Government of Canada / Gouvernement du Canada

Screening Assessment Report

Phenol, 4,4'-(1-methylethylidene) bis[2,6-dibromo-

Chemical Abstracts Service Registry Number
79-94-7

Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis

Chemical Abstracts Service Registry Number
4162-45-2

Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)-

Chemical Abstracts Service Registry Number
25327-89-3

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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 phenol, 4,4'-(1-methylethylidene) bis[2,6-dibromo-, commonly known as Tetrabromobisphenol A (TBBPA; Chemical Abstracts Service Registry Number[1] [CAS RN.] 79-94-7) and two derivative substances— ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis, commonly known as TBBPA bis(2-hydroxyethyl ether) (CAS RN. 4162-45-2) and benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)-, also called TBBPA bis(allyl ether) (CAS RN. 25327-89-3). These substances were identified in the categorization of the Domestic Substances List (DSL) as priorities for screening assessment as they met the criteria for persistence and inherent toxicity to non-human organisms. TBBPA was determined to present an intermediate potential for exposure of individuals in Canada.

Globally, TBBPA and its derivatives are predominantly anthropogenic, and TBBPA is the highest selling brominated flame retardant, with world market production over 120 000 tonnes in 2001 and over 170 000 tonnes in 2004, and future production will likely increase. TBBPA is incorporated into polymers as a reactive or additive flame retardant for use in flame-retarded epoxy and polycarbonate resins and, to a lesser extent, in acrylonitrile-butadiene-styrene (ABS) resins and phenolic resins. A major usage of flame-retarded epoxy resins containing TBBPA is in rigid epoxy-laminated printed circuit boards; other uses include glass-reinforced construction panels and motor housings and terminal boards. Applications of flame-retarded polycarbonate resins include communications and electronics equipment, appliances, transportation devices, sports and recreation equipment, lighting fixtures and signs. ABS resins containing TBBPA are used in automotive parts, pipes and fittings, refrigerators and other appliances, business machines and telephones. TBBPA is also used in the production of derivative substances which are used in specialty or niche applications. TBBPA bis(allyl ether) is a reactive and additive flame retardant used in expanded polystyrene foams and adhesives. TBBPA bis(2-hydroxyethyl ether) is used as an additive flame retardant in engineering polymers, epoxy resins, thermoset and thermoplastic polyesters, polyurethane, laminates for electronic circuit boards, and adhesives and coatings.

Results from an industry survey conducted for the year 2000 indicated that, although TBBPA was not manufactured in Canada in that year, between 100 and 1 000 tonnes were imported into Canada, including TBBPA in mixtures and products. Recent estimates suggest TBBPA imports into Canada remain in the 100 to 1 000 tonne range, including pure TBBPA, unreacted TBBPA in printed wire boards, and additive TBBPA in acrylonitrile-butadiene-styrene (ABS) and high impact polystyrene (HIPS) products. It is estimated that current import of TBBPA bis(allyl ether) to Canada is now in the range of 100 to 1 000 tonnes. However there is no recent evidence that pure TBBPA bis(2-hydroxyethyl ether) is imported into Canada.

Environment

TBBPA is characterized by low to moderate water solubility, low vapour pressure, and a moderately high octanol/water partition coefficient which is dependent on ionization state and responsive to pH. When released into the environment, TBBPA will likely distribute into sediment and soil, binding to the organic fraction of particulate matter and to the lipid fraction of biota. Few measured data are available on the two TBBPA derivative substances; however, predictions based on modelled data suggest these substances have properties that can be related to and extrapolated from TBBPA.

Based on the empirical and modelled data, TBBPA meets the persistence criteria in water, soil, sediment and air as defined in the *Persistence and Bioaccumulation Regulations* under CEPA 1999. Although the substance will degrade by processes of anaerobic and aerobic biodegradation, complete transformation in the environment has not been established. Its measured presence in remote Arctic regions suggests that the substance may be capable of being transported from its source to remote areas. TBBPA has been shown to degrade under anaerobic conditions to form bisphenol A. Bisphenol A has been determined to meet the criteria defined in section 64 of CEPA 1999. Based on the modelled data, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) also meet persistence criteria for soil, water and sediment as defined in the *Persistence and Bioaccumulation Regulations*, but they do not meet the criterion for air.

Empirical and modelled data indicate that TBBPA may accumulate to some degree in the tissues of biota, but does not meet the criteria for bioaccumulation as defined in the *Persistence and Bioaccumulation Regulations*. Modelled data indicate that TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) also do not meet the bioaccumulation criteria.

TBBPA is hazardous to a variety of aquatic organisms, with adverse effects on survival, reproduction and development at very low concentrations. Recent research suggests that TBBPA may be capable of disrupting normal functioning of the thyroid system in amphibians and fish, and enhancing immune system activity in marine bivalves. Modelled ecotoxicity endpoint concentrations for TBBPA bis(2-hydroxyethyl ether) are similar to those predicted for TBBPA. For TBBPA bis(allyl ether), although most predicted aquatic ecotoxicity endpoints result in no effects at saturation, chronic toxicity is predicted at very low concentrations in the range of its water solubility.

Combustion of TBBPA under certain conditions may lead to the formation of brominated dibenzo-*p*-dioxins and dibenzofurans. Small amounts of these compounds have been detected as impurities in TBBPA. These products are analogues of polychlorinated dibenzofurans and dibenzo-*p*-dioxins, two substances listed on Schedule 1 of CEPA 1999.

It is expected that TBBPA and TBBPA bis(allyl ether) may be released to the Canadian environment as a result of industrial processing activities, although there are very few measurements of these substances in the Canadian environment. TBBPA has been

measured in all environmental media, with the highest concentrations being found in samples from urban and industrial areas. Generic industrial scenarios for the aquatic environment (which considered any available site information including potential quantities of each substance used) were developed separately for each substance to provide estimates of exposure. Risk quotient analyses, integrating conservative estimates of exposure with ecotoxicity information, were performed for the aquatic, sediment and terrestrial compartments for TBBPA and TBBPA bis(ally ether). These analyses showed that risk to organisms in Canada are unlikely.

A risk quotient analysis for TBBPA bis(2-hydroxyethyl ether) was not conducted given its apparent lack of usage in Canada; the derivative substance may be considered to have low exposure potential and therefore to present a negligible risk to the Canadian environment.

Based on the information available, there is currently low risk of harm to organisms or the broader integrity of the environment from TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether). It is therefore concluded that TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) do not meet the criteria set out in paragraphs 64(*a*) or 64(*b*) of CEPA 1999, as these substances are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Human Health

Known sources of general population exposure to TBBPA are anthropogenic and include environmental media (ambient air, water, soil, sediment) and household dust, indoor air, human breast milk, food and products treated with TBBPA for its flame retardant properties. While most TBBPA is covalently bound within products, small quantities of the unreacted substance are available for migration and may be a potential source of exposure. Although the volatilization of TBBPA is low, there exists potential for offgassing from its presence in electronic components that become heated during operation as well as dust accumulated from those products.

In Canada, the highest derived upper-bounding estimate of exposure was for breast-fed infants. Hazard characterization of TBBPA was based primarily upon the assessment of the European Union, with more recent data taken into consideration. The critical effect for the characterization of risk to human health is liver toxicity observed in female offspring of mice following exposure to TBBPA in a reproductive toxicity study.

Based on the comparison of upper-bounding estimated intake of TBBPA for breast-fed infants and the critical effect for the characterization of risk to human health, it is considered that the resulting margins of exposure are adequate to address uncertainties in the health effects and exposure databases.

Sources of exposure for the two derivatives, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether), are also anthropogenic and include the same sources as that of TBBPA since the derivatives are used in the same manner. TBBPA bis(2-hydroxyethyl ether) is an additive flame retardant and TBBPA bis(allyl ether) can be used as a reactive or additive flame retardant. When used in additive form, these substances are more likely to migrate out of the product and become a potential source of exposure. In the case of pure TBBPA bis(2-hydroxyethyl ether), given there is no confirmed use in Canada, any human exposure would likely result from use of products containing this substance rather than the pure substance itself. Although data is limited to quantify the potential for migration of the derivatives and upper bounding estimates of intake have not been derived, there is potential for exposure to both TBBPA and the two derivatives.

An upper bounding estimated intake for TBBPA was derived which is expected to take into consideration any additional contribution to intake from the two derivatives. Similarly, the critical effect for the characterization of risk to human health was considered to represent hazard potential for TBBPA and the two derivatives. It is considered that the resulting margins of exposure are adequate to address uncertainties in the health effects and exposure databases for TBBPA and the two derivatives.

Based on the information in this screening assessment, it is concluded that TBBPA, TBBPA bis(allyl ether), and TBBPA bis(2-hydroxyethyl ether) are not entering the environment in quantities or concentrations or under conditions that constitute or may constitute a danger in Canada to human life or health, and therefore do not meet the criteria set out in paragraph 64(c) of CEPA 1999.

Conclusion

Based on available information for environmental and human health considerations, it is concluded that tetrabromobisphenol A, tetrabromobisphenol A bis(2-hydroxyethyl ether) and tetrabromobisphenol A bis(allyl ether) do not meet any of the criteria set out in section 64 of the *Canadian Environmental Protection Act, 1999*.

Although there is currently limited exposure in Canada to TBBPA and its concentrations currently in the environment are not indicative of harm to organisms in Canada, there may be concerns if new activities were to occur, including increased volume of manufacture, import or use, which may result in increased exposure to organisms in Canada. Therefore, options on how best to monitor changes in the use of this substance will be investigated, such as addition to the National Pollutant Release Inventory and/or amending the Domestic Substances List to indicate that the Significant New Activity provisions applies with respect to this substance, so that new activities pertaining to the use, manufacture, or import are notified and undergo ecological and human health risk assessment.

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.

The substance Tetrabromobisphenol A (TBBPA; CAS RN 79-94-7) and two derivative substances, TBBPA bis(2-hydroxyethyl ether) (CAS RN 4162-45-2) and TBBPA bis(allyl ether) (CAS RN 25327-89-3)) were three substances on the DSL selected for screening assessments. These substances were identified in the categorization of the DSL as priorities for screening assessment as they met the criteria for persistence and inherent toxicity to non-human organisms. TBBPA was determined to present an intermediate potential for exposure of individuals in Canada.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution[2].

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure for TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether). Data relevant to the screening assessment of these substances were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to February 2013 for ecological sections, and up to January 2013 for human health exposure and effects sections. Key studies were critically evaluated; modelling results may have been used to reach conclusions. In addition, an industry survey was conducted in 2000 through a *Canada Gazette* notice issued under section 71 of CEPA 1999. This survey collected data on the Canadian manufacture, import, use and release of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (Environment Canada 2001). In 2011, information was gathered from industry to update this information on TBBPA, TBBPA bis(2-hydroxyethyl ether), and TBBPA bis(allyl ether) in Canada (Environment Canada 2011a).

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

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

that were used for prioritizing the substance). This screening assessment presents Canadian derived upper-bounding estimates of intake from environmental media. An exposure intake table for the general population of Canada is presented in Appendix 3. 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 indentified 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 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. Comments received from a recent external science review on the ecological portion of this assessment and from scientific experts on the technical portions relevant to human health were considered in this assessment. In addition, public comments received from the 60-day public comment period (November 10, 2012 – January 9, 2013) have been considered and reflected in this assessment. While comments were taken into consideration, the content and outcome of the screening 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, Phenol, 4,4'-(1-methylethylidene) bis[2,6-dibromo- will be referred to as TBBPA, which has been derived from the chemical name 2,2',6,6'-tetrabromo-4,4'-isopropilidene diphenol or Tetrabromobisphenol A derived from the EINECS inventory. The two derivatives of TBBPA, Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis and Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)- will be referred to as TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether), respectively. The chemical structures of TBBPA and the two derivatives are shown in Table 1.

TBBPA is produced by the bromination of bisphenol A in the presence of a halocarbon solvent with water or 50% hydrobomic acid or alkyl monoethers, methanol and acetic acid (WHO 1995). Commercial TBBPA is available in two grades; an epoxy grade and a higher quality polycarbonate grade (HSDB 2002). Commercial formulations are typically high in purity (around 98%), with no stated additives (American Chemistry Council Brominated Flame Retardant Industry Panel [ACCBFRIP] 2001c; EU RAR 2008).

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) that are relevant to their environmental fate.

TBBPA is characterized by low to moderate water solubility, low vapour pressure, a high organic carbon-water partition coefficient, and a moderate to high octanol/water partition coefficient, which is dependent on ionization state (see Table 2). As a phenolic compound, TBBPA is weakly acidic and can exist in undissociated (neutral) or dissociated (ionized) forms. Monobasic and dibasic ionized forms of TBBPA occur, depending on whether one (monobasic) or both (dibasic) hydrogen atoms on the hydroxyl groups of the molecule are lost by ionization.

Few data are available for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether); however, predictions based on modelled data suggest that these substances have comparable properties to TBBPA. No information was found regarding the potential for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) to ionize in the environment in a manner similar to that of TBBPA. The similarities of the structure of the side chains of TBBPA bis(2-hydroxyethyl ether) and ethanol suggest that TBBPA bis(2-hydroxyethyl ether) may ionize in a similar manner to ethanol, which has little tendency to ionize in the environment. For TBBPA bis(allyl ether), the absence of phenolic groups on the molecule suggests it is less likely to ionize in a manner similar to that of TBBPA.

Sources

Sources of exposure to TBBPA are anthropogenic, primarily from waste streams or effluents of electronic and plastic moulding, manufacturing and processing plants using TBPPA as a reactive or additive flame retardant (de Wit 2002). There are no natural sources of TBBPA apart from the (bis(3,5-dibromo-4-hydroxyphenyl)methane) analogue of structural similarity to TBBPA produced by the segmented marine worm *Thelepus setosus* (EU RAR 2006). This was deemed to be an insignificant process for a TBBPA source in nature. TBBPA has also been found in sewage sludge and landfill leachate, and may be released from waste processing activities (EU RAR 2006; Osako et al. 2004). These findings indicate dispersive sources in both the domestic and industrial environments.

Results from a *Notice with Respect to Certain Substances on the Domestic Substances List (DSL)* industry survey conducted under section 71 of CEPA 1999 show that TBBPA was not manufactured in Canada in 2000, although amounts in the range of 100 000 to 1 000 000 kg were imported into the country in that year. Recent estimates suggest TBBPA imports to Canada remain in the 100 000 to 1 000 000 kg range and include pure TBBPA, unreacted TBBPA in printed wire boards, as well as additive TBBPA in acrylonitrile-butadiene-styrene (ABS) and high impact polystyrene (HIPS) products (Environment Canada 2011a). While there may be instances of non flame retardant use (Environment Canada 2011a), the primary use of TBBPA is reported as a flame retardant (Environment Canada 2001). In 2000, there were no responses to the industry survey for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether), which suggests that, at the time of the survey, these substances were not being manufactured or imported into the country in quantities greater than 100 kg. It is estimated that current import of TBBPA bis(allyl ether) into Canada is now in the range of 100 000 to 1 000 000 kg. However there is no recent evidence that pure TBBPA bis(2-hydroxyethyl ether) is being imported into Canada (Environment Canada 2011a).

In 2001, TBBPA was the largest selling brominated flame retardant, with world market demand of about 120 000 tonnes (BSEF 2003). Global production of TBBPA increased nearly 300% from 1991 to 2000, and 35% from 1999 to 2000 alone (OECD 2002). TBBPA market demand by region in 2001 (metric tonnes and percentages) include 89 400 tonnes (74.7%) for Asia; 18 000 tonnes (15%) for the Americas; 11 600 tonnes (9.7%) for Europe; and 600 tonnes (0.5%) for other countries; adding to a total market demand of 119 700 tonnes. Global production remained consistently high between 2002 (150 603 tonnes) to 2004 (170 000 tonnes), and has likely increased further (Morose 2006, BSEF 2004, Law 2009, Environment Canada 2011a). TBBPA is manufactured in Israel, the US, Jordan, Japan and China (BSEF 2009).

TBBPA has been considered a substitute for certain polybrominated diphenyl ethers (PBDEs), that have been concluded to meet the criteria as defined under paragraph 64(a) of the CEPA 1999 (Environment Canada 2006b), like the commercial Octabromodiphenyl ether (OctaBDE) product. OctaBDE has been subject to a global production phase-out (DEFRA 2002). OctaBDE was applied additively to ABS resins

used in the housings of electrical and electronic equipment; total worldwide market demand for OctaBDE was estimated to be around 3790 tonnes in 2001 (BSEF 2003). Substituting TBBPA for OctaBDE in ABS may have increased additive applications to a certain degree, affecting global use patterns and demand, and influencing the potential for release into the environment.

Up to 10% of TBBPA world production is consumed in the synthesis of other flame retardants, termed TBBPA derivatives. These derivatives are used in niche market applications and include TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether). The TBBPA bis(2-hydroxyethyl ether) is an additive flame retardant used in engineering polymers, epoxy resins, thermoset and thermoplastic polyesters, polyurethane, laminates for electronic circuit boards and various coatings and adhesives (WHO 1995). The TBBPA bis(allyl ether) derivative is a reactive flame retardant used in both adhesives and expanded polystryrene foams, and as an additive flame retardant in polystyrene foams (de Wit et al. 2011). Other derivatives of TBBPA include TBBPA carbonate oligomers and TBBPA diglycidyl ethers. These derivatives are also synthesized from its parent, TBBPA (WHO 1995).

Uses

Estimates for TBBPA use as a reactive flame retardant in epoxy and polycarbonate resins and/or electrical and electronic equipment range from 70 to 90%, while estimates of TBBPA use as an additive to plastics (e.g. ABS and phenolic resins) range from 10 to 20% (Heart 2008, BSEF 2009). When used reactively, TBBPA incorporates into the molecule, covalently bonding to or integrating into the matrix of the polymer being treated (EU RAR 2006). Although most of the TBBPA involved in the reaction is chemically bonded to the polymer, there is evidence that a small fraction—estimated to be in the range of 0.0004 to 0.06%—of the total amount used in the resin remains unreacted and may leach from the finished product (Selleström and Jansson 1995, EU RAR 2008).

TBBPA is used as a reactive flame retardant in the production of flame-retarded epoxy and polycarbonate resins (WHO 1995). Flame-retarded epoxy resins containing TBBPA are used in the manufacture of rigid epoxy-laminated printed circuit/wire boards and in glass-reinforced construction panels, motor housings and terminal boards (Danish Environmental Protection Agency 1999). For example, 2003 US estimates indicate approximately 10 000 tonnes of epoxy resin were used in the manufacturing of laminates for printed wiring boards used in a variety of end-use markets; computers and peripherals (35%); communication systems (20%); automotive (15%); consumer electronics, televisions (10%); military (10%); other applications such as business machines and industrial equipment (10%) (Morose 2006). Applications of TBBPA flame-retarded polycarbonate resins include communications and electronics equipment, appliances, transportation devices, sports and recreation equipment, lighting fixtures and signs (WHO 1995). TBBPA may also be incorporated into unsaturated polyesters used in simulated marble floor tiles, bowling balls, furniture parts, sewer pipe coupling compounds,

automotive patching compounds and buttons, and for encapsulating electrical devices (Gustafsson and Wallen 1988).

Despite the large global use of TBBPA in reactive epoxy resins for printed wire boards, it is not known with certainty that TBBPA currently enters Canada to be added to epoxy resins or to flame retard printed wire boards. TBBPA that enters Canada in printed wire boards will already have been reacted and will only be present at residual levels. Rather, a large proportion of the TBBPA imported in to Canada is used for reactive applications to a polymer product (Environment Canada 2011a).

