gene mutation in the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay, in chromosomal aberrations in Chinese hamster ovary (CHO) cells with or without metabolic activation (Batt et al. 1992) or in micronuclei in CHO cells without activation (Brooks et al. 1996). In an *in vivo* animal study, no significant increase in the frequency of chromosomal aberrations in rat bone marrow cells harvested at 12, 24 or 36 hours was observed after administration of a single oral dose of 300, 600 or 1200 mg TBP/kg-bw in rats (Batt et al. 1992). No significant increase in sex-linked recessive lethal mutation was observed in the fruit fly *Drosophila melanogaster* assay (Hanna and Dyer 1975). All the evidence showed that TBP was not genotoxic in bioassays from bacteria, cultured mammalian cells or experimental animals.

Arnold et al. (1997) conducted a study to determine the mechanism by which TBP caused urinary bladder tumours in male Sprague-Dawley rats. The results suggested that urinary bladder changes (tumours and hyperplasia) were due to cytotoxicity or a cellular proliferative process by TBP or its metabolites, rather than direct genotoxicity. In addition, the effect of regenerative hyperplasia in bladder epithelium was reversible upon withdrawal of treatment. The *de novo* development and analysis of the mode of action of a chemical are beyond the scope of a screening assessment; however, the risk assessment reports conducted separately by the Organisation for Economic Co-operation and Development (OECD 2002) and the Health Council of the Netherlands (HCN 2005) both concluded that TBP was not mutagenic and that the observed urinary bladder tumours in rats might be attributed to a non-genotoxic mechanism.

Regarding the observed increased incidence of hepatocellular adenomas in male mice exposed to TBP at the highest dose (585 mg/kg-bw per day), the liver tumour is not considered a critical effect in this assessment for the following reasons: 1) this benign tumour was observed only in male mice at the highest dose, but was not seen in female mice or in male or female rats; 2) the incidence of hepatocellular adenomas was statistically significantly different for the current control group, but only slightly above the historical control range (2/59 to 10/60); 3) in a subchronic mouse study, TBP increased levels of liver enzymes in serum and caused elevated liver weights and hepatocyte hypertrophy (Auletta et al. 1997), which may be linked to the development of the hepatocellular adenomas observed in the chronic study; and 4) the benign liver tumours associated with TBP administration did not progress to malignant tumours during the course of the study (Auletta et al. 1998b).

The non-neoplastic effects induced by TBP in short-term, repeated-dose, subchronic or chronic toxicity studies included decreased body weight gain; increased liver, kidney or brain weight; salivation; and urothelial hyperplasia (Mitomo et al. 1980; Oishi et al. 1980; Cascieri et al. 1985; Laham et al. 1985; Bio/dynamics Inc. 1990; Bio/dynamics Inc. 1991e; Noda et al. 1994; Healy et al. 1995; Arnold et al. 1997; Tyl et al. 1997; Auletta et al. 1998a). Among these studies, the non-cancer critical effect was identified as urinary bladder hyperplasia (Cascieri et al. 1985; Laham et al. 1985; Bio/dynamics Inc. 1991e Arnold et al. 1997; Tyl et al. 1997; Auletta et al. 1998a). The oral lowest-observed-adverse-effect level (LOAEL) for urinary bladder hyperplasia ranged from 15 to 300 mg/kg-bw per day. The lowest oral LOAEL was determined to be 15 mg/kg-bw per day (200 mg/kg in diet) in Sprague-Dawley CD rats exposed to TBP at 0, 15, 53 or 225 mg/kg-bw per day in diet for 10 weeks in a two-generation reproductive toxicity study (Tyl et al. 1997). Other slightly higher LOAELs based on the urinary bladder hyperplasia effect were identified to be 35 mg/kg-bw per day in Sprague-Dawley rats in a 10-week study (0, 10, 35 or 150 mg/kg-bw per day in diet) (Arnold et al. 1997) and 38 mg/kg-bw per day in Sprague-Dawley rats in a 24-month study (0, 10, 38 or 163 mg/kg-bw per day in diet) (Auletta et al. 1998a).

TBP was not considered to be a developmental toxicant or teratogen at levels that were not maternally toxic. Three dose range-finding studies for the developmental toxicity of TBP and their subsequent teratogenicity studies have been conducted in rabbits and rats. The maternal toxicity included decreased maternal body weight and decreased feed intake; fetal toxicity included increased number of resorptions and reduced fetal body weight. In a study with New Zealand White rabbits, maternal toxicity was observed at 400 mg/kg-bw per day in rabbits (n = 18) treated with TBP at doses of 0, 50, 150 or 400 mg/kg-bw per day by gavage on gestational days 6–18. A statistically non-significant increase in fetal resorption rate was observed at the maternally toxic dose, but no teratogenicity was seen (Bio/dynamics Inc. 1991a, b; Schroeder et al. 1991). In a study with Sprague-Dawley CD rats, the LOAEL for maternal toxicity was 188 mg/kg-bw per day in rats (n = 24) treated with TBP at doses of 0, 188, 375 or 750 mg/kg-bw per day by gavage on gestational days 6–15. Significant fetal toxicity (delayed ossification and reduced fetal body weight) was observed at 750 mg/kg-bw per day; however, no teratogenicity was observed at the highest dose (Bio/dynamics Inc. 1991c, d; Schroeder et al. 1991). In the third teratological study, pregnant Wistar rats were treated with TBP at 0, 62.5, 125, 250 or 500 mg/kg-bw per day by gavage on gestational days 7–17, and the LOAEL was 125 mg/kg-bw per day based on a significant decrease in maternal body weight gain. A significantly increased incidence of fetuses with rudimentary lumbar ribs was observed at the highest dose. However, no other fetal toxicity, skeletal malformations or visceral anomalies were seen (Noda et al. 1994). These studies showed that TBP was not teratogenic in rats or rabbits at doses that did not cause maternal toxicity.

TBP was not considered to be a reproductive toxicant at levels that are not maternally toxic. In a two-generation reproductive toxicity study, group of 30 Sprague-Dawley CD rats per sex were exposed to TBP in the diet at 200, 700 or 3000 mg/kg (corresponding to 15, 53 or 225 mg/kg-bw per day) for 10 weeks and randomly mated within groups for 3

weeks. There was no evidence of reproductive toxicity, reproductive organ histopathology or effects on gestation or lactation at any dose (Tyl et al. 1997). At a dose of 15 mg/kg-bw per day, urinary bladder hyperplasia was observed in F_0 and F_1 males and in F_0 (not F_1) females, and transient body weight reductions were seen in F_1 females; only F_2 pup body weights were significantly reduced on postnatal day 14. The LOAEL for parental toxicity was 15 mg/kg-bw per day based on the occurrence of urinary bladder hyperplasia and reduced body weight; the NOAEL for postnatal toxicity was 15 mg/kg-bw per day; and the NOAEL for reproductive toxicity was 225 mg/kg-bw per day (Tyl et al. 1997). The paper concluded that TBP was not a selective reproductive toxicant.

The neurotoxicity of TBP has been evaluated in acute and subchronic animal studies. No delayed neurotoxicity (evaluated by abnormal behaviour and histological examination) was observed in hens exposed to TBP by gavage at 1840 mg/kg-bw (close to the median lethal dose [LD_{50}] of 1800 mg/kg-bw) on day 1 and day 21 (histological examination carried out on day 42) (Johannsen et al. 1977). In another similar study by Carrington et al. (1989), neither neurological deficits nor histopathological changes were seen in hens treated with two oral doses of 1500 mg TBP/kg-bw (LD_{50}) at a 21-day interval. No gross (significant changes in motor activity and functional observation) or neurohistopathological findings were observed in Sprague-Dawley rats exposed to TBP by gavage either acutely at 1000 mg/kg-bw or subchronically at 32.5, 100 or 325 mg/kg-bw per day for 3 months (Healy et al. 1995). These findings suggest that TBP is not neurotoxic. However, a significant ($p < 0.05$) reduction in conduction velocity of the caudal nerve was observed at the highest dose in male Sprague-Dawley rats orally treated with 0, 274 or 407 mg TBP/kg-bw per day for 14 days; morphological changes in unmyelinated fibres of the sciatic nerve were observed in electron microscopic examination (Laham et al. 1983). In addition, inconsistent effects (decreased, increased or no effects) on cholinesterase activity have been reported for TBP, and these effects are reversible (Sabine and Hayes 1952; Kalinina 1971; Oishi et al. 1980, 1982; Carrington et al. 1989).

The toxicokinetics and metabolism of TBP were studied in Sprague-Dawley rats and Yucatan minipigs in accordance with US Toxic Substances Control Act (TSCA) guidelines (MRI 1992a, b, c). The experimental animals were administered TBP or ^{14}C-labelled TBP by oral gavage, intravenous injection or occlusive dermal application at doses of 5, 10 or 350 mg/kg-bw. In rats, upon oral administration, TBP was rapidly and completely absorbed from the gastrointestinal tract, with peak plasma levels occurring within 3 h at the dose of 10 mg/kg-bw. Following dermal exposure of rats to 10 or 350 mg TBP/kg-bw in undiluted form, 40% or 56% of the applied dose was absorbed, respectively, with peak plasma levels occurring within 5 h. However, minipigs showed very low dermal absorption. In the same experiment, an absorption rate of 3.6–5.4% for TBP was observed in Yucatan minipigs by occlusive 6-hour dermal application at 10 mg/kg-bw, and less than 1% absorption was observed at the dose of 350 mg/kg-bw. In the toxicological evaluation of TBP by BG Chemie (2000), a maximum dermal absorption rate of 4% was proposed for TBP in minipigs.

The dermal penetration rate of TBP in pigs was 0.35 µg/cm^2 per minute, and the maximum steady-state rate of penetration in humans was 0.18 µg/cm^2 per minute (Marzulli et al. 1965).