In contrast to reactive flame retardants, additive flame retardants are physically combined with the material being treated, rather than being chemically bonded. Therefore, additive flame retardants are considered more likely to leach from the polymer matrix. When used additively, TBBPA may be combined with antimony trioxide to improve performance (WHO 1995). For example, TBBPA may be used as an additive flame retardant in ABS, HIPS and phenolic resins. TBBPA levels in ABS are 17.6-22.0% and 14% in HIPS (WHO 1995, EU RAR 2008). ABS resins containing TBBPA are used in automotive parts, pipes and fittings, refrigerators and other appliances, business machines and telephones (WHO 1995). Plastics containing TBBPA are found in television and computer monitor casings, printed circuit boards, and as components of printers, fax machines, photocopiers, vacuum cleaners, coffee machines, and electric plugs and sockets (RPA 2001; EU RAR 2008).

Additional uses for TBBPA are in the preparation of TBBPA-derivative flame retardants, flame retarding of adhesives and coatings, and for enhancing corrosion resistance in unsaturated polyesters used in chemical processing equipment (Gustafsson and Wallen 1988).

Little information is available on the TBBPA derivative substances used commercially as flame retardants; however, total worldwide use is estimated to be approximately 25% of that of TBBPA itself (WHO 1995). TBBPA bis(2-hydroxyethyl ether) is considered to have general use patterns similar to those of TBBPA, primarily in epoxy resins and some additive uses in ABS and polybutylene terephthalate (2006 email from an Environmental Quality Manager of a chemical importing company to Existing Substances Branch, Environment Canada; unreferenced), as well as an additive flame retardant used in engineering polymers (such as polybutylene terephthalate and polycarbonate), epoxy resins, thermoset and thermoplastic polyesters, polyurethane, laminates for electronic circuit boards, and adhesives and coatings. The substance may also be used reactively in unsaturated polyesters (Walker 1995).

TBBPA bis(allyl ether) is used as an additive or reactive flame retardant in polystyrene foams (including expanded polystyrene foam) (de Wit et al. 2011), and as a reactive flame retardant for adhesives (2006 email from an Environmental Quality Manager of a chemical importing company to Existing Substances Branch, Environment Canada; unreferenced). Currently, it is expected that TBBPA bis(allyl ether) is sold to resin

manufacturers in Canada. The flame retarded resin may be used for construction applications.

Releases

Data on the environmental release of TBBPA in Canada are not available. It is not a reportable substance under the National Pollution Release Inventory. In the U.S., the 2008 Toxic Release Inventory had reported all total on-site releases for all facilities to be 48 926 lbs (22 192 kg) and total off-site releases at 153 500 lbs (69 626 kg) (US EPA 2008). Releases were primarily from facilities involved in manufacturing TBBPA, printed wiring circuit boards or materials for encapsulating electronics components.

Releases of TBBPA into the environment may occur during manufacture, processing, use and disposal of the substance or products containing it. Releases occur primarily through various waste streams generated during manufacture, processing and upon disposal of the substance and products containing the substance (i.e. dismantling, recycling, landfills, incineration, accidental fires and sewage sludge applications for agricultural purposes). TBBPA may be released to air, water, soil and sediment.

Since production of TBBPA is not known to occur in Canada, potential releases from this source were not considered in this assessment. TBBPA released during processing activities may enter the air or be discharged into wastewater. Since major uses are in polymer production and electrical and electronic equipment, most releases would likely be in urban and industrial areas. Whether TBBPA is present in the air as dust particles or adsorbed to particulates, its relatively high specific gravity (2.18; WHO 1995) suggests that removal by settling would be relatively rapid (EU RAR 2008). TBBPA released into wastewater would likely be transported to a treatment facility. Moderately high partition coefficients suggest that most TBBPA entering a treatment plant will sequester into sludge, which can be applied to soil; however, small amounts (e.g. up to 0.025 µg/L; Kuch et al. 2001) have also been measured in final effluents discharged into receiving waters. TBBPA entering surface waters would be expected to partition into bed sediments, after sorption to suspended particulates in the water column and subsequent settling.

Release over the service life of end products may take place through volatilization or leaching. Studies investigating the potential for loss through volatilization failed to detect TBBPA that had been applied reactively (de Boer et al. 1998, Wolf et al. 2000, ERGO 2002), although measurable quantities were found with additive uses (Luijk and Govers 1992, ERGO 2002). In addition, TBBPA may enter into the environment as a result of particulate losses of polymeric products during their service life. The potential for TBBPA release from dismantled or disposed products at the end of their service life, and the collection, separation and regrinding of printed circuit boards appear to be limited owing to the relatively low residual or free TBBPA content of the polymer (EU RAR 2008).

The total amount of TBBPA estimated as "waste remaining in the environment" (i.e., TBBPA in the environment released from products and articles over their service life and disposal) was estimated as 0.080 tonnes/year for the European Union (EU RAR 2008). This amount is based on 4 000 tonnes/year of TBBPA used additively in products, and 21.6 tonnes/year found in products where it is applied in a reactive application (EU RAR 2008). However, the EU noted that these data are highly uncertain. There is no agreed upon methodology for estimating waste TBBPA from products and articles. For the time being, there are not enough data to conclude with certainty if there is any significance of TBBPA release from products during and at the end of their service life (EU RAR 2008).

Solid waste containing TBBPA may comprise scrap materials generated during processing operations, particulates released through aging and wear of end products during use, and disposal of products at the end of service life. Materials in landfills are subject to weathering, releasing TBBPA particulates or polymer-associated TBBPA, primarily into soil and, to a lesser extent, water and air. Currently, there have been no experiments conducted on the leachability of TBBPA from polymers in landfills; however, leaching over extended time periods is a possibility given that TBBPA has some solubility in water (EU RAR 2008). If leaching of TBBPA from plastic occurs in landfills, it is likely to strongly adsorb to particulates and degrade under anaerobic conditions, and hence, reduce its potential for leaching groundwater. The low vapour pressure would limit losses due to volatilization of TBBPA from landfills (EU RAR 2008). While potential release into air from incineration of materials containing TBBPA is possible, the effective use of emission control devices likely precludes this. Uncontrolled burns and accidental fires may release TBBPA into air, and ash from both controlled and uncontrolled incineration may contain TBBPA and other potentially hazardous degradation products.

As mentioned, little information is available on the production and uses of TBBPA derivative substances used commercially as flame retardants. TBBPA bis(2-hydroxyethyl ether) is considered to have general use patterns similar to those of TBBPA. However, as no companies responding to the 2000 section 71 *Notice* industry survey indicated they were involved in manufacturing or importing TBBPA bis(2-hydroxyethyl ether), and there is no evidence to suggest that this has changed, potential releases from activities associated with the production and processing of TBBPA bis(2-hydroxyethyl ether) in Canada are considered to be near zero.

It is expected that TBBPA bis(allyl ether) is currently imported to Canada for use in polystyrene foams. As a result, potential releases from the processing of TBBPA bis(allyl ether) are assumed to be similar to those of TBBPA, and may enter the air or be discharged into wastewater, primarily in urban and industrial areas.

For both derivatives, releases from end products during service life and at disposal may still occur.

Industrial release of TBBPA and TBBPA bis(allyl ether) are described further in the Ecological Exposure section.

Environmental Fate

A summary of selected measured and predicted physical and chemical properties for TBBPA and the two derivative substances is presented in Table 2.

TBBPA has low to moderate water solubility that is responsive to both temperature and pH, low vapour pressure, a high organic carbon-water partition coefficient, and a moderately high octanol/water partition coefficient (log K_{ow}), which is dependent on ionization state (see Table 2). The predominant species of TBBPA present in an aquatic system is related to the pH of the system, with the undissociated form prevalent at lower pH.

For this assessment, Level III Fugacity modelling was conducted using experimental log K_{ow} (log K_{ow} =5.9 (ACCBFRIP 2001b)) and water solubility values (water solubility = 0.063 mg/L, pH 7.6 to 8.1, NOTOX 2000) corresponding to pH values representative of natural surface waters (pH 6-9). At this pH range, there is some dissociation, and a proportion of TBBPA is present in mono and dibasic forms, resulting in a lower log K_{ow} than in neutral form. Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (Table 3a) suggest that TBBPA is expected to reside predominantly in soil and/or sediment, depending on the compartment of release.

If released to air, a low (<0.1%) amount of the substance is expected to reside in air (see Table 3a). Based on the low experimental vapour pressure of 1.19 x10-5 Pa and Henry's Law constant of <0.1Pa•m3/mol, if released solely to air, the major two compartments in which this substance will partition to will be soil (97.6%) and sediment (~2.22%, see Table 3a).

If released into water, TBBPA is expected to strongly adsorb to suspended solids and sediment based upon high estimated log K_{oc} value of 4.52 to 5.43 (Table 2). Volatilization from water surfaces is expected to be an unimportant fate process based upon this compound's Henry's Law constant. Thus, if water is a receiving medium, TBBPA is expected to mainly partition to sediment (96.4%), with 2.84% remaining in water (see Table 3a).

If released to soil, TBBPA is expected to have high adsorptivity to soil (i.e., expected to be relatively immobile) based upon its log K_{oc}. Volatilization from moist soil surfaces seems to be an unimportant fate process based upon its Henry's Law constant. Therefore, if released to soil, TBBPA will mainly (99.8%) reside in this environmental compartment, which is illustrated by the results of the Level III-fugacity modelling (see Table 3a).

These results represent the partitioning of the substance in a hypothetical evaluative environment resulting from intermedia partitioning, and loss by both advective transport (out of the modelled region) and degradation/transformation processes. The partitioning

values shown in Table 3 represent the net effect of these processes under conditions of continuous release when a non-equilibrium "steady-state" has been achieved.

Few measured data are available for the physical-chemical properties of TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether); however, predictions based on modelled data suggest that these substances have properties related to TBBPA (see Table 2). The two derivatives are also predicted to partition in a similar manner to TBBPA, moving preferentially into sediment and soil, and binding to the organic fraction of their particulate matter (see Tables 3b and 3c). Slightly higher predicted partition coefficients for TBBPA bis(allyl ether) suggest that it may partition more readily into organic fractions and be more strongly adsorbed than the other two substances (Table 3b). For TBBPA bis(2-hydroxyethyl ether) released to water, a slightly higher fraction of the substance may remain in water (i.e. 9.43% in water) than predicted for the other two substances (Table 3c). No information was found regarding the potential for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) to ionize in the environment in a manner similar to that of TBBPA. The similarities of the structure of the side chains of TBBPA bis(2-hydroxyethyl ether) and ethanol suggest that TBBPA bis(2-hydroxyethyl ether) may ionize in a similar manner to ethanol, which has little tendency to ionize in the environment. For TBBPA bis(allyl ether), the absence of phenolic groups on the molecule suggests it is less likely to ionize in a manner similar to that of TBBPA.

Persistence and Bioaccumulation Potential

Environmental Persistence

Laboratory and field studies indicate that TBBPA can experience primary degradation in the environment, but complete mineralization of the substance has not been demonstrated.

No biodegradation of TBBPA was observed in the standard 14-day Japan Ministry of International Trade and Testing ready biodegradation test; therefore, TBBPA is considered not readily biodegradable (CITI 1992). In laboratory studies using standard soils, approximately 36% to 82% of TBBPA added at test initiation remained at termination under aerobic test conditions (Brominated Flame Retardants Industry Panel 1989d) and 44% to 91% remained under anaerobic conditions (Brominated Flame Retardants Industry Panel 1989e), indicating that only partial biodegradation had occurred over the 64-day test period.

Wildlife International (2006a) conducted degradation studies using ring-labelled ^{14}C-TBBPA in soils (loamy sand, sandy clay loam, silt loam and silty clay loam) under aerobic and anaerobic conditions over a duration of six months. For the aerobic soil experiments, the DT_{50} for TBBPA in soils was approximately 5.3-7.7 days; however, the EU RAR (2008) suggests that it is possible that the DT_{50} values may have largely represented adsorption to soils rather than biotransformation. The amount of ^{14}C found in mineralized products increased slowly over the duration of the study reaching approximately 18-22% after 6 months. In the anerobic component to the study, large

proportions of the radiolabelled substance also appeared to be adsorbed to the soils. In the anaerobic biodegradation study, the level of complete mineralization was up to approximately 12-18% (depending on soil type) after 4 months in one series of the experiment. In a second series, complete mineralization of approximately 3-9% was observed after six months. The anaerobic degradation results in soil were difficult to interpret because full anaerobic conditions were not present in the soil test system throughout the duration of the study.

Wildlife International (2006b) also conducted an anaerobic degradation of TBBPA in water and sediments originating from two freshwater sources in Maryland. From their 102 day study, the DT_{50} for TBBPA was estimated at 28 and 24 days for the total sediment-water system. Minimal mineralization was evident in the sediments (total mineralization of 4.0% and 0.8%) over the 102 day test. The results showed that biodegradation to bisphenol A had occurred via three main intermediate products. Although there was uncertainty in the analysis, it was speculated that di- and tribromobisphenol A may have been formed, as well as potentially, mono- and dimethylether of TBBPA.

In an aerobic sediment and water microbial test system, approximately 45% to 61% of TBBPA remained after 56 days of testing resulting in estimated half-lives of 48 to 84 days (Brominated Flame Retardants Industry Panel 1989f). Under aerobic test conditions and using river sediments from southern Taiwan, the degradation rate constants for TBBPA (50μg/g) ranged from 0.053 to 0.077 day^{-1} (i.e., half life of 9.0 to 13.1 days) (Chang et al. 2012). For the nonsterilized sediment samples, 21.4 to 39.5% of TBBPA remained after 20 days of incubation. This study also noted that *Bacillus pumilus* and *Rhodococcus ruber* were the dominant bacteria in the process of TBBPA biodegradation in the river system. The aerobic degradation of TBBPA was enhanced by selected additive substances, among which rhamnolipid yielded a higher TBBPA degradation than others.

Although some experimental data on the degradation of TBBPA are available, a QSAR-based weight-of-evidence approach was also applied using the degradation models shown in Table 4. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that TBBPA is expected to be released to this compartment, biodegradation in water was primarily examined. TBBPA does not contain functional groups expected to undergo hydrolysis.

There are consistent model results for biodegradation. The five ultimate biodegradation models (BIOWIN 4.10 submodels, TOPKAT 2004 and CATABOL 2004-2008) suggest that biodegradation is very slow or recalcitrant and that the half-life in water would be ≥182 days. In addition, a primary biodegradation model, BIOWIN Sub-model 4 (primary survey model), predicts the substance has a primary half-life of ≥182 days. Therefore, considering all model results, there is evidence indicating that the predicted biodegradation half-life of TBBPA is ≥ 182 days in water. This indicates that TBBPA is expected to be persistent in water according to criteria set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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 TBBPA is expected to be persistent in soil and sediment according to criteria set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

There are no measured biodegradation data for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether). For TBBPA bis(2-hydroxyethyl ether), two of three BIOWIN (version 4.10) ultimate degradation submodels, as well as the primary degradation submodel, suggest that biodegradation is slow or very slow. For TBBPA bis(allyl ether) all BIOWIN (version 4.10) biodegradation suggest that biodegradation is very slow or recalcitrant. Therefore, considering all model results, there is reliable evidence to suggest the biodegradation half-lives of both TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) are ≥ 182 days in water. 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 the TBBPA derivatives are expected to be persistent in water, soil and sediment.

TBBPA has been shown to degrade under anaerobic conditions to form bisphenol A. Bisphenol A has been found to meet the criteria set out in section 64 of CEPA 1999. This substance is acutely toxic to aquatic organisms and has been shown to adversely affect growth and development in both aquatic and terrestrial organisms. There is evidence that low-level exposure (e.g., below 1 mg/L) to bisphenol A, particularly at sensitive life cycle stages, may lead to permanent alterations in hormonal, developmental or reproductive capacity of aquatic organisms and amphibians (Canada 2008).

Biodegradation of TBBPA to bisphenol A has been shown to occur in contaminated freshwater sediments maintained in an anaerobic environment (Ronen and Abeliovich 2000) and in anoxic marine sediments (Voordeckers et al. 2002), but it may also occur in other anaerobic systems. Ravit et al. (2003, 2005) documented the biotransformation of TBBPA to bisphenol A in sediment samples through two species of salt marsh macrophyte: smooth cord grass (*Spartina alterniflora)* and common reed (*Phragmites australis)*. It is also possible that TBBPA may degrade to bisphenol A under the conditions present during anaerobic treatment of sewage sludge. Empirical data to quantify rates of bisphenol A production in sludge or the environment resulting from to TBBPA transformation is not available. In saline and marine sediments, TBBPA was found to dehalogenate completely in step-wise fashion to form bisphenol A, which was not further degraded rapidly (Ronen and Abelovich 2000; Voordeckers et al. 2002; EU RAR 2006).

A dimethyl ether derivative of TBBPA (Me-TBBPA) has been detected in some environmental samples and is thought to be formed by microbial transformation of TBBPA in the environment (Watanabe et al. 1983). Watanabe et al. (1983) expressed concern that Me-TBBPA may be potentially more bioaccumulative than TBBPA. Few details are available on the physical and chemical properties of Me-TBBPA. The

measured vapour pressure of 2.67 x 10^{-5} Pa (25°C; Watanabe and Tatsukawa 1989) suggests that Me-TBBPA has greater volatility and therefore greater atmospheric presence than TBBPA (measured vapour pressure of 6.24 x 10^{-6} Pa at 25°C). However, Level III fugacity modelling predicts that only a very small proportion (no more than 0.5%) of Me-TBBPA released into the environment will partition into air, with most of it going into sediment and soil. The literature reports octanol/water partition coefficients (expressed as log K_{ow}) of 6.4 (Watanabe and Tatsukawa 1989) and 7.6 (Sellström and Jansson 1995). These values suggest that Me-TBBPA will adsorb strongly to organic material in sediment and soil, and to the lipid fraction of biota. In tests comparing sediments upstream and downstream of a Swedish plastics factory, TBBPA and its dimethylated derivative were both found in significantly higher concentration downstream of the factory (Sellström and Jansson 1995). The source of the dimethylated derivative of TBBPA was undetermined.

Combustion of TBBPA and the two derivative substances under certain conditions may lead to the formation of brominated dibenzo-*p*-dioxins and dibenzofurans, two substances listed on Schedule 1 of CEPA 1999, which are potentially hazardous degradation products. Small amounts of the derivative substances have also been detected as impurities in TBBPA (EU RAR 2008).

The predicted half-life for atmospheric degradation of TBBPA due to reaction with the hydroxyl radical is 3.615 days (AOPWIN 2008) (Table 4). This half-life exceeds the two-day limit for persistence in air set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000), suggesting that TBBPA may remain in the atmosphere long enough to undergo long-range transport. However, based on Level III fugacity modelling, only a very small proportion of TBBPA released into the environment is expected to partition into air; therefore, atmospheric concentrations of the substance are expected to be low. The moderately high octanol/water partition coefficient of TBBPA (experimental log K_{ow} 5.9) suggests that TBBPA released directly into air will likely adsorb to particulates, with subsequent removal to soil or water by wet and dry deposition (Hazardous Substances Databank [HSDB] 2002). There is also evidence that TBBPA is susceptible to both abiotic and biotic degradation. These processes are apparently slow but may act to reduce quantities of TBBPA in the atmosphere available for transport. Wania (2003) used four predictive models to assess the long-range transport of TBBPA, concluding that the potential for the substance to be transported is very low and depends on the behaviour of the atmospheric particles to which it sorbs. However, published data report the presence of TBBPA in air (Alaee et al. 2003; Xie et al. 2007), marine sediment (Fjeld et al. 2004) and biota (Fjeld et al. 2004) samples collected from several locations in the Arctic. This contamination may be local in origin, given the widespread use of TBBPA in many commercial products. However, these findings may also provide evidence that, under some circumstances, TBBPA may remain sufficiently long in the atmosphere to allow transport over long distances and to remote locations.

TBBPA may also be photolyticly decomposed in air. The major degradation product of photolysis in ultraviolet light is 2,4,6-tribromophenol; more than 20 products of

photolytic decomposition in air were tentatively identified (Eriksson and Jakobsson 1998).

TBBPA is susceptible to photolytic decomposition in water, producing a number of substituted phenols. The major decomposition products are 4-hydroxy-2,6-dibromophenol, 4-(2-hydroxyisopropyl)-2,6-dibromophenol, and 4-isopropylene-2,6-dibromophenol (Eriksson et al. 2004). In addition, Han et al. (2009) showed that singlet oxygen induced oxidation of TBBPA can occur in aqueous solutions by the irradiation of TBBPA dissolved in a humic acid solution. In their study, when an aqueous mixture of humic acid was irradiated (at 400 nm) in the presence of TBBPA, oxygen was consumed, and 2,6-dibromo-p-benzosemiquinone anion radical was generated and detected using electron paramagnetic resonance. They suggest that their findings indicate that solar radiation in the presence of humic acids may play an important role in the natural environment.

Bastos et al. (2008) utilized TBBPA in the development of a method to determine oxidative degradation rates of chemicals as an indicator of their susceptibility to undergo oxidation reactions. This method evaluates oxidative degradation in water in the presence of potassium permanganate, and as such, does not mimic environmental degradation, but rather is intended to suggest which substances would be amenable to oxidizing in nature. Their study showed that the rates of decay for TBBPA were rapid with half-lives ranging from 140 seconds (at 0 ºC) to 23 seconds (at 21 ºC) at pH 7.6, thus indicating that this substance is susceptible to oxidation reactions in the environment.

Atmospheric half-lives for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) derived using AOPWIN (version 1.92) are 0.418 and 0.159 days, respectively. These values fall below the 2 day criterion for persistence in air set out in the CEPA 1999 *Persistence and Bioaccumulation Regulations* (Canada 2000). Level III fugacity modelling predicts that both derivative substances, when released into the environment, will move primarily into the sediment and soil, with only very small amounts (less than 0.6%) partitioning into the air. Moderately high octanol/water partition coefficients (predicted log K_{ow} of 5.48 to 7.48 for TBBPA bis(2-hydroxyethyl ether) and of 8.71 to 10.33 for TBBPA bis(allyl ether)) suggest that these substances, when released directly into the air, will adsorb to airborne particulates in a manner similar to that of TBBPA. In this way, they may, to some extent, be transported locally in air currents but are unlikely to remain resident in the atmosphere long enough to be transported long distances before being removed by wet or dry deposition.

In summary, based on the empirical and modelled data, TBBPA meets the persistence criteria in water, soil and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days), and air (half-life in air ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on the modelled data, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) meet the persistence criteria in water, soil and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days), but do not meet the persistence

criteria for air (half-life in air ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The bioaccumulation potential of TBBPA in the aquatic environment is related to the proportion of the neutral, undissociated form present, which predominates at lower pH values. As shown in Table 2, TBBPA is characterized by a moderate to high log K_{ow} at low pH (e.g. log K_{ow} of 6.53 at pH 3.05) (Kumarochi et al. 2008), while at pH values more representative of natural surface waters (pH 6-9), dissociated forms of TBBPA increase resulting in lower log K_{ow} values. Reported experimental log K_{ow} values for TBBPA range from 4.5 to 5.9. Modelled log K_{ow} values based on experimental water solubility values were determined to be 5.1 (water solubility = 0.240 mg/L, pH 6.7 to 7.3, ACCBFRIP 2002b) and 5.7 (water solubility = 0.063 mg/L, pH 7.6 to 8.1, NOTOX 2000) (WSKOWWIN 2008). For this assessment, the experimental log K_{ow} value of 5.9 (ACCBFRIP 2001b) was selected as a conservative value representing the high end of TBBPA bioaccumulation potential in Canadian surface waters.

The experimental bioaccumulation data for TBBPA which is available for several species of fish and aquatic invertebrates generally suggests low to moderate potential for bioaccumulation. Table 5a presents the available empirical bioconcentration factor (BCF) values for TBBPA. Bioconcentration and elimination of TBBPA were evaluated in the fathead minnow, *Pimephales promelas* (Brominated Flame Retardants Industry Panel 1989c). The BCF for fathead minnow was determined as 1200, and the predicted BCF value based on the observed rates of uptake and depuration was 1300. Radio-labelled ^{14}C-TBBPA was rapidly eliminated from the tissue, with a half-life of less than 24 hours. Ninety-five percent elimination of the ^{14}C-residues occurred between days 1 and 4 of the depuration period; and 98% had been eliminated by test termination on day 6. OECD (2001a) notes that radioactivity measurements incorporate the presence of the parent substance as well as possible metabolites. In reviewing this BCF study, the EU RAR (2008) estimated that the quantity of parent TBBPA present relative to the total body burden of radioactivity was ~13%, and therefore, that the resulting BCFs expressed in terms of the parent TBBPA present in the organism would be ~160 (based on measured concentration) or ~177 (based on the kinetic data).

The bioconcentration of TBBPA in bluegill sunfish, *Lepomis macrochirus*, was evaluated using a radiolabelled commercial TBBPA product at a final test concentration of 10 µg/L (Velsicol Chemical Corporation 1978f). Over the 28-day treatment period, BCFs for TBBPA were determined at 20 (edible tissue) and 170 (visceral tissue). Concentrations in both tissues decreased rapidly during the withdrawal period, reaching non-detectable levels by day 7 in edible tissue and day 10 in the viscera. The report authors concluded TBBPA did not show a potential for bioaccumulation in the bluegill sunfish.

A bioconcentration study was conducted using carp, *Cyprinus carpio,* exposed for eight weeks to water concentrations of 80 µg/L or 8 µg/L TBBPA (CITI 1992). While study details are limited, the results demonstrate that TBBPA accumulated 30 to 341 times in

the fish exposed to 80 µg/L TBBPA and 52 to 485 times in fish at the 8 µg/L concentration.

The bioconcentration and elimination of TBBPA in Eastern oysters, *Crassostrea virginica,* was measured during a 20 day exposure period at a nominal concentration of 1.0 µg/L TBBPA (Brominated Flame Retardants Industry Panel 1989b), followed by a 14 day depuration period. Tissue concentrations of TBBPA in the oysters reached steady state on day 5. A BCF of 720 was calculated based on measured concentrations, and an estimated BCF value of 780 was obtained using uptake and depuration rates. TBBPA was continuously eliminated from the oysters over the course of the 14 day depuration period; the calculated half-life for TBBPA in the oyster tissue was between days 3 and 5 of the depuration period.

Bioaccumulation of TBBPA and the degree to which sediment organic carbon (OC) concentrations affected bioaccumulation potential were studied in the freshwater midge, *Chironomus tentans,* during a 14 day exposure period (Brominated Flame Retardants Industry Panel 1989h). Test sediments (nominal concentrations of 200, 100, 50, 25 and 13 mg TBBPA/kg dw sediment) represented a range of high (6.8%), medium (2.7%) and low (0.25%) total OC content. BCFs were calculated as the ratio of the body TBBPA concentration to that of the surrounding interstitial water, and were 240 to 510 in the high OC sediment, 490 to 1100 in the medium OC sediment, and 650 to 3200 in the low OC sediment.

Uptake and accumulation of TBBPA in the earthworm, *Eisenia fetida*, was investigated as part of a toxicity study (ACCBFRIP 2003). Adult earthworms were exposed to mean measured TBBPA concentrations 0.562, 1.16, 2.11, 4.50, 9.01, 16.7 and 35.4 mg/kg soil dw. Tissue concentrations were measured at the termination of the 28-day exposure period and compared with corresponding soil concentrations for estimated bioaccumulation factors (BAFs) for the worms. A BAF of 5.1 was obtained for worms at the lowest test concentration, while BAFs for the remaining concentrations ranged from 0.24 to 0.019. While a factor of greater than 1 is generally considered significant for a soil/sediment accumulation study (e.g. soil BAF), the authors suggest that the decrease in BAFs with increasing soil concentrations indicated that TBBPA did not bioaccumulate within the worm tissue during the 28-day exposure period.

Halldin et al. (2001) examined the uptake and distribution of TBBPA in adult and embryonic Japanese quail, *Coturnix japonica*. In the first experiment, fertilized quail eggs were injected on day 3 of incubation and analyzed radiometrically on day 6 or day 9. In the second experiment, a single dose of radiolabelled TBBPA was injected into eggs on days 6, 10 and 15 of incubation, and one 15-day old embryo from each treatment was subsequently analyzed by autoradiography. In the final experiment, egg-laying females were orally dosed or intravenously-injected with radiolabelled ^{14}C-TBBPA. Orally-exposed birds were sacrificed after 24 hours or 9 days, and the bird injected intravenously was sacrificed after 1 hour. The results from the three experiments indicated that transfer of TBBPA to the developing embryo was low, and that which was taken up was readily metabolized and excreted. In egg-laying females orally or intravenously dosed with

TBBPA, relatively rapid elimination via the bile and feces occurred with only small amounts of the radioactive compound present in the gastro-intestinal tract after 9 days. The researchers proposed that the risk of embryonic exposure to TBBPA following dietary uptake by egg-laying females (i.e., maternal transfer) should be low.

In mammals, studies with rats (see, for example, Hakk et al. 2000; Szymańska et al. 2001) show that TBBPA is largely metabolized and excreted, and, therefore, that it is unlikely to be bioaccumulative.

To further examine TBBPA potential for bioaccumulation, a predictive approach was applied using available BAF and BCF models as shown in Table 5b. According to the *Persistence and Bioaccumulation Regulations* (Canada 2000) a substance is bioaccumulative if its BCF or BAF is $\geq$ 5000; however, measures of BAF are the preferred metric for assessing bioaccumulation potential of substances. This is because BCF may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{ow} > ~4.0 (Arnot and Gobas 2003). Kinetic mass-balance modelling is in principle considered to provide the most reliable prediction method for determining the bioaccumulation potential because it can accommodate physiological and kinetic parameters which can be adjusted when data permit.

BCF and BAF estimates, corrected for potential biotransformation, were generated using the BCFBAF model (EPIsuite 2008). Metabolic rate constants were derived using an *in vivo* BCF normalization routine described further in Arnot et al. (2008a, 2008b, 2009). Since metabolic potential can be related to body weight and temperature (Hu and Layton 2001, Nichols et al. 2007), the BCFBAFWIN model further normalizes the k_M for a 10g fish at 15^{o}C to the body weight of the middle trophic level fish in the Arnot-Gobas model (184 g) (Arnot et al. 2008b). The middle trophic level fish was used to represent median exposure conditions in Canadian waters and is most representative of fish weight likely to be consumed by an avian or terrestrial piscivore. After normalization routines, median k_M values ranged from 0.29 to 1.71, with a mean value of 1.12 days^{-1}. Additional estimates of BCF were also generated using the CPOPs model (CPOPs 2008; BBM with Mitigating Factors 2008).

Using a conservative log K_{ow} of 5.9 to represent ambient surface waters, one would expect some fraction of the total TBBPA to be present in ionized form (EU RAR 2008). With metabolic transformation considered, predicted BCF values are comparable to the measured BCFs, ranging from 150 (BCFBAFWIN model) to 347.9 (CPOPs model). With consideration given to metabolic transformation, the predicted BAF is 174. BCF and BAF predictions show limited potential for bioconcentration and bioaccumulation (Table 5b).

The available evidence indicates that TBBPA is expected to have low bioaccumulation potential due to a combination of its physical and chemical properties (e.g., moderately large maximum diameter of 1.3 nm to 1.4 nm, ionization at environmentally relevant pH, varying log K_{ow}), low experimental BCFs and soil BAFs, and evidence that TBBPA is

largely metabolized and excreted in aquatic and terrestrial organisms. Metabolism-corrected BCF and BAF values are <5000, which is consistent with the physical-chemical data and empirical BCF data. Based on the consistency of available empirical and kinetic-based modelled values corrected for metabolism and considering empirical evidence for metabolic potential, TBBPA does not meet the bioaccumulation criterion (BAF > 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Bioaccumulation studies of TBBPA bis(allyl ether) are not available. One recent study screening for brominated flame retardants in herring gull eggs in the Great Lakes area (Letcher and Chu 2010) detected TBBPA bis(allyl ether) concentrations ranging from 0.08 to 0.56 ng/g wet weight. Although concentrations were very low, the study suggests that the substance is being transferred from gull to egg. However, there are no experimentally derived BAFs for TBBPA bis(allyl ether), therefore it is necessary to rely on QSAR estimates for assessment of bioaccumulation. BCFBAF (EPIsuite 2008) predicts the substance will have moderate bioconcentration potential when biotransformation is not considered, with an estimated BCF of approximately 1930 (linear regression method) based on an EVA corrected log K_{ow} value of 8.71. BCF and BAF estimates, corrected for biotransformation (QSAR generated k_M = 0.0018 for 10g fish at 15°C), were 1757 and 2 312 000, respectively (EPIsuite 2008). Arnot and Gobas (2006) critically evaluated available bioaccumulation data (BCF and BAF) for fish and other organisms. In Figure 6 and 9 of Arnot and Gobas (2006), at the log K_{ow} for TBBPA bis(allyl ether) of 8.71, the empirical distribution of "acceptable" fish BCF and BAF data shows that there are no chemicals with BCFs or BAFs exceeding 5000, suggesting that the predicted results are not within the domain of the empirical data and thus must be treated as highly uncertain. It is very likely that lack of bioavailability mitigates exposure and uptake in aquatic organisms for TBBPA bis(allyl ether).

The BCFmax model with mitigating factors (CPOPs 2008; BBM with Mitigating Factors 2008) predicts that molecular size and metabolism will mitigate bioaccumulation. The CPOPs results suggests that the range of D_{max} for TBBPA bis(allyl ether) (i.e., 1.4 to ~2.0 nm), can mitigate the rate of uptake via the gills due to steric effects thus allowing elimination processes to exceed the rate of uptake and limit the total accumulation in fish from water borne exposures. The k_M estimated by this model is ~0.02 $days^{-1}$, which is in the slow range of biotransformation rates (Arnot et al. 2008b) and could suggest that accumulation via the diet (i.e., biomagnifications factor (BMF) or BAF), which is not subject to the same steric mitigation as the gills, can be significant. However, no empirical dietary bioaccumulation data exist to support this hypothesis.

Data on the TBBPA bis(allyl ether) derivative are thus limited and highly uncertain. However, when considering the nature of the uncertainty in light of the available information on log K_{ow}, steric effects, low bioavailability and lack of empirical support for bioaccumulation at log K_{ow} >~8, the error driving the uncertainty does not suggest that a precautionary conclusion is warranted. There are greater lines of evidence to suggest that bioaccumulation potential of this derivative is limited by lack of bioavailability, some metabolism and steric uptake restriction. Therefore, it is concluded that TBBPA bis (allyl ether) does not meet the bioaccumulation criterion as set out in the

Persistence and Bioaccumulation Regulations (Canada 2000). Empirical measures of the potential for dietary bioaccumulation would help support this conclusion, when available.

Experimental study results for TBBPA bis(2-hydroxyethyl) ether suggest low bioaccumulation potential, with BCFs ranging from 10 to 53, (CITI 1992). TBBPA bis(2-hydroxyethyl ether is predicted to have moderate bioconcentration potential when biotransformation is not considered, with an estimated BCF of 1060 (linear regression method, EPIsuite 2008), based on an Experimental Value Adjusted ((EVA) KOWWIN v.1.67) predicted log K_{ow} of 5.48. A metabolic rate constant was derived using the *in vivo* BCF normalization routine described above for the CITI 1992 study, estimating a median k_M value of 13.8^{-1} which is consistent with the ether structure. Using this value, the estimated metabolism corrected BCF was 14.4 and the metabolism corrected BAF was 14.3, both for mid trophic level fish. CPOPs model (CPOPs 2008; BBM with Mitigating Factors 2008) estimated a BCF of 29.1, and predicted both metabolism and molecular size as the main mitigating factors that influence bioaccumulation potential. The range of the maximum diameter (D_{max}) for this TBBPA ether derivative ranges from 1.4 nm to 1.9 nm, which is consistent with low observed BCFs. Although data on this derivative are limited, steric characteristics, estimated metabolism rates, experimental and modelled data suggest that TBBPA bis(2-hydroxyethyl) ether has low potential for bioaccumulation and so does not meet the bioaccumulation criterion as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

Ecological Exposure Assessment

Levels in the Environment

TBBPA has been measured in all environmental media (see Tables 6 and 7), with the highest concentrations found in urban and industrial areas. There are almost no North American data characterizing concentrations of the derivative substances and only limited data available from other parts of the world.

Zweidinger et al. (1979a) analyzed air samples collected in the vicinity of two southeastern United States organobromine synthesis facilities and detected concentrations of the commercial TBBPA product Tetrabrom of up to 0.028 µg/m^3 near one facility and 1.8 µg/m^3 near the second. TBBPA was also detected in air particulates collected from sampling sites located near large bromine chemical manufacturing facilities in Arkansas (DeCarlo 1979); however, the concentrations measured were not reported.

TBBPA at a concentration of 0.00007 µg/m^3 was measured in an archived air sample collected in 1994–1995 at Dunai in the Russian Arctic (Alaee et al. 2003). Despite this very low concentration, the finding is significant, since it provides evidence of possible transport to remote Arctic regions.

Xie et al. (2007) reported concentrations of 5.0 x 10^{-8} µg/m^3 and 1.7 x 10^{-7} µg/m^3 in the vapour phase of two of seven air samples collected in 2004 from the Arctic region of the northeast Atlantic, between Norway and Iceland. The authors suggest this provides further evidence that TBBPA might have long-range transport potential.

Studies in Europe have detected the presence of TBBPA in air and precipitation samples. Peters (2003) measured 0.0006 µg/L to 0.0026 µg/L (average was 0.0011 µg/L) in 8 of 50 rainwater samples collected from locations in the Netherlands, Belgium and Germany (detection limit: 0.0005 µg/L). Open sample collectors were used to gather the samples; therefore, it was not possible to differentiate between wet and dry deposition. TBBPA was the most commonly detected of 15 brominated flame retardants analyzed in the study, which also examined levels of 13 polybrominated diphenyl ethers and hexabromocyclododecane. The authors speculated that diffuse emissions from consumer products may be a major source of TBBPA in the atmosphere.

Duyzer and Vonk (2003) measured TBBPA in air and precipitation samples collected in 2000 and 2001 from 18 locations across the Netherlands. TBBPA was present in 41% of the air samples collected in 2000 (average concentration was 1 x 10^{-7} µg/m^3) and 31% of the air samples from 2001 (average concentration was 2 x 10^{-6} µg/m^3; detection limit was not specified). TBBPA was also detected in 41% of precipitation samples gathered in 2000 (average was 0.0002 µg/L) and 69% of those collected in 2001 (average was 0.0029 µg/L; detection limit was not specified). The highest concentration, 0.0041 µg/L, was reported in a sample from 2001.

Xie et al. (2007) analyzed the vapour and particulate phases of air samples from northern Germany and the Wadden Sea region of the North Sea. TBBPA was present in all the particulate phase samples from northern Germany, at concentrations ranging from 1.6 x 10^{-7} µg/m^3 to 8.5 x 10^{-7} µg/m^3. The substance was also detected in six of the seven vapour phase samples, at concentrations ranging from 5 x 10^{-8} µg/m^3 to 2.5 x 10^{-7} µg/m^3. The two North Sea samples contained concentrations of 2.1 x 10^{-7} µg/m^3 and 5.0 x 10^{-7} µg/m^3 in the vapour phase, and 1.0 x 10^{-7} µg/m^3 and 1.9 x 10^{-7} µg/m^3 in the particulate phase.