TBP was rapidly metabolized and eliminated from experimental animals. The major route of elimination was via the kidney. There was no bioaccumulation of TBP or its metabolites in the body (MRI 1992a, b, c). In rats exposed to a single oral dose of ^{14}C-labelled TBP (14 mg/kg-bw), about 80–90% of the radioactivity was eliminated after 5 days (Suzuki et al. 1984a). The major metabolic pathways included oxidation of the butyl chains, dealkylation and glutathione conjugation, and the major metabolites included dibutyl hydrogen phosphate, butyl dihydrogen phosphate and butyl 3-hydroxylbutyl hydrogen phosphate (Suzuki et al. 1984b).

TBP was irritating to the skin and eyes of humans and laboratory animals but did not cause sensitization in humans (BIBRA 1991; IPCS 1991; OECD 2002). Severe irritation was reported after covered contact with neat liquid in rats for 5 days (Sabine and Hayes 1952) or in guinea pigs for 24 h (Du Pont 1953). Redness and swelling were also seen in guinea pigs after covered contact with 25% TBP in mineral oil (Freeman 1990). Slight to severe irritations were reported in rabbits after application of a 10% aqueous solution or neat liquid to the intact or abraded skin (Dow Chemical Co. 1956; FMC Corp. 1981). TBP was found to be irritating to the eye in rabbits and rats (FMC Corp. 1976). No sensitization was reported in guinea pigs after a 6-hour covered patch test with 10% TBP in mineral oil once a week for 3 weeks (Freeman 1990). In a human patch test, no sensitization was shown in 53 volunteers exposed to 15 applications of a less than 25% solution of TBP (Monsanto Chemical Co. 1980).

The confidence in the toxicity database for TBP is considered to be moderate to high, as short-term, subchronic and chronic toxicity, carcinogenicity, genotoxicity, reproductive toxicity, developmental toxicity and neurotoxicity studies are available. The detailed mode of action for the observed carcinogenicity in mouse liver has not been fully elucidated. The available genotoxicity dataset suggests that the observed carcinogenicity might not be due to a genotoxic mode of action.

Characterization of Risk to Human Health

Based principally on the weight of evidence–based assessment or classifications of several national and international agencies (European Commission 2002, 2004; OECD 2002; HCN 2005; ESIS 2009), the critical effects for human health risk characterization of TBP are carcinogenicity and epithelial hyperplasia in urinary bladder. In chronic experimental animal studies, TBP caused tumours and epithelial hyperplasia in the urinary bladders in rats and tumours in the liver in male mice at the high doses. Available genotoxicity data indicated that TBP was not mutagenic in *S. typhimurium* or *E. coli* mutation assays; did not cause gene mutation, micronuclei formation or chromosomal aberrations in cultured mammalian cells; and did not cause chromosomal damage in bone marrow in rats after administration. Due to the lack of positive results in genotoxicity bioassays, genotoxicity is unlikely to be responsible for the tumour induction.

The non-cancer critical effects for TBP included increased liver weight, increased kidney weight, reduced body weight and urinary bladder hyperplasia. TBP was not considered to be a reproductive toxicant, teratogen or developmental toxicant at levels that were not maternally toxic. TBP was not neurotoxic in animals, although it caused slight or transient effects on cholinesterase activity. A mechanistic study suggested that cytotoxicity with marked regenerative hyperplasia might be the precursor event to the observed tumours. Additionally, in a rat study, the hyperplastic effects were reversible upon withdrawal of TBP treatment. The risk assessments from OECD (2002) and HCN (2005) also concluded that TBP was a non-genotoxic carcinogen and that the observed tumours might be attributed to cytotoxicity and cellular proliferation at the high dose levels.

On the basis of the evidence, the carcinogenic activity of TBP is likely associated with cytotoxicity and cellular proliferation at high dose levels, rather than genotoxicity. Therefore, protecting humans from the precursor events, such as urinary bladder hyperplasia, is considered to be sufficient to protect humans from TBP's potential carcinogenic effects. Thus, the optimum approach to characterization of risk to human health for TBP is a margin of exposure (MOE) approach using hyperplasia in urinary bladder as the critical effect. The lowest oral LOAEL is identified as 15 mg/kg-bw per day in Sprague-Dawley CD rats.

The principal sources of multimedia exposure to TBP are expected to be indoor air and food. Comparison between the lowest oral LOAEL for a subchronic study (15 mg/kg-bw per day) and the highest upper-bounding estimate of intake of TBP by the general population in Canada (0.40 µg/kg-bw per day) results in an MOE of 37 500, which is considered adequate to cover the uncertainties associated with the exposure and effects databases for the general population of Canada.

The general population may be exposed to TBP at higher levels during use of certain consumer products containing TBP, such as paints and brake fluid. The maximum integrated exposure estimates (inhalation and dermal absorption) during use of these products ranged from 0.001 to 0.03 mg/kg-bw per event, depending on the type of product used. Comparison of the highest integrated exposure estimates with the critical effect level via the oral route (15 mg/kg-bw per day) results in a wide range of MOEs: 500–750 for waterborne, waterborne wall and solvent-rich paints, 2500 for brake fluid and 15 000 for aerosol paint, where the MOEs of some paints were considerably lower than the MOEs of other products.

Considering the low frequency of use of these products (1–2 times per year) based on consumer product exposure models (US EPA 1986; ConsExpo 2006) and the fact that these MOEs were calculated by a direct comparison of the per-event exposure with the lowest LOAEL for a subchronic study, the lower MOEs of 500–750 are considered to be adequate to cover the uncertainties associated with the exposure and effects databases for the general population of Canada.

Overall, although a wide range of MOEs has resulted from estimates of exposure during the use of consumer products containing TBP, taking into account the uncertainties associated with the datasets on effects and exposure, the range of estimated MOEs is considered adequately protective of human health in Canada.

Uncertainties in Evaluation of Risk to Human Health

There are only a few studies indicating carcinogenicity in experimental animals through the oral route of exposure. The overall weight of evidence for the genotoxicity of TBP is negative, and genotoxicity is not likely to be involved in tumour induction. It is prudent to use the LOAEL for the non-cancer critical effect of hyperplasia, a possible precursor event, to evaluate the risk to human health. Data on metabolism in humans and experimental animals may help to understand the differences in tumours between species. There are limited data on critical effects via the inhalation or dermal route of exposure. Uncertainties exist when the critical effect level from oral studies is used for the calculation of an MOE for inhalation or dermal exposure.

Uncertainty associated with the upper-bounding multimedia exposure estimates for the general population of Canada results mainly from the lack of recent Canadian data. The only available Canadian data were on concentrations of TBP in indoor air and drinking water from the 1980s, which may not reflect the current situation in Canada. More recent data available in other countries were used to derive the multimedia exposure estimates. As much as they may well represent similar levels of TBP in the Canadian environment, uncertainty associated with the use of data from other countries is high. Uncertainty is also associated with the use of non-Canadian-specific default assumptions in the modelled consumer product exposure scenarios. However, concentrations of TBP in the selected products are Canadian-specific information. Uncertainty associated with the use of a dermal absorption rate from the minipig study has been taken into consideration.

Conclusion

Based on the information presented in this screening assessment, it is concluded that TBP is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term 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 concluded that TBP 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 therefore concluded that TBP does not meet the definition of “toxic” as set out in section 64 of CEPA 1999. Additionally, TBP does not meet the criteria for persistence or

bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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Appendix 1a. Upper-bounding estimates of daily intake of TBP by various age groups of the general population in Canada

Route of exposure	Daily intake (µg/kg-bw per day)							
	0–0.5 years			0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	Breast milk fed[1]	Formula fed[2]	Not formula fed[3]					
Ambient air[9]	0.001	0.001	0.001	0.003	0.002	0.001	0.001	0.001
Indoor air[10]	0.044	0.044	0.044	0.093	0.073	0.041	0.036	0.031
Drinking water[11]	0.000	0.007	0.002	0.003	0.002	0.001	0.001	0.001
Food and beverages[12]	0.000	0.000	0.353	0.149	0.092	0.039	0.032	0.031
Soil[13]	0.002	0.002	0.002	0.004	0.001	0.000	0.000	0.000
Total intake	0.047	0.054	**0.403**	0.252	0.170	0.083	0.070	0.070

[1] No data were identified on concentrations of TBP 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 TBP in water used to reconstitute formula was based on modelling. No data on concentrations of TBP in formula were identified for 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). Health Canada recommends exclusive breastfeeding for the first 6 months (details available from: http://www.hc-sc.gc.ca/fn-an/nutrition/child-enfant/infant-nourisson/excl_bf_qa-qr_am_excl-eng.php).

[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 TBP in ambient air were identified. The calculation was based on the maximum concentration identified in the literature, 0.033 µg/m^3 (Ohura et al. 2006). The number of samples taken was 25 in summer and 21 in winter. The instrumental detection limit was 0.256 ng/m^3. Modelling using ChemCAN 6.0 (ChemCAN 2003) and selecting Average for Canada region indicated that the concentration of TBP in ambient air would be approximately 0.267 ng/m^3, based on the upper-end range of TBP (100 000 kg) released to water, derived from information submitted by industry (Environment Canada 2008). Canadians are assumed to spend 3 h outdoors each day (Health Canada 1998).

[10] Based on the maximum concentration identified in the literature, which was 0.178 µg/m^3 from a study conducted in Japan in 2006 (Ohura et al. 2006). The number of samples taken was 25 in summer and 21 in winter. The instrumental detection limit was 0.256 ng/m^3. One Canadian study from 1986 was identified reporting the maximum concentration of TBP in indoor air at 0.130 µg/m^3 (Otson and Benoit 1986). Canadians are assumed to spend 21 h indoors each day (Health Canada 1998).

[11] Based on the maximum concentration of TBP found in drinking water in Canada, 62 ng/L (Williams and LeBel 1981).