No reports of TBBPA detected in surface water in Canada were located. TBBPA measurements in surface water from outside of Canada are discussed in the Human Health Section of this report, and range from < 3.0 x 10^{-5} µg/L (Labadie et al. 2010) to 0.05 µg/L (Environment Agency Japan 1989, 1991).

Kuch et al. (2001) analyzed surface water samples collected upstream and downstream of sewage treatment plants in Germany. TBBPA was detected in 4 of 15 upstream samples, at concentrations ranging from 0.00081 µg/L to 0.0204 µg/L, and in 3 of 15 downstream samples, at concentrations ranging from 0.0011 µg/L to 0.0188 µg/L (detection limit: 0.0002 µg/L). Me-TBBPA was present in two of the upstream samples, at concentrations of 0.00042 µg/L and 0.00086 µg/L, and in one of the downstream samples, at a concentration of 0.00106 µg/L (detection limit: 0.0002 µg/L). This reference did not provide information to indicate why the detection frequency of TBBPA and Me-TBBPA was higher upstream than downstream.

Concentrations up to 472 μg/kg (ng/g) dry weight (mean of 104 μg/kg dry weight; median of 96.7 μg/kg dry weight) were detected in 15 of the 17 sewage sludge samples collected in 2009 from 17 wastewater treatment plants in Catalonia, Spain (Gorga et al. 2013). Concentrations of monobromobisphenol A (6 of 17 samples with levels up to 807 μg/kg dry weight) and tribromobisphenol A (10 of 17 samples with levels up to 886 μg/kg dry weight) were determined. As well, when comparing with TBBPA, higher concentrations of these two compounds, (3 to 9 times for monobromobisphenol A, and 1.5 to 20 times tribromobisphenol A) were observed. Concentrations of BPA, ranging from 55.6 to 2595 μg/kg dry weight, were detected in all samples. This finding was reported to be likely due to both the TBBPA degradation and industrial production and use of BPA itself.

TBBPA was measured in surface sediments in the Pearl River Delta, southern China, ranging from 0.06 μg/kg to 304 μg/kg dry weight (Feng et al. 2012). The highest mean concentration of TBBPA was detected in sediments collected from the lower reaches of Dayanhe River (64.7 μg/kg dry weight) where an e-waste area is located. Sampling was conducted from July 2009 to October 2010. Also, concentrations of TBBPA, ranging from 657 μg/kg to 732 μg/kg dry weight (mean=694 μg/kg dry weight) were reported from two sewage sludge samples collected from a wastewater treatement plant in Guangzhou where both domestic and industrial wastewater (at a ratio of ~6:4, respectively) are treated.

Concentrations up to 21.7 μg/kg dry weight (particulates) and 0.085 μg/L (dissolved phase) were measured in influent samples collected in 2002 from five sewage treatment plants in southeast England (Morris et al. 2004). The substance was not detected in the effluents (detection limit: 3.9 μg/kg dry weight) but was present at 15.9 μg/kg to 112 μg/kg dry weight (mean of 59 μg/kg dry weight) in sludge samples. All five treatment plants were reported to receive only domestic wastewater. The same study measured sludge concentrations at six sewage treatment plants in Ireland. Concentrations in the samples ranged from less than 2.4 μg/kg to 192 μg/kg dry weight (mean of 95 μg/kg dry weight).

Sampling of influent and effluent was conducted at the Leeuwkuil Wastewater Treatment Plant, South Africa. TBBPA was measured at 6.6 μg/L, 6.8 μg/L 6 and 3.3 μg/L in influent (filtered), influent raw (unfiltered) and outfluent samples, respectively. (Chokwe et al. 2012).

TBBPA was detected in the particulate fraction of final effluents collected in 2002 from five sewage treatment plants in the Netherlands (Morris et al. 2004). Concentrations ranged from 3.1 μg/kg to 63 μg/kg dry weight (mean of 42 μg/kg dry weight). Sewage sludge samples collected the same year from eight Dutch sites contained up to 600 μg/kg dry weight (mean of 79 μg/kg dry weight) (Morris et al. 2004).

A concentration of 0.9 μg/L was measured in leachate collected from a landfill located at a metal dismantling site in Finland (Peltola 2002). TBBPA was also detected in leachate

from three of nine landfill sites in the Netherlands (de Boer et al. 2002). Concentrations in the samples ranged from 43 µg/kg to 320 µg/kg dry weight, and were associated with the particulate phase.

TBBPA was detected in one leachate sample, among a total of 40 pre-treatment and 10 post-treat samples collected at ten selected municipal solid waster landfills across Canada during the 2009 and 2010 sampling programs conducted by Environment Canada, at a reported concentration of 0.049 µg/L (49 ng/L) in 2009 (CRA 2011). Reported laboratory detection limits ranged from 0.020 to 20 µg/L.

In a study of landfill leachate in Japan, researchers found concentrations of TBBPA up to 0.62 µg/L (620 000 pg/L) of leachate. Significant reductions in TBBPA concentrations after the leachate was treated were observed in the Japanese study. The sources of TBBPA in this study were thought to include both waste electronic and electrical equipment and incinerator ash from plastics containing TBBPA (Osako et al. 2004).

Quade (2003) measured TBBPA in suspended sediments collected from eight sampling stations in the Detroit River and Trenton Channel, in the Great Lakes region (sites within Canada and the United States) during July 2000. Concentrations in the sediments ranged from 0.60 µg/kg to 1.84 µg/kg dry weight (detection limit of 0.002 µg/kg dry weight), and were highest downstream of the Detroit sewage treatment plant (1.84 µg/kg dry weight). High levels of TBBPA were also present downstream of the mouth of the Rouge River (1.82 µg/kg dry weight), a highly industrialized and heavily populated watershed, and in the Trenton Channel (1.30 µg/kg and 1.31 µg/kg dry weight, respectively). TBBPA levels were lowest at the southern Lake St. Clair sampling station (0.60 µg/kg dry weight), upstream of major industrial activity. The author concluded that there was a strong association between TBBPA concentrations and human activity in the watershed.

The same study examined bottom sediments from eight locations in Lake Ontario (Quade 2003). Preliminary results indicated that concentrations of TBBPA in sediment from Lake Ontario were substantially lower than those found in the Detroit River, ranging from not detected to 0.063 µg/kg dry weight (detection limit was not specified). Although less contamination was evident, the study confirmed the presence of TBBPA in Canadian sediments.

TBBPA concentrations ranging from not detected to 330 000 µg/kg dry weight (detection limit approximately 100 µg/kg dry weight) were measured in sediment samples collected in 1977 in the vicinity of two U.S. chemical manufacturing plants that used brominated organic compounds (Zweidinger et al. 1979b). Although the highest concentrations were associated with samples collected closest to the plant properties, the presence of detectable levels in samples collected up to 750 m away from the plants provides evidence that TBBPA is mobile and may be transported in the environment.

A number of studies on contamination of sediments in Norway, the Netherlands, Belgium, the United Kingdom, Germany and Japan were conducted during the period 2000-2003. The highest recorded concentration of TBBPA was 9,750 µg/kg (ng/g) dry

weight near a site of brominated flame retardant manufacture in the United Kingdom (Morris et al. 2004).

Additional recent studies have revealed concentrations of TBBPA in river and lake sediments, sampled from England, France, and China, ranging from 0.07 µg/kg (ng/g) to 230 µg/kg (ng/g) dry weight (Harrad et al. 2009; Zhang et al. 2009, Labadie et al. 2010, and Xu et al. 2012).

The existing literature contains few references to soil concentrations of TBBPA. DeCarlo (1979) detected the commercial TBBPA product Tetrabrom in soil samples collected in the vicinity of bromine manufacturing facilities in Arkansas; however, the study reported neither the concentration of TBBPA measured nor the location of the sampling site. Pellizzari et al. (1978) reported a maximum soil concentration of 222 000 µg/kg (wet or dry weight not specified) near production facilities in southern Arkansas. Arnon (1999) measured a TBBPA concentration of 450 000 µg/kg (wet or dry weight not specified) in soil collected at a contaminated site in Israel. Leisewitz et al. (2001) reported a concentration of approximately 0.2 µg/kg dry weight in soil collected near a production site. The site location, type of production and sampling year were not specified. These data, although limited, provide evidence that TBBPA may accumulate to high levels in soils, particularly in the vicinity of production facilities.

A recent study measured TBBPA in soil samples collected from farmlands near an e-waste recycling site in Beijing, China. This study found that 2 out of the 11 collected samples had concentrations of 0.8 and 5.6 µg/kg dry weight while balance of samples had TBBPA concentrations below the detection limit of 0.04 µg/kg (Xu et al. 2012).

Lee and Peart (2002) evaluated the presence of TBBPA in samples of sludge collected from July 1994 to January 2001 at 35 Canadian municipal sewage treatment plants. Raw and digested sludge was sampled from primary sedimentation tanks and secondary clarifiers, respectively, at plants in 21 large, medium and small municipalities in seven provinces. TBBPA was present in 34 of the 35 samples, with concentrations ranging from 2.9 µg/kg to 46.2 µg/kg dry weight (detection limit was 1 µg/kg dry weight). The highest concentration was recorded in a sample of raw sludge collected in 2000 from a treatment plant in the Toronto area. The researchers proposed that industrial wastewaters associated with the production of textiles, furniture, toys and printed circuit boards might have been the sources of the TBBPA found in the samples from the sewage treatment plants.

Saint-Louis and Pellertier (2004) in a laboratory analytical method development study measured TBBPA in one dehydrated sewage sludge sample collected in 2003 at a wastewater treatment lant, in the province of Quebec. The sample had a water content of 69.4% and was very heterogeneous and fibrous. Two batches of four sub-samples were analyzed at six months interval, in October 2003 and April 2004. TBBPA was detected in these two batches at a mean level of 330 $\pm$ 70 µg/kg dw (n= 3) and 310 $\pm$ 90 µg/kg dw (n=5), respectively. Only after the supplementary clean-up step, the mean recoveries for the extraction of TBBPA form this sample were 92 $\pm$ 12% (n=4) and 91 $\pm$ 12% (n=4), respectively. The researchers noted that sludge from this facility is incinerated.

TBBPA was detected and measured in 4 out of the 40 grab sludge or biosolids samples collected for the three consecutive weekdays in 2010 and 2011, from seven Canadian municipal wastewater treatment plants, at concentrations ranging from 53 to 195 μg/kg (ng/g) dry weight (detection limits of 23.2 – 65.6 μg/kg dry weight) (Smyth 2013). These four samples were collected from the same chemically assisted primary treatment plant which has no sludge digestion. Influent to the plant was considered to mainly consist of residential inputs, with a lessor amount of industrial-commercial inputs (including heavy industry, hospitals and universities). The fraction of organic carbon was not measured; however, volatile solids and total solids were measured for the study. Surrogate recoveries in the sludge or biosolids samples collected were frequently low, and ranged from 2.27% to 82.0%. The surrogate recoveries in the four sludge or biosolids samples having measurable concentrations of TBBPA ranged from 4.06% to12.0%. Smyth suggested that the surrogate was being destroyed or bound in the sample matrix.

Authors of a report with analytical results for TBBPA in sewage sludge from a Montreal sewage treatment plant reported that dried sludge from that plant is incinerated. By scaling up from the measured concentration of TBBPA, the authors estimated about 8 kg per year enter the environment from incineration of Montreal sewage sludge (Saint-Louis and Pelletier 2004). In some parts of Canada, there may be instances where sewage sludge is spread on farm fields to amend the soil; however, disposal to landfills may also occur.

Quade (2003) measured concentrations of TBBPA in sewage sludge collected from five treatment plants in southern Ontario and seven in the United States. The samples represented a variety of sewer and wastewater inputs and treatment types. All Canadian plants carried out primary and secondary (aerobic digestion) treatment, and one plant also conducted tertiary treatment. The US plants used one of three treatment types: anaerobic digestion, lime stabilization or compost. Sampling at the Canadian plants was conducted between October and December 2002, while the US samples were collected between March 1999 and August 2001. TBBPA was present in all the samples analyzed, with concentrations ranging from 9.04 μg/kg to 43.1 μg/kg dry weight in the sludge from the Canadian sites and 2.98 μg/kg to 196 μg/kg dry weight in those from the U.S. No correlation with treatment type was evident from the results.

TBBPA has been reported in sewage sludge in several European countries and Japan at ng/g levels (Morris et al. 2004; Öberg et al. 2002; MOE Japan 2003). In most cases, the treatment plant was not the recipient of industrial wastewater discharges known to contain TBBPA.

A recent study reported concentrations of TBBPA ranging from 67.1 μg/kg to 618 μg/kg dry weight and from 4.01 μg/kg to 144 μg/kg dry weight in sewage sludge samples taken from municipal wastewater treatment plants, and industrial wastewater treatment plants, respectively in Korea (Hwang et al. 2012).

TBBPA has been detected in a variety of biota, including fish, invertebrates, marine mammals and birds. One study reporting the occurrence of TBBPA in North American biota was found in the published literature. Johnson-Restrepo et al. (2008) measured concentrations of the substance in the blubber of bottlenose dolphin, *Tursiops truncates*, and in the muscle tissue of bull shark, *Carcharhinus leucas*, and Atlantic sharpnose shark, *Rhizoprionodon terraenovae*, collected from the coastal waters of Florida from 1991 to 2004. TBBPA was present in all 31 samples analyzed, with concentrations ranging from 0.056 µg/kg to 8.48 µg/kg lipid weight in bottlenose dolphin, from 0.035 µg/kg to 35.6 µg/kg lipid weight in bull shark, and from 0.495 µg/kg to 1.43 µg/kg lipid weight in Atlantic sharpnose shark.

Samples collected from European species of eel, salmon, perch, pike and cod were found to contain concentrations of TBBPA ranging from 0.021 µg/kg to 5.0 µg/kg wet weight (Kemmlein 2000; Peltola 2002; SFT 2002). De Boer et al. (2002) analyzed samples from a variety of aquatic species in 1999 and 2000 in the United Kingdom, the Netherlands and the North Sea, finding TBBPA in eel, whiting, cod, starfish, whelk and hermit crab. Concentrations ranged from less than 0.1 µg/kg to 3.3 µg/kg wet weight and less than 97 µg/kg lipid weight to 245 µg/kg lipid weight for the fish species. The concentrations for the starfish were 4.5 µg/kg wet weight and, for the other invertebrates, ranging from less than 1 µg/kg to 96 µg/kg lipid weight. De Boer also found TBBPA in samples of cormorant liver (0.07 µg/kg to 0.28 µg/kg wet weight) and harbour porpoise blubber (0.05 µg/kg to 376 µg/kg wet weight). Me-TBBPA was measured in 4 out of 10 common tern eggs, at concentrations of 0.4 µg/kg to 0.8 µg/kg wet weight (de Boer et al. 2002). Morris et al. (2004) evaluated concentrations in biota samples collected from 1998 to 2001 in rivers and estuaries discharging into the North Sea basin from the United Kingdom, Belgium and the Netherlands. The highest concentrations were measured in harbour porpoise (up to 418 µg/kg lipid weight), whiting (up to 245 µg/kg lipid weight), sea star (one sample, 205 µg/kg lipid weight) and whelk (up to 96 µg/kg lipid weight). TBBPA was also found in hermit crab (less than 1 µg/kg to 35 µg/kg lipid weight), cormorant (2.5 µg/kg to 14 µg/kg lipid weight), eel (less than 0.1 µg/kg to 13 µg/kg lipid weight) and cod (less than 0.3 µg/kg to 1.8 µg/kg lipid weight). Herzke et al. (2005) recorded the presence of TBBPA in eight eggs collected from species of predatory birds in Norway. Concentrations in the eggs ranged from less than 0.004 µg/kg to 0.013 µg/kg wet weight. SFT (2002) detected TBBPA in moss samples from Norway, at concentrations of 0.019 µg/kg to 0.89 µg/kg wet weight. The researchers suggested that the presence of TBBPA in moss may indicate the potential for atmospheric transport of the substance. Liver samples from Atlantic cod collected from two sites in northern Norway contained 0.5 µg/kg and 2.5 µg/kg lipid weight (Fjeld et al. 2004). The presence of TBBPA in biota from remote northern locations provides further evidence of possible long-range atmospheric transport.

TBBPA has been measured in several species of Japanese fish, at concentrations ranging from 0.8 µg/kg to 4.6 µg/kg wet weight and 3.4 µg/kg to 23 µg/kg lipid weight (Watanabe and Tatsukawa 1989; Ohta et al. 2004). Me-TBBPA was detected at approximately 5 µg/kg wet weight in mussels from Osaka Bay (Watanabe et al. 1983).

There are very few data available for TBBPA bis(allyl ether) measurements in the environment and in biota. A recent study by Qu et al. (2011) measured TBBPA bis(allyl ether) in environmental samples collected from the Liuyang river in South China, In 2009, water concentrations ranged from non-detect to 0.0491 µg/L (49.1 ng/L) (n=18), with the highest concentrations found directly downstream of a brominated flame retardant plant. Sediment concentrations showed the same pattern, ranging from 143.4 to 10183.41 µg/kg (ng/g) (n=18), with the highest levels measured in the same location downstream of the manufacturing plant.

Ismail et al. (2006) detected TBBPA bis(allyl ether) in 5 of 30 lake trout samples collected in Lake Ontario between 1997 and 2004. These concentrations ranged from 0.2 to 1.7 µg/kg (ng/g) wet weight. Letcher and Chu (2010) sampled herring gull eggs in the Great Lakes and determined that TBBPA bis(allyl ether) was detectable in 83% of the samples, with detected concentrations ranging from 0.08 to 0.56 µg/kg (ng/g) wet weight. Although concentrations were very low, the study suggests that the substance is being transferred from gull to egg.

No data are available for TBBPA bis(2-hydroxyethyl ether) measured in biota in the environment. However, in a study by Nyholm et al. (2008), female zebrafish were exposed for 42 days via diet to a mixture of brominated flame retardants, which included TBBPA bis(2-hydroxyethyl ether). After exposure, TBBPA bis(2-hydroxyethyl ether) was not detected in samples.

Industrial Release

Limited data concerning the concentrations of TBBPA and its derivatives in water in the Canadian environment have been identified. Therefore, environmental concentrations have been estimated from available information. Environmental concentrations of TBBPA and TBBPA bis(allyl ether) have been estimated for an industrial release scenario, as described in the following sections.

Aquatic exposure to TBBPA and TBBPA bis(allyl ether) is expected if the substances are released from industrial manufacture, formulation or to a wastewater system that discharges its effluent to a receiving surface water body. The concentration of the substances in the receiving water near the discharge point of the wastewater system is used as the predicted environmental concentration (PEC) in evaluating the aquatic risk of the substance. It can be calculated using the equation:

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

where

$C_{water-ind}$:	aquatic concentration resulting from industrial releases, mg/L
Q:	total substance quantity used annually at an industrial site, kg/yr
L:	loss to wastewater, fraction
R:	wastewater system removal rate, fraction
N:	number of annual release days, d/yr
F:	wastewater system effluent flow, m^3/d
D:	receiving water dilution factor, dimensionless

As TBBPA and TBBPA bis(allyl ether) are used for product formulation by industrial facilities and are reported to be released to water, aquatic industrial release scenarios were developed for both substances. Although some known sites were available, to maintain confidentiality two generic scenarios per substance were presented, based on known and potential uses in Canada. Based on the known sites, the substances were treated separately (i.e., it was assumed that TBBPA and TBBPA bis(allyl ether) were not processed at the same sites).

For TBBPA, the generic scenario #1 represents the upper range (maximum) mass in commerce and has been prepared according to activities declared by a user of TBBPA in Canada. In this scenario, TBBPA is assumed to be used in a reactive polymer application where no process water is used. Water is only used to cool material and runs in a closed loop system. While polymerised products can come in contact with cooling water in the process, contaminated cooling water is sent to an authorized off-site facility for treatment. Hence, no TBBPA discharge to wastewater is possible. The generic scenario #2 represents another user of TBBPA in Canada, and considers a lower and upper mass range in the use of TBBPA. In this scenario, TBBPA is assumed to be used in a resin production application where no process water is used. There is a dust collection system with no drain on the floor where TBBPA is used or stored. Cooling water does not directly come into contact with TBBPA; however, TBBPA is a component of the plastic matrix which is in contact with water. Thereafter, contaminated water, if any, is released through an on-site wastewater treatment plant prior to entering surface water.

Table 8 presents the TBBPA inputs used to estimate resulting aquatic concentrations close to the industrial point of discharge. The first scenario yields no PEC as no water is involved in the process and there are no releases to surface water. For the second scenario, PEC values ranged from 0.72 – 7.2 µg/L (Environment Canada 2013). It should be noted that the PEC estimation for scenario #2 is considered to be a conservative worst case scenario and thus, a PEC calculated at or below the lower range is more reasonable to consider.

For TBBPA bis(allyl ether), the generic scenarios represented 1) the upper range mass in commerce used in an additive application by a polymer manufacturer located near a large wastewater treatment system that discharges to a large river and 2) the lower range mass

in commerce used in an additive application by a polymer manufacturer located near a small wastewater treatment system that discharges to a small river. Table 9 presents the TBBPA bis(allyl ether) inputs used to estimate resulting aquatic concentrations close to the industrial point of discharge. Based on these assumptions, this first scenario yields a PEC of 1.31 µg/L, and the second scenario yields a PEC of 24.21 µg/L (Environment Canada 2011b). These PEC values represent the level of exposure in the receiving water near the point of the discharge from the wastewater treatment system at each site. However it is noted that these estimated PEC values exceed the predicted water solubility for TBBPA bis(allyl ether).

Consumer or Commercial Release

Although there is uncertainty with respect to the significance of TBBPA and its derivatives releases from consumer and commercial products, it is expected that release to water may be low. For products containing reactive TBBPA or TBBPA bis(allyl ether), the substance is chemically bound to the resin. The level of unreacted TBBPA is very low, of the order of 0.0004 to 0.06% (EU RAR 2008), limiting leakage into the environment. In products where TBBPA use is additive, diffuse emissions may occur from articles, but it is expected the rate may be low. Furthermore, many products made with TBBPA and TBBPA bis(allyl ether) will not be in contact with water on a regular basis, e.g. circuit boards, construction foam. For example, products will be installed in buildings. Once construction is complete, products are enclosed for years until renovation or demolition. Potential of release from service life is estimated at 0.05% per year to water if the substance is for indoor use or 0.16% per year if use is outside. The large majority of products would be enclosed/indoor use and are not expected to be heated during service life, therefore the release rate of 0.05% to air or water over service life is most applicable (OECD 2004).

Ecological Effects Assessment

The bioavailability and uptake of ionizing organic substances such as TBBPA is an area of uncertainty and ongoing research. While ionized organic species may have a relatively high affinity for the polar/charged surfaces of biological membranes, they are generally expected to translocate very slowly across the hydrophobic core of these membranes, when compared to neutral species (Escher and Sigg 2004). Thus, in the absence of ion pairing or active uptake processes, the absorption of ionized species into tissue is expected to be limited when compared to neutral species. Furthermore, overall substance bioavailability is expected to decrease as pH approaches and exceeds pKa, due to increasing ionization of the substance. This expected behaviour is supported by studies with chlorophenols that indicated a decrease in bioavailability to fish with increasing ionization (Kobayashi and Kishino 1980; Holcombe et al. 1980; Saarikoski and Viluksela 1981; Spehar et al. 1985; Saarikoski et al. 1986; Stehly and Hayton 1990; Howe et al. 1994; Kishino and Kobayashi 1995).

Multiple mechanisms have been proposed to explain the overall uptake of hydrophobic ionizing organic substances, maintaining bioavailability and absorption even for a pH at which significant ionization would be expected. While detailed assessment of effects, based on the potentially complex uptake kinetics of TBBPA and toxicity differences of the neutral and ionized species, would be preferred, the current knowledge of TBBPA bioavailability and toxicity does not support it. Therefore, equal bioavailability and toxicity of the neutral, monobasic and dibasic forms of TBBPA species are considered conservative but defensible assumptions for the risk characterization.

The specific mechanism of toxic action of TBBPA has not been determined. The neutral (undissociated) form of the substance may be expected to act as a narcotic or baseline toxicant, exerting adverse effects on membrane integrity and function by virtue of its presence and concentration in the membrane. Ionized forms of TBBPA have lower bioavailability and likely, therefore, less toxicity. However, Escher and Sigg (2004) have proposed that ionized forms of weak organic acids, such as substituted phenols (a category that includes TBBPA), may act as uncouplers of oxidative photophosphorylation, making them potential disruptors of the electron transfer chain that is integral to energy production in cells (Escher and Sigg 2004).

TBBPA has demonstrated toxicity in a variety of aquatic and terrestrial species (see Table 10). In aquatic species, a 96-hour median effective concentration EC_{50} of 0.098 mg/L and a 96-hour Lowest Observed Effect Concentration (LOEC) of 0.018 mg/L were determined for the marine Eastern oyster, *Crassostrea virginica,* based on significantly reduced shell deposition rates (Brominated Flame Retardants Industry Panel 1989a). The 70-day LOEC and No Observed Effect Concentration (NOEC) for growth inhibition in the common mussel, *Mytilus edulis,* were 0.032 mg/L and 0.017 mg/L, respectively, based on shell length and dry weight, and 0.126 mg/L and 0.062 mg/L, respectively, based on wet weight (ACCBFRIP 2005b, c). An overall 21-day LOEC and NOEC of 0.98 mg/L and 0.30 mg/L, respectively, were measured in the water flea, *Daphnia magna,* based on significantly reduced reproduction (Brominated Flame Retardants Industry Panel 1989g). Wollenberger et al. (2005) reported a 5-day EC_{50} of 0.125 mg/L for inhibition of larval development in the marine copepod, *Acartia tonsa*.

The 35-day LOEC and NOEC for fathead minnow, *Pimephales promelas,* were 0.31 mg/L and 0.16 mg/L, respectively, based on significantly reduced embryo and larval survival (Brominated Flame Retardants Industry Panel 1989i). Kuiper et al. (2007) reported acute effects (abnormal swimming behaviour, reduced respiration, progressive loss of equilibrium) in adult zebrafish, *Danio rerio,* exposed for 30 days to concentrations of 3.0 μM and 6.0 μM (1.63 mg/L and 3.26 mg/L, respectively) of TBBPA. Egg production was decreased at 0.047 μM (0.026 mg/L), while significantly reduced hatching occurred at a lowest test concentration of 0.023 μM (0.013 mg/L). Recent investigations into possible sublethal effects in aquatic organisms indicate that TBBPA may influence enzyme function and oxidative capacity in fish (Ronisz et al. 2001; Christiansen et al. 2000; Jurgella et al. 2006). Hu et al. (2009) studied the effects of TBBPA in an acute toxicity study on zebrafish embryos in combination with three biomarkers, superoxide dismutase, lipid peroxidation, and heat shock protein. Results

indicated that concentrations of >0.75 mg/L TBBPA can cause lethality or malformation. Biomarker activities for superoxide dismutase, lipid peroxidation, and heat shock protein 70 levels were increased with increasing concentration, indicating that TBBPA can cause oxidative stress and overexpression of heat shock protein 70.

In a study by Nyholm et al. (2008), female zebrafish were exposed for 42 days via diet to a mixture of brominated flame retardants, which included TBBPA and TBBPA bis(2-hydroxyethyl ether). Following this exposure, TBBPA was measured in zebrafish eggs indicating that transfer of the substance is possible from the adult fish to eggs. In addition, an egg/fish concentration ratio (dividing the concentration of TBBPA in eggs by the concentration measured in fish) was shown to be greater than one, indicating a significant exposure of the eggs. In contrast, TBBPA bis(2-hydroxyethyl ether) was not detected in samples.

Breitholz et al. (2008) studied mixture toxicity of ten brominated flame retardants including TBBPA, in the benthic copepod, *Nitocra spinipes*. Using silica gel as a particulate carrier, the individual BFRs were tested for range finding purposes. TBBPA had the second lowest value for both a 96-hour acute toxicity test (LC_{50}=0.39 mg/L), and for a 6-day partial life cycle larval development ratio test (LDR) ($NOEC_{LDR}$ = 0.007 mg/L), which measures the proportion of animals that have transitioned from larval stage to copepodite stage. Using these results, six of the ten BFRs were applied as a mixture based on NOEC proportions (set as 0.008, 0.04, 0.2, 1 and five times the $NOEC_{LDR}$ concentrations for each individual BFR) and applied to *Nitocra spinipes* in a full life cycle test (26 days). The nominal $NOEC_{LDR}$ concentrations used in the mixture ranged from 0.002 mg/L to 0.300 mg/L. Survival was significantly decreased after 6 and 26 days exposure at the 1x $NOEC_{LDR}$ mixture concentration as compared to the control. At the 5x NOEC mixture concentration, all animals were dead, and survival success in the three lowest mixture concentrations showed a clear concentration-response pattern related to mortality over the full life cycle. No significant responses on reproductive endpoints due to the BFR mixture were measured. The authors concluded that low concentrations of individual substances not intended to be biologically active may cause toxicity in the copepod *Nitocra spinipes* if exposed in mixtures.

ACCBFRIP (2002d, e) conducted toxicity studies using the freshwater oligochaete, *Lumbriculus variegates*. Twenty-eight day-LOECs, based on reduced survival and reproduction, and growth, were 151 mg/kg and 426 mg/kg dry weight for sediments with OC content of 2.5% and 5.9%, respectively.

A 28-day EC_{50} of 235 mg/kg sediment dry weight was calculated for emergence in the midge, *Chironomus riparius* (ACCBFRIP 2005d). The corresponding LOEC and NOEC for the study were 250 mg/kg and 125 mg/kg dry weight, respectively, based on emergence ratio, development rate and development time.

A 16-day early life stage study on sea urchin *Psammechinus miliaris* reported morphological abnormalities were induced at a concentation higher than 1000 nM (0.54

mg/L) TBBPA, and larval development was delayed above 500 nM (0.27 mg/L) TBBPA (Anselmo et al. 2011).

TBBPA may be able to disrupt thyroid hormone function in developing amphibians. Kitamura et al. (2005a) evaluated tail resorption and limb growth in premetamorphic Japanese wrinkled frog, *Rana rugosa*, exposed to water concentrations of 10^{-8} to 10^{-6} M (approximately 0.005 mg/L to 0.5 mg/L). TBBPA was found to have a mitigating effect on the functioning of the thyroid hormone, triiodothyronine (T_3), which is critical to the triggering and control of metamorphosis in amphibians (Brown et al. 1996; Kashiwagi et al. 1999; Hanada et al. 2003). Veldhoen et al. (2006) exposed premetamorphic tadpoles of the Pacific tree frog, *Pseudacris regilla*, to 10^{-8} M (0.0054 mg/L) or 10^{-7} M (0.054 mg/L) of TBBPA and found that normal thyroid hormone-mediated gene expression profiles were significantly altered at both test concentrations. The results demonstrated that changes in endocrine-regulated gene expression at a sensitive life stage in the frog life cycle can occur within hours of exposure to low concentrations of TBBPA. Further evidence of the disruption of thyroid hormone function in developing amphibians is reported by Jagnytsch et al. (2006), Kudo et al. (2006) and Fini et al. (2007).

The effect of TBBPA on the survival and reproduction of the earthworm, *Eisenia fetida*, was investigated in three 56-day toxicity studies (ACCBFRIP 2003, 2005a). No significant effects were observed on adult worm survival in the first study (ACCBFRIP 2003); however, reproduction was significantly affected at all test concentrations relative to that in the controls. A second study was initiated (ACCBFRIP 2003) to obtain more information on potential reproductive impacts. Based on the results of both studies, the 28-day NOEC for earthworm survival was 4840 mg/kg soil dry weight, and the EC_{10} was greater than the highest treatment concentration of 4840 mg/kg. The 56-day LOEC for reproduction was 4.50 mg/kg soil dry weight, and the NOEC was 2.11 mg/kg dry weight of soil. The 56-day EC_{10} and EC_{50} values for reproduction were 0.12 mg/kg and 1.7 mg/kg dry weight of soil, respectively. A subsequent study (ACCBFRIP 2005a) was conducted to further clarify the reproductive results. No mortality was observed in any of the test containers, and the NOEC for survival was >20 mg/kg soil dry weight, the highest concentration tested. A 56-day LOEC and NOEC of 0.63 mg/kg and 0.31 mg/kg of soil dry weight, respectively, were determined for the study, based on significantly reduced reproduction in treated soils relative to the controls. The 56-day EC_{50} (reproduction) was calculated as 0.91 mg/kg dry weight and the 56-day EC_{10} was less than the lowest test concentration of 0.31 mg/kg dry weight.

The effects of TBBPA on the emergence and growth of plant seedlings were evaluated in a 21-day study using corn (*Zea mays*), onion (*Allium cepa*), ryegrass (*Lolium perenne*), cucumber (*Cucumis sativa*), soybean (*Glycine max*) and tomato (*Lycopersicon esculentum*) (ACCBFRIP 2002e). There were no apparent adverse treatment-related effects on seedling emergence. Growth, as measured by seedling height and dry weight, was adversely affected in all species, except soybean. The lowest endpoint values were a 21-day LOEC of 78 mg/kg dry weight of soil for cucumber and a 21-day EC_{50} of 49 mg/kg soil dry weight for ryegrass.

Li et al. (2008) examined biochemical responses of wheat (*Triticum aestivum)* to TBBPA exposure. Soil treatments with sterilized wheat seeds were exposed to concentrations of 0, 0.5, 5, 50, 500, and 5000 mg/kg dry weight TBBPA. The cultures were analyzed for changes in chlorophyll, malondialdehyde (MDA) content, and soluble proteins and enzyme activity in leaves, at days 0, 7, and 12. It was found that chlorophyll content decreased significantly (compared to control) with increasing TBBPA up to 50 mg/kg, but showed little difference between 50 mg/kg to 5000 mg/kg. MDA formation increased significantly with TBBPA concentration at 7 days and 12 days, peaking at the day 7 exposure to 5000 mg/kg TBBPA. Proteins and enzyme activity were also affected by TBBPA: increasing antioxidant enzyme activity with exposure was suggested to reflect a protection mechanism; however, this activity decreased at high concentrations (50 mg/kg to 5000 mg/kg) over longer exposure. The study determined that TBBPA significantly affected physiological processes. While wheat had a capacity to tolerate oxidative stress, this capacity was diminished after prolonged exposure and increasing TBBPA concentration. No dose-response effects were measured between activity of antioxidant enzymes and the concentration of TBBPA.

An eight-week study of fate of TBBPA in soil and uptake by plants has been conducted by Li et al. (2011). The study found that concentrations of TBBPA in soil rapidly decreased by approximately 90% mainly due to abiotic sorption to soil particles. Some uptake in plants was however determined with concentrations of TBBPA in cabbage and radish measured up to 18 and 5 μg/kg tissue dry weight, respectively. In this study, sterilized cabbage and radish seeds were planted in soil spiked with TBBPA to a concentration of 1000 μg/kg dry soil.

Sverdrup et al. (2006) examined the sublethal toxicity of TBBPA to soil nitrifying bacteria, red clover (*Trifolium pratense*) and the earthworm, *Enchytraeus crypticus*. TBBPA was toxic to enchytraeid worms, with a 21-day LOEC of 10 mg/kg of soil dry weight for significantly reduced reproduction and a 21-day EC_{10} value of 2.7 mg/kg dry weight. Significant inhibition of soil nitrifying bacteria occurred at a LOEC of 1000 mg/kg dry weight, and the 28-day EC_{10} was 295 mg/kg dry weight. No effects were seen on seedling emergence and growth, and on worm survival.

A cytoxicity study for TBBPA was conducted on two freshwater microalgae, *Pseudokirchneriella subcapitata* and *Nizschia palea* (Debenest et al. 2011). The study exposed the microalgae to 1.8, 4.8, 9.2, 12.9 and 16.5 μM (979, 2611, 5004, 7016 and 8974 μg/L) of TBBPA for both 72-hours. Significant effects on cell viability, size and growth for both microalgae were reported at the three highest experimental concentrations.

There are few data on potential effects on wildlife species; however, a number of studies have examined toxicity in rodents. These studies are summarized in the Human Health portion of this assessment.

There are few measured data describing the toxicity of TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether). CITI (1992) determined a 48-hour LC_{50} value of 30 mg/L for orange-red killifish exposed to TBBPA bis(2-hydroxyethyl ether). This value is considerably higher than the predicted water solubility of less than 1 mg/L predicted for the substance (see Table 2). Further details on the study, including composition and purity of the test substance are not available; however, it is likely a solvent was used (following protocol). The oral LD_{50} in rats is greater than 5000 mg/kg body weight (bw) for both TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (Brominated Flame Retardants Industry Panel 1974 and 1981); these studies are summarized in the Human Health portion of this assessment. Qu et al. (2011) identified TBBPA bis(allyl ether) as a possible toxicant in bioassays (viability of primary cultured cerebellar granule neurons) using extracts from environmental samples (i.e. sediment).

Toxicity modelling provides predicted toxicity estimates using a range of aquatic organisms; however, several of these predictions exceed water solubility and/or were obtained using log K_{ow} estimates that exceed the log K_{ow} cut-off for the model; therefore, the results (including chronic endpoints) are generally considered highly uncertain. Predicted ecotoxicity endpoint concentrations for TBBPA bis(2-hydroxyethyl ether) are similar to those predicted for TBBPA (see Table 11), although the predicted modes of action for the substances differ (OECD 2010). For TBBPA bis(allyl ether), although most predicted ecotoxicity estimates result in "no effects at saturation" (i.e. effect levels above predicted water solubility limit), there is some evidence of chronic value estimates predicted at very low concentrations in the range of TBBPA bis(allyl ether) solubility (see Table 11). In the absence of sufficient experimental and reliable predicted data, it is assumed that the toxicities of TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) are likely to be similar to that of TBBPA. However, it must be recognized that this assumption carries with it considerable uncertainty, given the sometimes divergent characteristics in structure and properties of these three substances.

Tables 10 and 11 summarize the key toxicity studies and predicted data used in the ecological effects assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether). As well, Robust Study Summaries for key ecotoxicological studies relevant to this assessment are included in Appendix 2.

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine available scientific information and develop conclusions based on a weight-of-evidence approach and application of precaution, as required under CEPA 1999. Lines of evidence relate to persistence, bioaccumulation potential, ecotoxicity, environmental occurrence, and trends and use. The assessment also considers risk quotients which integrate known or potential exposure to the substance with known or potential effects on the environment.