[12] No Canadian-specific data on concentrations of TBP in food were identified. Maximum concentrations of TBP found in the Total Diet Study conducted in 1991–1993 through 2003–2004 in the United States, in which data were collected between September 1991 and October 2003, were used instead (US FDA 2006a). Concentrations of TBP identified in different food items are summarized in Appendix 1b. Amounts of foods consumed on a daily basis by each age group are described by Health Canada (1998) except for three food items ("Fruit-flavoured cereal, pre-sweetened," "Oat ring cereal" and "Prune juice bottled"), where US FDA's (2006a) food consumption data were used after adjustment to Canadian age groups. Data for "Shredded wheat cereal" and "Raisin bran cereal" were grouped, and the maximum concentration 0.038 µg/g was used to calculate the consumption of the Canadian equivalent "cereal dry wheat and bran." Data for "Orange juice, frozen concentrated, reconstituted" and "Grapefruit

juice, frozen concentrated, reconstituted" were grouped, and the maximum concentration of 0.04 µg/g was used to calculate the consumption of the Canadian equivalent "Citrus juice canned."

[13] No Canadian-specific data on concentrations of TBP in soil were identified. The maximum concentration of TBP in house dust identified in the literature, which was 610 µg/kg from a study conducted in Sweden in 2003 (Marklund et al. 2003), was used to estimate the upper-bounding daily intake. Modelling using ChemCAN 6.0 (ChemCAN 2003) and selecting Average for Canada region indicated that the concentration of TBP in soil would be approximately 0.21 µg/kg, based on the upper-end range of TBP (100 000 kg) released to water, derived from information submitted by industry (Environment Canada 2008).

Appendix 1b. Concentrations of TBP reported in various food items (US FDA 2006a)[1]

Description	Number of samples ≥ LOQ	Mean (µg/g)	Minimum (µg/g)	Maximum (µg/g)
Rice, white, enriched, cooked	1	0.0001	0.0050	0.0050
Oatmeal, plain, cooked	1	0.0001	0.0060	0.0060
Cream of wheat (farina), enriched, cooked	6	0.0020	0.0080	0.0300
Corn flakes cereal	4	0.0031	0.0250	0.0450
Fruit-flavoured cereal, pre-sweetened	1	0.0002	0.0080	0.0080
Shredded wheat cereal	3	0.0012	0.0080	0.0310
Raisin bran cereal	1	0.0002	0.0080	0.0080
Crisped rice cereal	1	0.0009	0.0380	0.0380
Oat ring cereal	1	0.0003	0.0150	0.0150
Apple (red), raw (with peel)	1	0.0004	0.0190	0.0190
Applesauce, bottled	15	0.0043	0.0090	0.0200
Orange juice, frozen concentrated, reconstituted	1	0.0005	0.0200	0.0200
Grapefruit juice, frozen concentrated, reconstituted	1	0.0009	0.0400	0.0400
Prune juice, bottled	2	0.0009	0.0090	0.0300
Peach, canned in light/medium syrup	1	0.0005	0.0200	0.0200
Dill cucumber pickles	1	0.0002	0.0100	0.0100
Tomato juice, bottled	1	0.0002	0.0080	0.0080
Sugar, white, granulated	1	0.0005	0.0200	0.0200
Baby food, cereal, mixed, dry, prepared with water	5	0.0043	0.2000	0.0500

Abbreviation: LOQ, limit of quantification.

[1] Number of analyses: 44 per food item (no sample detected TBP at trace level).

Appendix 2. Upper-bounding estimates of exposure to TBP in consumer products

a) Paints scenarios using ConsExpo 4.1 (ConsExpo 2006; RIVM 2007)

Type of paint	Assumptions[1]	Exposure estimates[2] (mg/kg-bw per event)
Solvent-rich paint	Maximum TBP concentration: 0.5953%[3] **Inhalation[4]:** exposure frequency of 1/year, applied amount of 1.0×10^3 g, release area of 1×10^5 cm^2, molecular weight matrix of 300 g/mol, mass transfer rate of 2.31×10^3 m/min **Dermal[5]:** direct contact with product by constant rate	**Inhalation** 0.01 **Dermal** External: 0.3 Internal: 0.01 **Integrated** External: 0.3 Internal: 0.02
Waterborne paint	Maximum TBP concentration: 1.1%[6] **Inhalation[4]:** exposure frequency of 1/year, applied amount of 1.25×10^3 g, release area of 1×10^5 cm^2, molecular weight matrix of 45 g/mol, mass transfer rate of 0.204 m/min **Dermal[5]:** direct contact with product by constant rate	**Inhalation** 0.002 **Dermal** External: 0.6 Internal: 0.02 **Integrated** External: 0.6 Internal: 0.02
Waterborne wall paint	Maximum TBP concentration: 1.1%[6] **Inhalation[4]:** exposure frequency of 2/year, applied amount of 3.75×10^3 g, release area of 1.5×10^5 cm^2, molecular weight matrix of 120 g/mol, mass transfer rate of 0.204 m/min **Dermal[5]:** direct contact with product by constant rate	**Inhalation** 0.006 **Dermal** External: 0.6 Internal: 0.02 **Integrated** External: 0.6 Internal: 0.03
Aerosol paint	Maximum TBP concentration: 0.0345%[6] **Inhalation – Exposure to spray, spraying away from exposed person:** exposure frequency of 2/year, exposure duration of 20 min, room volume of 34 m^3, ventilation rate of 1.5/h, mass generation rate of 0.33 g/s, spray duration of 15 min, airborne fraction of 1, weight fraction non-volatile of 0.3, density non-volatile of 1.5 g/cm^3, room height of 2.25 m, inhalation cut-off diameter of 15 µm, non-respirable uptake fraction of 1 **Dermal – Direct dermal contact with product by constant rate:** contact rate of 100 mg/min, release duration of 900 s, uptake fraction of 0.04 (MRI 1992c)	**Inhalation** 0.0004 **Dermal** External: 0.007 Internal: 0.0003 **Oral non-respirable** External: 0.0004 Internal: 0.0004 **Integrated** External: 0.008 Internal: 0.001