Risk Quotient Analysis

A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for the aquatic, sediment, and terrestrial compartments for TBBPA and TBBPA bis (ally ether), to determine whether there is potential for ecological harm in Canada. Summaries are provided in Table 12 and 13, respectively. These substances were evaluated separately, considering the available information on their use in Canada (i.e. based on parent or "neat" quantities) which was not indicative of concurrent release resulting in cumulative environmental exposure of TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether. A risk quotient analysis for TBBPA bis(2-hydroxyethyl ether) was not conducted given the apparent lack of usage in Canada, and thus, the derivative substance may be considered to have low exposure potential in the Canadian environment at the present time.

The TBBPA generic industrial scenarios for the aquatic environment (which considered available information on TBBPA quantities used, release rates, and characteristics of the receiving environment) presented above yielded PECs ranging from 0.719 – 7.19 μg/L for scenario #2. A predicted no-effect concentration (PNEC) was derived from the critical toxicity value (CTV) of 310 μg/L (0.31 mg/L) (a chronic toxicity value selected as the most sensitive valid experimental freshwater value, Table 10) for a freshwater fish, *Pimephales promelas*, by dividing this value by an assessment factor of 100 (to account for interspecies and intraspecies variability in sensitivity and extrapolation from laboratory to field conditions) to give a value of 3.10 μg/L. The assessment factor of 100 was considered appropriate since TBBPA effects were shown to occur at a lower concentration for a more sensitive marine invetebrate species (i.e. LOEC of 18 μg/L for the marine oyster, *Crassostrea virginica*, see Table 10).The resulting risk quotients (PEC/PNEC) range from 0.23 to 2.3 (Table 12). However, according to the information provided by the user, scenario #2 is considered a worst case situation and therefore the risk quotient would be, in reality, well below 1. Therefore, a risk quotient of 0.23 is considered more reasonable, albeit still conservative, and this indicates no harm to aquatic organisms is likely at this site.

A risk quotient analysis was also performed for the sediment medium to determine whether there is potential for ecological harm in Canada. Since only very limited data for sediment TBBPA concentrations were available for North America, PECs for benthic organisms were determined using the equilibrium (sediment–water partitioning) approach (ECHA 2010) using the aquatic PECs generated for the industrial scenario above (see Table 12, footnote 4 for the detailed calculation and input values). This approach estimates concentrations in surface sediments, where the OC content is assumed to be 10%. The estimated sediment PECs, normalized to 100% OC to compare with the PNEC, ranged from 42.08 to 420.75 mg/kg. This range is considered high in comparison to the global dataset of sediment concentrations determined recently presented in Table 11(normalizing to 100% OC and assuming sediments contain 10% OC). A sediment PNEC for TBBPA of 60.4 mg/kg sediment dw was derived from a chronic toxicity value (see Table 10) of 151 mg/kg dry weight sediment for the oligochaete, *Lumbriculus variegates*, by dividing this value by an assessment factor of 100 to account for interspecies and intraspecies variability in sensitivity and extrapolation from laboratory to field conditions, and standardizing to the 100% OC. The resulting risk quotient

(PEC/PNEC) ranges from 0.7 to 7.0 (Table 12). However, based on the information provided by the user, scenario #2 is considered a worst case situation. Also considering the uncertainties inherent in estimating sediment concentrations using the equilibrium partitioning method and normalizing to 100% OC, it is more reasonable to consider a risk quotient at the lower range of 0.7 to represent a conservative exposure to sediment biota. This value indicates no harm to sediment organisms is expected at this site.

The database of measured soil TBBPA concentrations was also considered inadequate; therefore, soil exposure was derived using the Biosolids-Amended Soil Level 4 (BASL4) model (BASL4 2008). This model is fugacity-based and uses equilibrium partitioning principles to deduce the overall fate of a chemical in the soil. In this model, a chemical can be removed from the soil by volatilization, degradation, leaching, runoff and erosion processes. The model was run assuming a conservative biotransformation half-life of 187 days. A sludge concentration determined for a Quebec sewage treatment plant (Smyth 2013) was selected to represent potential levels in the sludge from a sewage treatment plant representing populated regions of Canada. The selected sludge value of 195 mg/kg dw (Smyth 2013), is considered conservative and higher than most concentrations of TBBPA measured in Canadian wastewater sludge. It is also similar to or higher than concentrations reported for other Canadian, US and European sewage sludge (Table 6). Although a 330 ug/kg dw of TBBPA was measured in sewage sludgetaken from a Quebec sewage treatment plant (Saint-Louis and Pelletier 2004), it is not clear at which stage the sample was taken during the treatment process, and information on the sampling methodology are very limited, and thus this value is considered uncertain. Sample OC content for the Smyth (2013) samples was estimated at 38.5% based on reported volatile solids and total solids (see table 12 for estimation). The resulting PEC is 0.000057 mg/kg soil dry weight normalized to a typical soil organic carbon level of 2% (European Communities 1996). A soil organism PNEC was derived from the chronic toxicity value of 0.12 mg/kg soil dry weight for the earthworm, *Eisenia fetida* (dividing this value by an assessment factor of 100 to account for interspecies and intraspecies variability in sensitivity and extrapolation from laboratory to field conditions, then normalizing to 2% OC, see Table 12, footnote 10) to yield a PNEC of 0.0005 mg/kg soil dw. Toxicity data used to determine Critical Toxicity Values (CTV) and Predicted No-Effect Concentrations are summarized in Table 10. The resulting risk quotient (PEC/PNEC) of 0.11 (Table 12). The risk quotient results suggest that current estimated exposure concentrations in Canadian soils do not exceed those leading to adverse effects in soil organisms. It is also noted that if primary degradation was considered, the resulting risk quotient would have been significantly lower.

The risk quotient derived for wildlife species highlights the potential for intake arising from the uptake of TBBPA in food. The CTV in wildlife estimate of 1.635 mg/kg bw day was determined from a Wildlife Toxicity Reference Value (TRV) approach (Sample et al. 1996), where effects in mice were normalized to a typical body weight of mink, *Mustela vison*, a surrogate wildlife species (see Table 12, footnote 11 for detailed calculation and input values). Toxicity endpoints from Tada et al. (2006) were selected to determine a TRV, based upon liver toxicity in female offspring in a reproductive assay with mice (see Health Assessment Section and Appendix 9 (Tada et al. 2006)). An assessment factor of 10 was applied to account for extrapolation from laboratory to field conditions. The

resulting PNEC was 0.1635 mg/kg food bw day. A PEC of 0.007 mg/kg bw day was determined using the Total Daily Intake (TDI) calculation for mink (*Mustela vison)* consuming fish, based on US EPA (1993). A TBBPA concentration in water (C_w) of 0.05 µg/L (Table 2, Environment Agency Japan 1989, 1991) and a BCF=485 (CITI 1992) were used to determine TBBPA fish tissue concentration (see footnote 11 of Table 12) for the TDI. The resulting risk quotient results (PEC/PNEC) = 0.043 indicated that current TBBPA concentrations in Canadian biota are unlikely to exceed minimum effects levels (Table 12).

For TBBPA bis(allyl ether), the generic industrial scenarios for the aquatic environment (which considered available information on substance quantities, release rates, and characteristics of the receiving environment) presented above yielded PECs of 1.31 – 24.21 µg/L. These PECs exceed the predicted water solubility for TBBPA bis(allyl ether) by more than a factor of 10; therefore they were not used in the risk quotient analysis. The risk quotient analysis was completed using the predicted water solubility as the PEC (0.0204 µg/L, Table 2). Empirical toxicity data for this substance were not available and suitable analogues for aquatic toxicity were not identified (OECD 2010); therefore modelled toxicity data were used for selecting a CTV. There is, however, uncertainty associated with the modelled toxicity data. In almost all cases the predicted endpoints exceeded the water solubility limit, resulting in no effects in saturation for both acute and chronic exposures (see Table 11). As well, in some cases, the high log K_{ow} of the substance (log K_{ow} =8.7) slightly exceeded the log K_{ow} limits for the models. A PNEC was derived from the modelled chronic fish CTV of 0.098 µg/L, as the most sensitive chronic value within a factor of 10 of the water solubility limit (Table 11). No assessment factor was applied to the PNEC; the CTV was considered already very conservative given it was lower than other predicted endpoints by a wide margin and all other predicted acute and chronic endpoints (within model domain) showed no effect at saturation, therefore it is assumed that the predicted value is conservative enough to account for foreseeable uncertainties related to laboratory to field extrapolation. The resulting risk quotient (PEC/PNEC) is 0.21 (Table 13), suggesting harm to aquatic organisms is unlikely at these sites.

A risk quotient analysis for TBBPA bis(allyl ether) was also performed for the sediment medium to determine whether there is potential for ecological harm in Canada. No measured sediment TBBPA bis(allyl ether) concentrations were available for North America, therefore PECs for sediment TBBPA bis(allyl ether) were determined using the equilibrium (sediment–water partitioning) approach (ECHA 2010), with water concentrations based on predicted water solubility (see Table 13, footnote 4). The estimated sediment PEC was 3.29 mg/kg after normalizing to 100% OC. As empirical toxicity data for TBBPA bis(allyl ether) was not available, and no modelled toxicity data were available for sediment organisms, the TBBPA sediment toxicity value was used as a conservative analogue CTV. A sediment PNEC of 60.4 mg/kg sediment dw was derived from a chronic toxicity value of 151 mg/kg dry weight mg/kg dry weight sediment for *Lumbriculus variegates* (dividing this value by an assessment factor of 100 to account for interspecies and intraspecies variability in sensitivity and extrapolation from laboratory to field conditions, and normalizing to 100% OC to compare with the PEC). The resulting

risk quotient (PEC/PNEC) is 0.054 (Table 13). Therefore, harm to sediment organisms is unlikely at these sites.

Empirical mammalian toxicity for TBBPA bis(allyl ether) are limited and not useful, therefore the TBBPA value was used as a conservative analogue CTV for wildlife. The CTV in wildlife estimate of 1.635 mg/kg bw day was determined from a Wildlife TRV (Sample et al. 1996), where effects in mice were normalized to a typical body weight of mink, *Mustela vison*, a surrogate wildlife species (see Table 13, footnote 8 for detailed calculation and input values). Toxicity endpoints from Tada et al. (2006), were selected to determine a TRV, based upon liver toxicity in female offspring in a reproductive assay with mice (see Health Assessment Section (Tada et al. 2006)). An assessment factor of 10 was applied to account for extrapolation from laboratory to field conditions. The resulting PNEC was 0.1635 mg/kg food bw day (see Table 13 for details). A PEC of 0.00005 mg/kg bw day was determined using the TDI calculation for mink (*Mustela vison)* consuming fish, following the approach of USEPA (1993). In calculating TDI, a lake trout fish tissue concentration (C_i) of 0.017 mg/kg ww was used based on the Lake Ontario study by Ismail et al. 2006, the only published study reporting concentrations of TBBPA bis(allyl ether) in Canadian or North American biota. The resulting risk quotient result (PEC/PNEC) 0.00031 indicated that current TBBPA bis(allyl ether) concentrations in Canadian biota are unlikely to exceed minimum effects levels (Table 13).

In summary, the analysis of risk quotients determined that TBBPA concentrations in the Canadian environment are not considered to cause adverse effects in populations of pelagic, sediment, and soil organisms or wildlife. As well, based on the risk quotient analysis, TBBPA bis(allyl ether) concentrations in the environment are unlikely to cause adverse effects in populations of pelagic organisms, sediment organisms or wildlife.

Weight of Evidence Analysis

TBBPA and its two derivatives are predominantly anthropogenic. Available information indicates that none are manufactured in Canada, but TBBPA and TBBPA bis(allyl ether) are being imported into Canada (in ranges of 100 to 1 000 tonnes per year) while there are no imports of TBBPA bis(2-hydroxyethyl ether). The substances are incorporated into polymers as flame retardant. Global production of TBBPA is increasing.

When released into the environment, TBBPA is expected to persist in air, water, soil, and sediment, meeting the criteria for persistence as defined in the *Persistence and Bioaccumulation Regulations* under CEPA 1999. In addition, the substance is present in samples collected from regions considered remote, including the Arctic, providing evidence that, under some circumstances, TBBPA may remain sufficiently long in the atmosphere to allow transport over long distances and to remote locations.

Empirical and modelled data indicate that TBBPA may accumulate to some extent in biota, but does not meet the criteria for bioaccumulation as defined in the *Persistence and Bioaccumulation Regulations*.

TBBPA has been shown to degrade under anaerobic conditions to form bisphenol A, which has been determined to meet criteria set out in section 64 of CEPA 1999. As well, a dimethyl ether derivative (Me-TBBPA) with potentially greater bioaccumulation potential has been reported in environmental samples and is thought to be formed by microbial transformation of TBBPA in the environment. Combustion of TBBPA under certain conditions may lead to the formation of brominated dibenzo-*p*-dioxins and dibenzofurans. These products are analogues of two substances listed on the Schedule 1 of CEPA1999; polychlorinated dibenzofurans and dibenzo-*p*-dioxins.

TBBPA is hazardous to a variety of aquatic organisms, with significant adverse effects on survival, reproduction and development at very low concentrations. Recent research suggests that TBBPA may be capable of disrupting normal functioning of the thyroid system in amphibians and fish, and enhancing immune system activity in marine bivalves. Exposure to soil organisms significantly inhibited growth of some terrestrial seedling plants and soil nitrifying bacteria, as well as reproduction in two earthworm species.

While TBBPA is considered persistent in the environment and may present potential ecotoxicological hazard at low levels, the risk quotient analysis indicates that predicted concentrations of TBBPA in the environment due to current processing activities in Canada are unlikely to cause harm to pelagic, sediment, and soil organisms or wildlife.

Based on modelled data, the two derivatives TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) are expected to persist in soil, water and sediment but not in air, according to criteria defined in the *Persistence and Bioaccumulation Regulations*. Modelled data also indicate that they also do not meet the criteria for bioaccumulation potential.

Empirical ecotoxicity data for TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) are generally not available. Predicted ecotoxicity endpoint concentrations for TBBPA bis(2-hydroxyethyl ether) are similar to those predicted for TBBPA. For TBBPA bis(allyl ether), it was found to have low toxicity to rodents and most predicted ecotoxicity estimates result in “no effects at saturation” (i.e. effect levels above predicted water solubility limit), although there is chronic toxicity predicted at very low concentrations, in the range of its water solubility.

Risk quotient analyses for the derivative TBBPA bis(allyl ether) nevertheless indicate that releases of substance to the environment as a result of processing activities in Canada are not likely to be causing harm to pelagic, benthic, and wildlife organisms.

Given the apparent lack of usage in Canada, TBBPA bis(2-hydroxyethyl ether) may be considered to have low exposure potential and therefore to present a negligible risk to the Canadian environment at the present time.

Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether). It is concluded that TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) do not meet the criteria under paragraphs 64(*a*) or 64(*b*) of CEPA 1999 as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) meet the criteria for persistence but do not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Uncertainties in Evaluation of Ecological Risk

Uncertainties are present due to the lack of information on the environmental concentrations in Canada, particularly in wastewater effluent and associated biosolids, soils, sediments and biota. In spite of this limitation, exposure scenarios for use in risk analysis were developed based on the best available information and they are considered sufficiently conservative to characterize potential risks from releases of TBBPA and TBBPA bis(allyl ether) to the Canadian environment. The assessment recognizes that there is limited information characterizing potential releases from partially-finished and finished goods in use and during dismantled or disposed of at the end of their service life. However, based on available information, releases are considered to be low. This assessment has not considered the potential formation of TBBPA in the environment resulting from the degradation of TBBPA derivative products and products containing them.

There is some uncertainty respecting the behaviour of TBBPA in the environment, including how changing proportions of dissociated and undissociated forms of TBBPA in response to environmental parameters such as pH may influence its bioavailability and toxicity to organisms. However, the available data indicate that the substance has low bioaccumulation potential and presents no risk to secondary consumers, although there is recognition that there may be circumstances or conditions under which the substance may accumulate to some degree in organisms.

This assessment also recognizes that there are information gaps on the toxicity of TBBPA to wildlife and effects on pelagic, sediment and wildlife species resulting from prolonged (e.g., lifetime and mutigenerational) exposure to TBBPA. The analysis of risk to secondary consumers (mink was used in this assessment) utilized a concentration of TBBPA in mink prey (fish) that was determined using a TBBPA water concentration from outside of North America (multiplied by BCF). The assessment recognizes that this TBBPA concentration may not be representative of Canadian regional waters; however, data analysis suggests the risk analysis conclusion for wildlife would not change even if the TBBPA concentration in water were much greater (e.g. by a factor of 100 times).

Based on physical, chemical and structural similarities, it is assumed that the derivative substances have properties related to those of TBBPA. However, there is limited information on the physical and chemical properties and potential fate for these substances to substantiate this assumption. It is recognized that measured concentrations in the environment and information on bioaccumulation potential for these TBBPA derivatives are also limited. A lack of empirical estimates for water solubility of TBBPA bis(allyl ether) is a source of uncertainty in the estimate of a PEC in water for this substance.

Finally, this assessment recognizes that there are information gaps on the toxicity of TBBPA bis(allyl ether) to aquatic, sediment, soil, and wildlife species: there is a lack of empirical studies and toxicity modelling is uncertain with limited applicability. Suitable analogues with a similar mode of action to TBBPA bis(allyl ether) were not identified for aquatic ecotoxicity. Use of TBBPA as a sediment toxicity analogue for the derivative is an additional source of uncertainty, but is expected to be conservative. TBBPA bis(allyl ether) likely exhibits limited bioavailability, and is unlikely to result in adverse effects at saturation.

Potential to Cause Harm to Human Health

Exposure Assessment

TBBPA, TBBPA bis(2-hydroxyethyl ether), and TBBPA bis(allyl ether) are flame retardants found in a range of consumer goods constructed using plastic polymers, such as computers, printed circuit boards, televisions and other finished electronic equipment. There is no evidence that TBBPA is used in textile apparel (EU RAR 2006; Sigman 2002). TBBPA and its derivatives can be used both as a reactive flame retardant in epoxy circuit boards and to a lesser extent, as an additive flame retardant in the manufacture of ABS resins, HIPS and phenolic resins. As a reactive flame retardant, only the residual compound is available for migration since the majority of the compound is covalently bound to the polymer matrix. This represents a relatively small source of exposure. When used as an additive, it does not react chemically with the other components of the polymer and there is potential for migration out of the matrix, due to abrasion and exposure to heat and high temperatures. This assessment uses the highest reported levels of TBBPA in air, soil, dust, water, and food to generate conservative intake values, given the lack of monitoring data on the two derivatives. It is considered that the derived intake values incorporate the potential contribution of the two derivatives.

Based on an industry survey in 2000, the amount of both TBBPA and TBBPA bis(allyl ether) imported into Canada were within the same range. In the case of pure TBBPA bis(2-hydroxyethyl ether), given there is no confirmed use in Canada, any human exposure would likely result from use of products containing this substance rather than the pure substance itself. Exposure can occur when individuals inhale, ingest or contact dust containing TBBPA or free TBBPA such as when unreacted TBBPA migrates from the polymer. It is however noted that a maximum of 0.06% of the total quantity used in

the resin remains unreacted and is therefore available for migration. As TBBPA has a low vapour pressure, it will not volatilize or off-gas from a product. Therefore in considering the potential for general population exposure to TBBPA, the relevant route of human exposure to small amounts of available free TBBPA then would be hand-to-mouth transfer of TBBPA in dust that deposits within the indoor environment. If free TPPBA migrates from plastic, because of its low vapour pressure, exposure resulting from volatilization is not expected.

Under conditions of increased temperatures, such as televisions and computers that generate heat during operation, there may be the potential for the vapourization of free TBBPA, and its deposition on surfaces within a home. In North America, Batterman et al. (2010) measured TBBPA at detectable levels in 3 of 10 offices sampled (2 University buildings at 1.2 x 10^{-8} mg/m^3 and 2.3 x 10^{-8} mg/m^3, and one computer server room/office at the highest level at 8.6 x 10^{-8} mg/m^3) in air, dust, ventilation system filters and carpets in 10 buildings in Michigan, USA. These levels are considered to be overestimates of levels that may occur in a residential setting.

The stability of ABS resins has been investigated over a range of temperatures (Luijk and Govers 1992). Very low levels of TBBPA were detected above 200 ^{o}C. Sjödin et al. (2001), measured TBBPA air levels in offices containing large numbers of computers. Four static samples had a mean value of 3.6 x 10^{-8} mg/m^3 [1-7 x 10^{-8} mg/m^3]. Wolf et al. (2000) also demonstrated no releases of brominated compounds from an epoxy resin printed circuit board containing TBBPA. Additionally, EU RAR (2006) also reported studies where no TBBPA was detected in the air inside or surrounding a television set or computer monitor casing even when the flame retardant was present in printed circuit boards (*reactive* form) or monitor casings (*additive* form) (De Boer et al. 1998 and Ball and Hermann 2002). For the latter, an office experiment tested release from monitor usage under simulated "real life" conditions. The monitors contained 12% TBBPA and the circuit boards within them contained between 4% and 8% TBBPA. Air levels of TBBPA measured in the enclosed chamber varied between 1.0 x 10^{-7} mg/m^3 and 2.0 x 10^{-5} mg /m^3; air levels of TBBPA measured in the office investigation peaked at 2.33 x 10^{-5} mg/m^3 before falling slowly to between 1.0 and 2.0 x 10^{-7} mg/m^3. Wipe samples from the test chambers showed a maximum TBBPA value of 0.569 mg/m^2 at the bottom of the sampling area, but particles were seen detected beforehand and may have represented contamination from the housing (EU RAR 2006). These data indicate that there is the potential for exposure to very low levels TBBPA in the areas in close proximity to operating computers and monitors.

More recent reports (D'Hollander et al. 2010; Wang et al. 2010; Roosens et al. 2010; Ni et al. 2010; Shi et al. 2009b; Zhang et al. 2009; Mascolo et al. 2010; Guerra et al. 2010) indicate wide variation in human exposure to brominated flame retardants, in particular TBBPA and its derivatives, depending on the country-specific usage, stage of industrial development, production, and regulatory framework under which usage is permitted. In the United States (Batterman et al. 2010) and United Kingdom (Harrad et al. 2010), exposure assessments show diverse levels and patterns which, in turn, are likely to differ from those in countries such as Belgium, (D'Hollander et al. 2010) where levels tend to

be about an order of magnitude lower. The level of general population exposure in North America is expected to be less than that reported by Batterman et al. (2010) in an office building.

The recent studies noted above assessed human exposure to brominated flame retardants, including TBBPA and its derivatives, via the indoor and outdoor environment (dust, soil, air and food) and report that although there is high variability in the data obtained, there is increased potential for exposure, especially in indoor air because TBBPA and its derivatives are being increasingly used as functional replacements in Europe for other substances. On the other hand, it is noted that when the increased number of available devices are considered together with the miniaturization trend for electronics (with an associated reduction in the actual mass and surface area of plastics in new products) the impact on exposure potential may be limited.

No Canadian data were identified to inform the exposure characterization of TBBPA and the two derivatives. Exposure to TBBPA and the two derivatives was characterized for the general population, based on upper-bounding estimates of exposure taking into consideration the maximum levels of TBBPA reported in the air, soil, dust, water, and food of currently available data and that which is considered to be most representative of Canadian exposures.

The use of the reported highest levels of TBBPA in the air, soil, dust, water, and food to characterize intakes is considered appropriately conservative given the lack of monitoring data on the two derivatives. It is considered that the derived intake values incorporate the potential contribution of the two derivatives.

Upper bounding estimates of total daily intake from exposure to TBBPA, TBBPA bis(2-hydroxyethyl ether), and TBBPA bis(allyl ether) by the Canadian general population are presented in Appendix 3. The estimated daily intake of TBBPA and the derivatives ranges from 1.0×10^{-5} mg/kg body weight per day for formula fed infants to 1.95×10^{-4} mg/kg body weight per day for breast fed infants. The latter was calculated from a known exposure algorithm for estimating exposures of infants from human milk (Health Canada 2008).

It is recognized that there is significant uncertainty in these estimates. These uncertainties have been previously recognized. The EU (EU RAR 2006) noted that "*Any attempt at quantitative assessments will result in disproportionately high errors because of the small exposures anticipated. The worst case combined exposure would be a consumer who is also exposed indirectly via the environment. Given that consumer exposure to TBBPA is negligible, calculation of the worst case combined exposure has not been performed.*"

Reported levels of TBBPA in indoor air, food and dust are summarized in Appendices 4, 5 and 6 and detailed discussions are presented below.

Ambient Air

No reports of monitoring for TBBPA in air in Canada were identified.

TBBPA was detected in ambient air (1.8×10^{-9} mg TBBPA/m^3 collected by high volume samplers taken at the perimeter of two organobromine plants in southern Arkansas, US, which produce the chemical (Zweidinger et al. 1979a). TBBPA was not detected in outdoor air samples taken in Berlin and Stockholm (Kemmlein 2000 and Sjödin et al. 2001), but was found at Dunai in the Russian Arctic using a high volume sampler at a concentration of 7.0×10^{-8} mg/m^3 (Alaee et al. 2003) and in the Netherlands at 2×10^{-9} mg/m^3 (Duyzer and Vonk 2003). TBBPA was measured in ambient air from $<4 \times 10^{-3}$ mg/m^3 in samples from northern European coastal regions to 8.5×10^{-10} mg/m^3 recorded in the UK, respectively (Xie et al. 2007; Abdallah et al. 2008).

For the upper bounding estimate for the Canadian population, the ambient levels reported at Dunai (Alaee et al. 2003) was used as this geographical location is considered to be comparable to Canada.

Indoor Air

Appendix 4 provides a summary of reports for TBBPA levels measured in indoor air.

Several measurements of TBBPA have been made in indoor air (locations have included classrooms, offices, and industrial settings), with emphasis on detecting emissions in the vicinity of computers. Computer parts may be exposed to elevated temperatures while in use and volatile substances may be emitted. TBBPA release from a computer monitor operating for extended periods of time has been measured in closed test chambers at 0.8 - 1.5×10^{-6} mg/m^3. This value is higher than those measurements in offices and classrooms shown in Appendix 4 (Ball and Hermann 2002). Indoor air of apartments and houses in Tokyo, Japan were sampled in 2003 and found to contain 0.3×10^{-9} mg/m^3 to 0.8×10^{-9} mg/m^3 TBBPA (Inoue et al. 2003). The results from the Japanese study of residential sites were higher than levels measured in offices and classrooms. In comparison, TBBPA in indoor air in United Kingdom residences had a mean of 1.6×10^{-8} mg/m^3 whereas Japanese houses had 8.0×10^{-7} mg/m^3 (Abdallah et al. 2008; Inoue et al. 2003). Measured levels in United Kingdom offices ranged up to 2.6×10^{-8} mg/m^3. Recent air levels measured from point source recycling plants ranged from 0.03 to 1.5×10^{-4} mg/m^3 (Tollback et al. 2006; Sjödin et al. 2001; Morf et al. 2005 as cited in Xie et al. 2007).

Batterman et al. (2010) measured brominated flame retardants, including TBBPA in air, dust, ventilation system filters and carpets in 10 buildings in Michigan, USA. TBBPA was only found at detectable levels in 3 of 10 offices sampled (2 University buildings at 1.2×10^{-8} mg/m^3 and 2.3×10^{-8} mg/m^3 and one computer server room/office at the highest level at 8.6×10^{-8} mg/m^3). TBBPA was also found in the particulate matter collected from a medical equipment manufacturing building and a university building and both had levels of 1.1×10^{-8} mg/m^3 while a tire store had levels of 1.2×10^{-8} mg/m^3 of TBBPA.

For the upper bounding estimate for the Canadian population, the most recent USA indoor air levels reported by Batterman et al. (2010) were used, as these data are considered to be more representative of current Canadian exposures.

Water
No reports of TBBPA detected in surface water in Canada were identified.

In surface waters, TBBPA was determined in one sample (5×10^{-2} µg/L, limit of detection (LOD) 3×10^{-5} µg/L) of a total of 297 taken in Japan between 1977 and 2000 (MOE Japan 2003). TBBPA was found (maximum 20.4 ng/L or 2.04×10^{-2} µg/L) in seven of thirty samples of German surface water taken in 2000. The presence of TBBPA in samples of river water in Germany was considered to be from local industrial discharge (Kuch et al. 2001, cited in OSPAR 2004).

TBBPA in surface water ranged from $< 3.0 \times 10^{-5}$ µg/L to 3.0×10^{-3} µg/L, in France and UK, respectively (Labadie et al. 2010; Harrad et al. 2009).

In commercial drinking water (i.e. bottled water) which had been stored in reusable polycarbonate containers, native TBBPA as well as brominated derivatives of the ^{13}C-bisphenol A (BPA) were detected. In two single carboy samples, ^{13}C-TBBPA was the major ^{13}C-BPA constituent (>85%) (Peterman et al. 2000 as cited in NTP 2002).

For the upper bounding estimate for a Canadian population, the values reported by Harrad et al. 2009 for surface waters in UK were used.

Soil, Sediment and Dust
Appendix 5 provides a summary of TBBPA levels reported in dust.

TBBPA was found in four of eight samples of dust taken from eight different European national parliament buildings in concentrations up to 4.7×10^{-2} mg/kg (Santillo et al. 2001). It was also found in four of ten pooled samples of dust vacuumed from houses in ten regions of Great Britain in concentrations up to 0.34 mg/kg, while dust samples from Finland and Denmark were found to have 0.025 mg/kg and 0.40 mg/kg TBBPA, respectively (Santillo et al. 2003). No explanation for the source of the TBBPA in the dust was offered in either report.

In a study conducted in the United Kingdom of dust levels in offices, houses, cars, and microenvironments, the highest dust level of 0.220 mg/kg was found in public microenvironments (n=4), bars and restaurants.

The highest dust level of TBBPA recorded was for the rear of television cabinets in a Japanese study at 1.9×10^{4} mg/kg (Takigami et al. 2008).

TBBPA has been reported in soil at contaminated sites associated with organobromine processing facilities, but these were not considered representative of levels to which individuals may be exposed in the environment and are not reported in Appendix 5.

TBBPA was detected in samples of sediment taken from Lake Ontario in 2002 and from the Detroit River and area in 2000 at concentrations ranging from non-detectable to 1.84

ng/g dry weight (Quade 2003). No other reports of TBBPA in Canadian sediment were located. A number of studies on contamination of sediments in Norway, the Netherlands, Belgium, the United Kingdom, Germany and Japan were made in the period 2000 to 2003. The highest recorded concentration of TBBPA was 9 750 ng/g (9.75×10^{-3} mg/kg) dry weight near a site of brominated flame retardant manufacture in the United Kingdom (Morris et al. 2004). Morris et al. (2004) also reported detection of TBBPA (0.1 mg/kg dry weight) in sediments taken from the Netherlands and the Western Scheldt, Belgium.

Analysis of TBBPA and its dimethylated derivative in Swedish river sediment taken from locations upstream and downstream of a plastics factory which used TBBPA showed significantly higher concentrations of the two chemicals downstream of the plastics factory than upstream (Sellström and Jansson 1995). A full list of studies can be found in Table 6.

Additional data revealed levels of TBBPA in sediments ranging from 0.07 mg/g to 230×10^{-6} mg/g dry weight (Harrad et al. 2009; Sanchez-Brunete et al. 2009; Zhang et al. 2009; Labadie et al. 2010).

Batterman et al. (2010) measured TBBPA levels in air, dust, ventilation system filters and carpets in 10 buildings in Michigan, US. TBBPA was found at mean concentrations of 2.23×10^{-4} mg/g in dust (median – 1.34×10^{-4} mg/g; range 20 mg/g to 938×10^{-6} mg/g) in a sampling of nine buildings (minimum of 1 sample each, 2 samples in 3 of the 9 for a total of 12 samples). The highest concentration was found in a medical equipment manufacturer building at 9.38×10^{-4} mg/g.

Harrad et al. (2010) reported that TBBPA levels in floor dust of child daycare centers and primary school classrooms in the United Kingdom were significantly higher ($p<0.05$) than in dust from cars (Abdallah et al. 2008) (n=20) and offices (n=28), but indistinguishable from those in homes (n=45). Mean values in primary and daycare classrooms were reported at 2.0×10^{-4} mg/g (median – 1.1×10^{-4} mg/g; n=43 with range of values from 17 to a maximum of 1.4×10^{-3} mg/g). These authors also compared exposure to children and adults as well as comparing exposures from air with that from dietary intake. These data have been used to calculate human exposure from dust for the Canadian population since it is considered the most relevant for assessing exposure to infants and toddlers although toddlers seem to be the most exposed age group, next to breast fed infants.

Food

No reports of TBBPA analysed in food in Canada were identified.

A number of reports of TBBPA measured in fish and other seafood have been recently published. TBBPA has been found in fish and shellfish. Samples from the Osaka area contained 0.8 µg/kg and 4.6 µg/kg (wet weight) methylated TBBPA, respectively. TBBPA was not detected in any other fish samples collected from other locations in Japan (Nakagawa et al. 2006).

The results of several studies are summarized in Appendix 6. The highest concentrations of TBBPA reported were 245 μg/kg lipid (equivalent to 1.5 μg/kg wet weight at 0.63% lipid content) found in whiting fish from the North Sea (Morris et al. 2004) and 3.4 μg/kg wet weight of eel found in the Netherlands (de Winter-Sorkina et al. 2003).

The concentration of TBBPA in one sample of cow milk was measured in Norway and was found to be 1.3×10^{-2} μg/kg lipid, or 5.1×10^{-4} μg/kg whole milk. The fat content of the cow milk was 3.9% (Thomsen et al. 2002a). In a survey of 84 food samples in the Netherlands, TBBPA was found in samples of cheese at a concentration of 0.08 μg/kg cheese, about 160 times higher than the measurement in cow milk when compared on a whole food basis (de Winter-Sorkina et al. 2003). This difference is due in part to the lipophilicity of TBBPA as evidenced by a high log K_{ow} and the higher fat content of cheese compared to milk.

A total diet survey of 121 categories of food was carried out in the United Kingdom in 2001 and the concentration of TBBPA was below the detection limit in all of the main food categories. The detection limits were in the order of 1 μg/kg (Food Standards Agency 2004). No TBBPA was detected in fish or seafood samples in the UK survey in contradiction to the findings of Morris et al. (2004) given in Appendix 6; however, the detection limits in the UK study were relatively high, e.g. 1.4×10^{-3} μg/kg lipid in milk compared to the measurement by Thomsen (2002a) of 1.3×10^{-2} μg/kg lipid in whole milk, equivalent. The detection limit for TBBPA in the UK diet study is 100 times higher than the reported value from Norway, so reports of no detectable concentration of TBBPA in food in the United Kingdom must be considered in the light of the detection limits which were relatively high for dairy and fish. No comparison is possible for other food groups because data are lacking.

Other various levels in food were reported with the highest level being measured in the Fourth, Total Diet Survey in China (Shi et al. 2009b) at 2.0 μg/kg lipid for an n=48. Highest measured levels included 1.3 μg/kg for meat, 0.7 μg/kg for eggs, 2.0 μg/kg for aquatic food and 0.8 μg/kg for milk. This data was selected for derivation of upper-bounding intakes of exposure as China is a large consumer of aquatic foods (to which TBBPA has been known to be found and accumulate) and Asia is a leading manufacturer of TBBPA and TBBPA flame retardant products (e.g. epoxy laminated electric circuit boards; Shi et al. 2009a).

Consumer Products

Upon consideration of the use patterns of TBBPA and the reported findings of the EU RAR (2006) for exposure from use of consumer products, available information indicates negligible exposures to TBBPA from consumer products and for this reason, no upper-bounding estimates of consumer product exposure are necessary for this screening risk assessment.

Biomonitoring of TBBPA

TBBPA detection and quantification in human milk and human blood samples showed that population exposure to TBBPA is reflected in increased milk and blood levels of the substance (Appendices 7 and 8).

As reported in Appendix 7, TBBPA has been detected in human milk in samples that were obtained from 1990 to 2001 from Norway, Denmark and Germany. The measured concentrations ranged from not detected to 11 ng/g lipid in one sample taken from a woman living in the Faroe Islands (Thomsen et al. 2002a and Kemmlein 2000). No information was provided on the occupational exposures of the women who contributed to the pool, so the measured concentration of the pooled samples is assumed to be representative of the general population. Dimethyl-TBBPA was also detected semi-quantitatively in pooled samples of human milk from three locations in Norway in concentrations of approximately 0.1 ng/g to 1.1 mg/g lipid. The source of the compound was not identified, but two explanations were offered by the authors: dimethyl-TBBPA has been infrequently used as a flame retardant and it may also be the product of biological methylation (Thomsen et al. 2003). A more recent study by Carginan et al. (2012) examined human milk samples collected in 2004-2005 from 43 women from Boston, MA (USA). TBBPA was found in 35% of samples (ranging from LOQ of 30 to 550 pg/g per lipid weight) and concentration means were not reported as the detection frequency (<50%) was too low.

Blood serum levels are reported in Appendix 8. The blood of 47 Members of the European Parliament was sampled in 2003 and analysed for a large number of contaminants. TBBPA was found in 27 of 40 samples which were analysed. The highest concentration of TBBPA found was 0.3 ng/g whole blood (WWF 2004). The highest previously reported finding of TBBPA was 3.7 ng/g lipid in a survey of Japanese adults (Nagayama et al. 2000). The 0.3 ng/g whole blood maximum found by World Wildlife Fund (WWF) is higher than any previously reported finding in blood or a blood fraction. A precise comparison of results reported on a whole blood basis and on a lipid basis is not possible without knowledge of the lipid content of the whole blood of the individual tested. The large difference between the WWF findings and those of Thomsen et al. (2002a) and Jakobsson et al. (2002) may be explained in part if TBBPA is adsorbed to the blood solids which are removed by centrifugation in preparing serum and plasma fractions.

Serum from archived samples of the blood of men aged 40 to 50, collected in five Norwegian county hospitals in the period 1975 to 1999, was analysed for TBBPA. No TBBPA was detected in any sample taken prior to 1986, after which it was detected in each sample at concentrations increasing from 0.44 ng/g to 0.65 ng/g lipids. Samples of serum collected in 1998 from males and females aged from birth to more than 60 years were also analysed. The concentration of TBBPA was higher in the serum of children aged from birth to four years than in all older sub-populations. The body burden of TBBPA was found to be independent of age after age four years (Thomsen et al. 2002b).

An analysis was made of several brominated flame retardants in the blood of three groups of workers in Norway: electronics dismantlers, circuit board producers, and laboratory

personnel with no occupational exposure to TBBPA. The level of TBBPA measured in the blood plasma of the dismantlers ranged from 0.64 ng/g to 1.8 ng/g lipid, and the mean concentration of TBBPA for this group was significantly higher than for the other two groups (Thomsen et al. 2001). These findings suggest that non-occupational exposure is occurring in the Norwegian population and that the electronics dismantlers experienced an additional burden from occupational exposure. In another study of workers in electronics dismantling plant in Sweden, the concentration of TBBPA in blood serum was measured during the time the subjects were working and for several days after occupational exposure had stopped. The authors concluded that the biological half life in humans is 2.2 days (Hagmar et al. 2000), indicating low propensity to concentrate in man.