[1] For all calculations, an adult body weight of 70.9 kg and an inhalation rate of 16.2 m^3/day are assumed.

[2] Exposure estimate was calculated "per event": acute exposure during use of product.

[3] 2008 personal communication from Valspar Inc. to Risk Management Bureau, Health Canada; unreferenced.

[4] The following assumptions were applied: Inhalation model was based on "exposure to vapour by evaporation" with the following default parameters: exposure duration of 132 min, room volume of 20 m^3, ventilation rate of 0.6/h, application duration of 120 min and uptake fraction of 1 (RIVM 2007).

[5] Dermal model was based on "direct dermal contact with product by constant rate" with following default parameters except for aerosol paint: contact rate of 30 mg/min, release duration of 7.20×10^3 s (RIVM 2007) and uptake fraction of 0.04 (MRI 1992c).

[6] 2008 personal communication from Canadian Paints and Coating Association to Risk Management Bureau, Health Canada; unreferenced.

b) Brake fluid exposure scenario using Versar, Inc. default values (US EPA 1986)

Consumer product	**Assumptions[1]**	**Exposure estimate (mg/kg-bw per event)**
Brake fluid	Maximum concentration of TBP: 5% (Radiator Specialty Co. of Canada 2007) **Dermal:** No ConsExpo scenario. The standard scenario in Versar, Inc. (US EPA 1986) describes a typical exposure to brake fluid while bleeding the brake lines of an automobile. The process involves opening a valve on the brake line while someone pumps the brake pedal. Dermal exposure can occur as a result of deposition of brake fluid onto skin while opening and closing the valve on the brake line. No inhalation scenario available. Thin-film thickness estimation with the following default values: film thickness (FT) of 15.88×10^{-3} cm and density of product (D) of 0.85 g/cm^3 (US EPA 1986); other values: exposed surface area $(SA)^2$ of 15 cm^2, weight fraction (WF) of 0.05, and uptake fraction of 0.04 Estimated external dose (per event) $= \frac{SA \times FT \times D \times WF}{BW}$ $= (15\ cm^2)\ (15.88 \times 10^{-3}\ cm)\ (0.85\ g/cm^3)\ (0.05) / (70.9\ kg\text{-}bw)$ $= 0.1428$ mg/kg-bw Estimated internal dose = (0.04) (estimated external dose) = (0.04) (0.1428 mg/kg-bw per event) = 0.0057 mg/kg-bw per event	**Dermal** External: 0.1 Internal: 0.006

[1] Body weight (BW) of 70.9 kg for an adult is assumed.

[2] Exposed surface area was assumed for finger tips while working with brake lines. It was assumed that each finger tip has an area of 1.5 cm^2 (1 cm × 1.5 cm), and therefore the total fingertip area is 15 cm^2.

Appendix 3. Summary of health effects information for TBP

Endpoints	Lowest effect levels[1]/Results
Acute toxicity	**Oral LD_{50}** (rat) = 1390–3350 mg/kg-bw (Kalinina 1971; Johannsen et al. 1977; Dave and Lidman 1978; Mitomo et al. 1980; Bayer AG 1986; Eastman Kodak 1986; Carrington et al. 1989) **Oral LD_{50}** (mouse) = 400–1240 mg/kg-bw (Kalinina 1971; Mitomo et al. 1980; Eastman Kodak 1986) **Oral LD_{50}** (hen) = 1800 mg/kg-bw (Johannsen et al. 1977) **Inhalation LC_{50}** (rat) = >4.2 to >42 mg/L (Eastman Kodak 1986; Bayer AG 1990) **Inhalation LC_{50}** (mouse) = 1.3 mg/L (Kalinina 1971) **Inhalation LC_{50}** (cat) = 24.5 mg/L (Fassett and Irish 1993) **Dermal LD_{50}** (rabbit) = >3100 mg/kg-bw (Johannsen et al. 1977) **Dermal LD_{50}** (guinea pig) = 9700–19 400 mg/kg-bw (Eastman Kodak 1986)
Short-term repeated-dose toxicity	**Lowest oral LOAEL:** 15 mg/kg-bw per day (200 mg/kg in diet) identified based on parental urinary bladder hyperplasia and reduced body weight in Sprague-Dawley CD rats exposed to TBP at 0, 15, 53 or 225 mg/kg-bw per day in diet for 10 weeks (Tyl et al 1997) Other oral studies: LOAEL of 35 mg/kg-bw per day (700 mg/kg in diet) identified based on urinary bladder hyperplasia in Sprague-Dawley rats exposed to TBP at 0, 10, 35 or 150 mg/kg-bw per day in diet for 10 weeks (Arnold et al. 1997). Other higher LOAELs in short-term studies were also identified (Mitomo et al. 1980; Laham et al. 1984; Bio/dynamics Inc. 1990; Noda et al. 1994) No inhalation or dermal studies identified
Subchronic toxicity	**Lowest oral LOAEL:** 75 mg/kg-bw per day identified based on urothelial hyperplasia in Sprague-Dawley rats with treatment of TBP in diet at 0, 0.6, 3, 15, 75 or 375 mg/kg-bw per day for 90 days (Cascieri et al. 1985) **Other oral studies:** Other higher LOAELs in subchronic toxicity studies in rats or mice were also identified (Mitomo et al. 1980; Laham et al. 1985; Bio/dynamics Inc. 1990). No inhalation or dermal studies for critical effects identified
Chronic toxicity/ carcinogenicity	**Oral carcinogenicity in rats:** Groups of 50 Sprague-Dawley rats per sex received diets containing 0, 200, 700 or 3000 mg TBP/kg for 24 months. A dose-related increase in the incidence of papillomas of the urinary bladder was observed in male rats (0/50, 0/50, 2/49, 23/49) and female rats (0/50, 0/50, 1/49, 11/49), with a significant increase at the highest dose ($p < 0.01$). Transitional cell carcinomas were present in the bladder of males (6/49) and females (2/50) at the highest dose. A dose-related increase in the incidence and severity of urinary bladder hyperplasia was also observed in male and female rats. A slight decrease in body weight gain was observed in females at 700 mg/kg, and a significant decrease was observed in both males and females at the highest dose. The NOEL for chronic toxicity was 200 mg/kg (9 mg/kg-bw per day for males and 12 mg/kg-bw per day for females) (Auletta et al. 1998a). **Oral carcinogenicity in mice:** Groups of 50 CD-1 mice per sex received diets containing 0, 150, 1000 or 3500 mg TBP/kg for 18 months. An increase in the incidence of hepatocellular adenomas was observed in male mice (3/50, 6/50, 7/50, 10/50), with significance at the highest dose ($p < 0.03$). No significantly increased incidence of liver tumours was observed in female mice. No other tumours were attributed to TBP administration. A significant dose-related increase in absolute and relative liver weights was observed in male and female mice receiving 1000 or 3500 mg TBP/kg. The NOEL

Endpoints	Lowest effect levels[1]/Results
	for chronic toxicity was 150 mg/kg (24 mg/kg-bw per day for males and 29 mg/kg-bw per day for females) (Auletta et al. 1998b). No inhalation or dermal studies identified
Reproductive toxicity	**Oral reproductive toxicity in rats:** In a two-generation reproductive toxicity study, groups of 30 Sprague-Dawley CD rats per sex were exposed to TBP in the diet at 200, 700 or 3000 mg/kg (corresponding to 15, 53 or 225 mg/kg-bw per day) for 10 weeks and randomly mated within groups for 3 weeks with continued exposure. No evidence of reproductive toxicity, reproductive organ histopathology or effects on gestation or lactation was observed at any dose. The LOAEL for parental toxicity was 15 mg/kg-bw per day based on the occurrence of urinary bladder hyperplasia and reduced body weight. Postnatal effects on the pup during lactation (reduced pup body weight) were observed at a dose of 53 mg/kg-bw per day administered to parental animals. The NOAEL for reproductive toxicity was 225 mg/kg-bw per day. The critical effect in this two-generation study in rats was hyperplasia in the urinary bladder (Tyl et al. 1997). No inhalation or dermal studies identified
Developmental toxicity	**Oral developmental toxicity in rats:** Pregnant Wistar rats were treated with TBP at 0, 62.5, 125, 250 or 500 mg/kg-bw per day by gavage on gestational days 7–17. A significantly increased incidence of fetuses with rudimentary lumbar ribs was observed at the highest dose. No other skeletal malformations or visceral anomalies were seen. The NOAEL for maternal toxicity was 62.5 mg/kg-bw per day, and the LOAEL was 125 mg/kg-bw per day, based on a significant decrease in maternal body weight gain. The NOAEL for fetal toxicity was 250 mg/kg-bw per day (Noda et al. 1994). **Other developmental toxicity:** The LOAEL for maternal toxicity (decreased body weight and body weight gain) was 188 mg/kg-bw per day and the NOAEL for developmental toxicity (reduced fetal body weights and delayed ossification) was 375 mg/kg-bw per day in pregnant Sprague-Dawley CD rats (n = 24 per group) exposed to TBP at 0, 188, 375 or 750 mg/kg-bw per day by gavage on gestational days 6–15 (Bio/dynamics Inc. 1991c, d; Schroeder et al. 1991). The LOAEL for maternal toxicity (decreased body weight) was 400 mg/kg-bw per day and the NOAEL for developmental toxicity was 400 mg/kg-bw per day in pregnant New Zealand White rabbits exposed to TBP at 0, 50, 150 or 400 mg/kg-bw per day by gavage on gestational days 6–18 (Bio/dynamics Inc. 1991b; Schroeder et al. 1991). No inhalation or dermal studies identified
Neurotoxicity	**Oral neurotoxicity in rats:** In Sprague-Dawley rats orally treated with 0, 274 or 407 mg TBP/kg-bw per day for 14 days, a significant reduction in conduction velocity of the caudal nerve was observed at the high dose in male rats, and morphological changes (retraction of Schwann cell processes) in unmyelinated fibres of the sciatic nerve were observed on electron microscopic examination (Laham et al. 1983). The LOAEL for neurotoxicity was 407 mg/kg-bw per day. **Other neurotoxicity:** No delayed neurotoxicity was observed in hens or rats (Johannsen et al. 1977; Carrington et al. 1989; Healy et al. 1995); the effects on cholinesterase activity were inconsistently reported (increased or decreased) from several studies (Kalinina 1971; Oishi et al. 1980, 1982). No dermal studies identified
Genotoxicity and related endpoints: *in vivo*	**Chromosomal aberration:** No significant increase in the frequency of chromosomal aberration in rat bone marrow cells harvested at 12, 24 or 36 h after administration with single oral dose of 300, 600 or 1200 mg TBP/kg-bw (Batt et al. 1992)

Endpoints	Lowest effect levels[1]/Results
	Sex-linked recessive lethal mutation: No significant increase in recessive lethal mutation tests in *Drosophila melanogaster* (Hanna and Dyer 1975)
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity in bacteria:** **Negative:** *S. typhimurium* TA97, TA98, TA100, TA1535 (up to 3333µg/plate) with or without induced rat or hamster liver S9 (Zeiger et al. 1992) **Negative:** *S. typhimurium* TA98, TA100, TA1535, TA1537 (up to 12 500 µg/plate) with or without induced rat liver S9 (Bayer AG 1985) **Negative:** *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 (up to 97 000 µg/plate) with or without induced rat liver S9 (Microbiological Associates, Inc. 1978) **Negative:** *S. typhimurium* hisC117, hisG46, TA1530, TA1535 (up to 9700 µg/plate) without activation (Hanna and Dyer 1975) **Negative:** *S. typhimurium* TA97, TA98, TA100, TA102 (up to 5000 µg/plate) without activation (Watabe et al. 1993) **Negative:** *S. typhimurium* TA102 (up to 98 000 µg/plate) with or without rat liver S9 (Pancorbo et al. 1987) **Negative:** *S. typhimurium* TA98 with liver S9 (Abe and Urano 1994) **Negative:** *S. typhimurium* TA102, TA2638 (up to 5000 µg/plate) without activation (Watanabe et al. 1996) **Positive:** *S. typhimurium* TA1535, TA1538 at 500 or 1000 µg/plate; negative at 100 µg/plate (Gafieva and Chudin 1986) **Negative:** *E. coli* strains WP2, WP2uvrA, CM561, CM571, CM611, WP67, WP12 (Hanna and Dyer 1975) **Negative:** *E. coli* strains WP2/pKM101 and WP2uvrA/pKM101 at 5000 µg/plate without metabolic activation (Watanabe et al. 1996) **HGPRT forward mutation assay:** **Negative:** in the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay in CHO cells with or without activation (Batt et al. 1992) **Micronuclei test:** **Negative:** in CHO cells at 0.1–0.3 mmol/L without activation (Brooks et al. 1996) **Chromosome aberrations:** **Negative:** CHO cells with and without metabolic activation (Batt et al. 1992)
Human studies	
Toxicity	Irritating to the skin, the eyes, the mucous membranes and the respiratory tract (IPCS 1991) No evidence of sensitization in patch studies in 53 volunteers dermally exposed to 25% TBP 15 times on alternate days (Monsanto Chemical Co. 1980) Exposed to air concentration of 15 mg TBP/m^3, workers complained of nausea and headache (ACGIH 1999)

[1] LD_{50}, median lethal dose; LOAEL = lowest-observed-adverse-effect level; LOEL = lowest-observed-effect level; NOAEL = no-observed-adverse-effect level; NOEL, no-observed-effect level.