TBBPA was also found in the blood of eight of fourteen samples from Japanese adults. The maximum concentration measured was 3.7 ng/g lipid and the median was 1.35 ng/g lipid (Nagayama et al. 2000). There was no information on occupational exposure of the Japanese test subjects. It is noteworthy that these higher levels are of the same order of magnitude as the results reported for the Norwegian electronics dismantlers by Thomsen et al. (2001). Another biomonitoring study conducted in Japan detected low levels of TBBPA in human umbilical cord blood samples in newborns (Kawashiro et al. 2008).

Since the publication of the European Union assessment (EU RAR 2006), several new biomonitoring studies have been published. These included a study by Shi et al. (2009b) measuring levels of TBBPA in human milk. Analysis was performed on 24 pooled samples. Levels in 75% of samples were below 1 ng/g lipid. Cariou et al. (2008) reported a mean TBBPA level of 4.1 ng/g lipid. Antignac et al. (2006) reported a median value of 0.17 ng/g lipid.

In terms of blood data, the highest mean level found was in cord serum from newborns in France with 103.5 +/- 149.7 ng/g lipid (Cariou et al. 2008). In a recent Canadian biomonitoring program of 50 599 blood serum samples, TBBPA was not detected. The LOD was 3×10^{-2} ng/g serum (Alberta Health and Wellness 2008). Dallaire et al. 2009 measured the plasma concentration of TBBPA in 771 Inuit participants in Nunavik, Quebec. TBBPA was detected in 5% of the subjects at levels ranging from 10 ng/L to 480 ng/L (LOD = 10 ng/L).

Several studies looked for TBBPA in adipose tissue. It was detected at a mean value of 0.05 ± 0.1 ng/g lipid, range of <0.003 to 0.5 ng/g lipid by Johnson-Restrepo et al. (2008). The combined human biomonitoring data demonstrate that a similar TBBPA concentration is noted in human milk, serum or adipose tissue. This data indicates that TBBPA is not preferentially sequestered in any human tissues or fluids and is equally distributed in all lipids in the body.

Health Effects Assessment

A risk assessment of TBBPA was published by the European Union (EU RAR 2006) and the results are presented below. In a search of literature from 2006 to January 2013, a

multitude of new studies were identified. These are presented in more detail in Appendix 9. Additionally, a summary of health effects for the derivatives of TBBPA, TBBPA bis(allyl ether) (CAS RN 25327-89-3) and TBBPA bis (2-hydroxyethyl ether) (CAS RN 4162-45-2) are presented in Appendix 9. Given the similarities in the chemical structures of TBBPA and its derivatives, and the common toxicological profiles among the compounds in comparable studies; the TBBPA hazard database was considered adequate to assess the toxicological potential and to characterize risk for TBBPA and its derivatives.

TBBPA has low acute toxicity following all routes of exposure. In animal studies, the LC_{50}, oral LD_{50}, and dermal LD_{50} values were all in excess of 2000 mg/m^3 (mg/kg-bw) (Appendix 9). Decreased motor activity, eye squint, slight dyspnea and erythema were observed in the acute inhalation study, but at a significantly high dose of 10 920 mg/m^3 (Velsicol Chemical Corporation 1978e). No signs of toxicity were evident following dermal or oral exposures in any species studied.

In an acute neurobehavioral study, Nakajima et al. (2009) exposed male mice to 0, 0.1, 5 or 250 mg/kg- bw TBBPA once by gavage. Behavioural changes were observed and high amounts of TBBPA were detected in the striatum at the two lowest dose groups. However, in the absence of an effect and the non-specific accumulation of TBBPA in the brain in the highest dose group, the effects noted in the lower dose groups were not considered to be treatment related.

The weight of evidence from animal studies indicates that TBBPA is not a skin or eye irritant (Appendix 9). In a 14-day inhalation study with rats, local irritation was observed in the upper respiratory tract (IRDC 1975). However, this was attributed to the high concentrations used in the study, i.e., the effects were more likely to be a consequence of mechanical irritation. TBBPA is not considered to be irritating to the respiratory tract.

The European Union (EU RAR 2006) did not identify case reports of either dermal or respiratory irritation. TBBPA did not result in skin sensitization with humans in a multiple insult test (IRDC 1978). The EU RAR (2006) concluded that TBBPA is neither a skin nor a respiratory sensitizer. No new human or animal studies were identified regarding the irritation or sensitization potential of TBBPA.

The EU RAR (2006) identified only one repeated dose inhalation toxicity study. Rats exposed to up to 18 mg/L (18 000 mg/m^3) for 14 days had no toxicologically significant systemic effects (IRDC 1975). In a 3-week dermal study, no adverse effects were observed in rabbits exposed to TBBPA in doses up to 2500 mg/kg-bw per day (IRDC 1979). According to the EU RAR (2006) several of the available repeated-dose studies via oral administration were poorly reported (IRDC 1972; Sato et al. 1996; Szymańska 1995; Frydrych and Szymańska 2001) and hence of limited utility. In a 28-day gavage study with Wistar rats, no significant dose-related hepatic effects were observed in the liver at up to 250 mg/kg-bw per day (Szymańska et al. 2000).

Post 2006, two short-term oral repeated dose studies reported effects on the liver at high doses. Tada et al. (2007) exposed male ICR mice by gavage for 14 consecutive days to 0, 350, 700 or 1400 mg/kg-bw per day TBBPA. Absolute and relative liver weight was significantly increased at the highest dose. At the mid- and highest dose, there was slight enlargement of hepatocytes, inflammatory cell infiltration and focal necrosis of hepatocytes. Germer et al. (2006) exposed Wister rats to dietary concentrations equivalent to intakes of 0, 30, 100 or 300 mg/kg-bw per day for 28 days. There were no effects upon hepatic mRNA or microsomes. Recent *in vitro* work has demonstrated that TBBPA is a potent peroxisome proliferator–activated receptor-(PPARγ) agonist and is able to induce adipogenesis in NIH3T3-L1 cells (Riu et al. 2011). Alternatively, when the ability of TBBPA was tested to activate human pregnane X receptor (PXR) and mouse PXR using a transfection assay, results were negative (Sui et al. 2012).

Two subchronic studies with rats were identified. No gross or histopathological lesions were observed in rats exposed by diet to 0, 0.3, 3, 30 or 100 mg/kg-bw per day for 90 days (The Dow Chemical Company 1975). No effects were observed in either functional observational battery or motor activity in a 13-week gavage study where rats were exposed to 0, 100, 300 or 1000 mg/kg-bw per day TBBPA (MPI Research 2002a). No adverse histopathological changes were found in the liver, thyroid, parathyroid or pituitary. There were no changes in serum levels of triiodothyronine (T3) or thyroid-stimulating hormone (TSH). Although there was a significant decrease in serum thyroxine (T4) in both sexes, in the absence of any other relevant thyroid-related effects, this was not considered adverse since the active form T3 was unchanged. The EU RAR (2006) concluded that there were no toxicologically significant effects at doses up to 1000 mg/kg-bw per day. No additional subchronic studies were identified.

The EU RAR (2006) concluded that TBBPA was not genotoxic in such *in vitro* systems as the Ames test (Mortelmans et al. 1986; The Dow Chemical Company 1985; Velsicol Chemical Company 1977, 1978a; Israel Institute for Biological Research 1978; Litton Bionetics Inc. 1976; Ethyl Corporation 1981) and chromosomal aberration test (ACCBFRIP 2001d). No *in vivo* data were identified and it was noted that there were no structural indications that TBBPA would be genotoxic. No new information has been published to contradict these findings.

No human or animal studies were identified with respect to the carcinogenic potential of TBBPA. However, there were no indications of tumour generation in the available repeat dosing studies.

Several reproductive and developmental studies were available to the EU RAR (2006). No effects upon fertility or reproduction were observed in a two-generation, GLP and OECD compliant study in rats, at doses of 0, 10, 100 or 1000 mg/kg-bw per day (MPI Research 2002b, 2003). Although there was a decrease in T4 levels in F0 and F1 males and females, there were no effects upon TSH levels or microscopic changes in pituitary or liver (thyroid was not examined). Mean serum T3 levels were significantly lower in F0 males at the highest dose, but no changes were measured in the F0 females or in either sex of the F1 generation. In a pilot range-finding study (Velsicol Chemical Corporation

1978c) and two standard developmental assays (Noda et al. 1985; MPI Research 2001), no developmental effects were observed at doses up to 10 000 mg/kg-bw per day. In a developmental neurotoxicity study in rats, no adverse effects upon neurodevelopment were observed at 0, 50 and 250 mg/kg-bw per day (Hass et al. 2003). In a single exposure protocol with neonatal mice, no effects were observed upon behaviour, learning or memory of 0.75 and 11.5 mg/kg (Eriksson et al. 1998, 2001).

A study of newborn rats, dosed by gavage from days 4 to 21 after birth at doses of 0, 40, 200 or 600 mg/kg-bw per day TBBPA found effects on the kidney (polycystic lesions associated with the dilation of the tubules) at the two highest doses (Fukuda et al. 2004). In the same study, five-week old rats were dosed at levels of 0, 2000 or 6000 mg/kg-bw per day for 18 days. No similar histopathological renal effects were observed. The effects observed in the neonatal animals were attributed to the immature metabolic capability and/or immature kidneys. The EU RAR (2006) selected the NOAEL of 40 mg/kg-bw per day for the purpose of risk characterization (LOAEL=200 mg/kg-bw per day, based upon histopathological effects in kidney).

Several new studies examining the developmental and reproductive effects of TBBPA have been identified. Tada et al. (2006) exposed ICR mice via diet from the first day of gestation to weaning at postnatal day 27. No dose-related reproductive effects were reported. A LOAEL of 140.5 mg/kg-bw to 379.9 mg/kg-bw per day has been assigned by Health Canada, based upon enlargement of hepatocytes and very slight focal necrosis of hepatocytes in female offspring.

Saegusa et al. (2009) exposed pregnant Sprague-Dawley rats from gestational day 10 to post natal day 20 (weaning) at dietary levels of 0, 100, 1000, or 10 000 ppm (0, 9.5 to 22.9, 86.8 to 202.1, or 818.9 to 2129.2 mg/kg-bw per day). TBBPA did not alter normal brain development. Relative organ weights were unaffected, with the exception of the uterus in female offspring at post-natal week 11 (LOAEL = 818.9 mg/kg bw to 2129.2 mg/kg-bw per day). There were no significant dose-related effects on T3, T4 or TSH at either post-natal day 20 or post-natal week 11.

The results of a one-generation dietary assay with Wistar rats have been published (van der Ven et al. 2008; Lilienthal et al. 2008). This was preceded by a 28-day repeated dose study, in which 10 rats per sex were exposed to dietary concentrations that resulted in intakes of 0, 30, 100 or 300 mg/kg-bw per day. Data were presented as the results of dose-response analyses with PROAST software (publicly available software from the National Institute for Public Health and the Environment [RIVM], Netherlands). The only effects in the 28-day study were a decrease in circulating T4 and increased T3 levels in male rats. In the main study, dietary exposure was for 70 days (male) or 14 days (female) prior to mating, during mating and throughout gestation and lactation. The F1 animals were exposed to the same as F0 until ~14 weeks of age. The intakes were 0, 3, 10, 30, 100, 300, 1000 or 3000 mg/kg-bw per day. There were no effects upon endpoints of reproduction. The main adverse effects were decreased circulating T4 levels in both sexes and increased weight of testis and pituitary gland in males. Other effects noted included delayed sexual development in females, and effects upon brainstem auditory

evoked potentials. The lowest benchmark dose levels (BMDL) were for increased F1 testis weight (critical effect dose, 1.4 mg/kg-bw per day; BMDL, 0.5 mg/kg-bw per day, critical effect size [CES] at 5%) and increased F1 male pituitary weight (critical effect dose, 2.2 mg/kg-bw per day; BMDL, 0.6 mg/kg-bw per day, CES at 10%). There were no exposure-related histopathological changes in the organs of the F1 animals. There were no effects upon sperm counts or morphology. There was no effect upon the immunisation response against sheep red blood cells in F1 males (CES at 20%). Another "major effect" was the developmentally induced increase of hearing latency at low frequency, with BMDLs of 7.8 mg/kg-bw and 8.4 mg/kg-bw per day for males and females, respectively (CES at 5%). It is noted that concerns have been published concerning the methodology (ie. use of the model as well as conduct) employed in this study (Banasik et al. 2009; Strain et al. 2009; Lilienthal et al. 2009; van der Ven et al. 2009).

A prepubertal exposure study by Imai et al. (2009) examined the effects of TBBPA on susceptibility to thyroid tumours induced by a further exposure to DHPN or DMBA in Fisher 344 rats. Although the results of a complex exposure scenario are not taken into consideration in the assessment of TBBPA alone, the initial administration of 1% (1249 mg/kg-bw) TBBPA to dams from parturition to weaning (3 weeks) showed a statistically significant increase in thyroid weights and a decrease in relative liver weights. These effects were not observed in any other developmental study available.

The European Union (EU RAR 2006) carried out a weight of evidence assessment of the potential for TBBPA to affect the endocrine system. Overall, the evidence from *in vitro* screening assays indicated that TBBPA had no significant estrogenic potential. Both *in vitro* and *in vivo* assays were identified which investigated the potential for TBBPA to compete with the binding of T4 to transthyretin (TTR). In an *in vitro* competitive binding assay, TBBPA had considerable ability to compete with the binding of T4 to TTR at concentrations up to 12.5 μM (Hamers et al. 2004, 2006; EU RAR 2006). Although no reduction in T4 binding to TTR was observed in maternal and foetal plasma following oral dosing of pregnant rats with TBBPA from day 10 to 16 of gestation, the limitations of the study were such that no firm conclusion could be drawn regarding the affinity of TBBPA for TTR *in vivo* (EU RAR 2006).

Additional data were identified since the European Union assessment regarding the effects on the endocrine system.

Estrogenic/Androgenic Effects

The effect of TBBPA on estrogen, androgen, and progesterone binding and/or activity was examined by several investigators using various *in vitro* methods. While some observed that TBBPA exhibited weak estrogen receptor (ER) effects *in vitro* (Kitamura et al. 2005b; Li et al. 2010), others found that TBBPA did not exert any effects, even at high concentrations (Dorosh et al. 2011; Lee et al. 2012). Similar equivocal observations can be said for effects on androgen receptor (AR) and progesterone receptor (PR) binding and activity (Hamers et al. 2006; Li et al. 2010; Christen et al. 2010). Further, Cantón et al. (2005) did not find any inhibition or induction of enzyme aromatase (CYP19) activity, a

key enzyme that mediates the conversion of androgens to estrogens, by TBBPA (See Appendix 9 for more detail).

In *in vivo* studies, Kitamura et al. (2005b) exposed ovariectomized B6C3F1 mice by intraperitoneal (*ip)* injection and noted increased uterus to body weight ratio in all exposed groups suggesting estrogenic activity, however there was a poor dose-response. More recently, Ohta et al. (2012) conducted a uterotrophic assay where TBBPA was administered daily via oral gavage and subcutaneous injection for 7 days using C57BL/6J ovariectomized adult female mice. Results from this study showed that TBBPA was negative for agonistic and antagonistic estrogenic responses by both routes of exposure using concentrations up to 1000 mg/kg bw/day (Ohta et al. 2012).

Overall, the *in vitro* studies examining the potential for estrogenic effects of TBBPA did not show estrogenic activity or related agonist/antagonist effects; limited evidence was presented suggesting weak estrogenic potential. *In vivo* studies corroborate the *in vitro* evidence as TBBPA does not appear to exert estrogenic effects *in vivo* when tested in the mouse uterotrophic assay. Additional studies evaluating the androgenic and progestagenic potential of TBBPA are still needed.

Thyroid Effects

A significant number of recent *in vitro* assays were conducted to examine the effects of TBBPA on the thyroid hormone system by investigating possible mode(s) of action by which TBBPA may affect thyroid function (binding to thyroid receptors, altering thyroid signaling, inhibition of deiodinase activity). Differing responses on growth hormone release from *in vitro* experiments using the GH3 cell line were noted by Kitamura et al. (2005b) and Freitas et al. (2010). While Kitamura suggested a weak agonist activity for TBBPA, Freitas noted antagonistic activity at micro molar concentrations.

Similarly inconsistent results were noted for thyroid receptor binding in cell line studies. Butt et al. (2011) noted reductions in deiodinase (DI) activity in hepatic microsomes with micromolar concentrations of TBBPA. Oka et al. (2012) noted effects in *medaka* fish, but not in human cell lines. Conversely, Fini et al. (2012) reported binding of TBBPA, but none of its sulfated conjugates, to human thyroid receptors when expressed on *X. laevis*, tadpoles. Gene expression studies also demonstrated agonist or antagonistic activity in the micro molar range, depending on the reporting system employed (Sun et al. 2009; Hofmann et al. 2009; Lévy-Bimbot et al. 2012).

In a short term *in vivo* study, Decherf et al. (2010) demonstrated that a seven day exposure of TBBPA (150 mg/kg bw) to pregnant mice induced a decrease in T3-independent transcription activation of both thyrotropin-releasing hormone gene, *Trh,*and the melanocortin receptor type 4 gene, *Mc4r* promoter in the hypothalamus of offspring. The implications of these findings on thyroid homeostasis and metabolism need further investigation.

In humans, a recent cross-sectional study in Belgium examining neurobehavioural function, thyroid hormone levels, and low level exposure to flame retardants in

adolescents, found no significant association between TBBPA levels and hormone serum levels of FT3, T4, or TSH after correction for possible confounders (Kiciński et al. 2012). It must be noted that levels of TBBPA were often below the level of quantification (LOQ = 0.015 ng/ml) and a mean concentration was not calculated (See Appendix 8).

Overall, most *in vitro* studies examining the effects of TBBPA on thyroid hormone receptors and signalling are narrow in focus (determination of mode of action) and the implications of these results remain unclear. TBBPA did not alter normal brain development nor had any effects on T3, T4 or TSH levels in offspring of rats (Saegusa et al. 2009). Further, although limited, the epidemiological study by Kiciński et al. (2012) did not find any association with TBBPA in serum with effects on thyroid hormone levels in 515 adolescents. However, the biomonitoring data suggests that current levels in humans are orders of magnitude lower than those which can alter thyroid measurements in *in vitro* experiments.

Neurotoxicity

Several *in vitro* neurotoxicity studies have examined the potential for flame retardants to affect cellular function. Some studies have observed that TBBPA and/or its derivative, TBBPA bis(allyl ether), induced cytotoxicity in various neuronal cell types at doses ranging from 15-25 μM (Qu et al. 2011; Ziemińska et al. 2012; Al-Mousa and Michelangeli 2012), however it cannot be concluded that TBBPA is neurotoxic.

The effect of TBBPA on neurodevelopment in relation to thyroid homeostatis is a critical concern. To this end, the impact and reversibility of TBBPA on neuronal development of neonatal rats was recently examined by Saegusa et al. (2012) at doses up 10,000 ppm (818.9 – 2129.2 mg/kg-bw per day) in diet of dams. There was an increase in reelin-expressing interneurons in the dentate hilus and a slight increase in apoptotic bodies in offspring of pregnant rats, but these effects were reversible by PND 77. Further, TBBPA did not cause any developmental hypothyroidism in these animals (i.e. no dose-related changes in thyroid serum levels; Saegusa et al. 2009). There was an excess of mature neurons in the hilus at later stages, but these effects were also reversible and there were no effects on organ to body weight changes in the brain or the thyroid. Overall, it was concluded that there was no obvious developmental hypothyroidism caused by TBBPA in these studies (Saegusa et al. 2009, 2012).

TBBPA did not appear to affect the levels of proteins involved in maturation of the brain, neuronal growth or synaptogenesis in neonate mice after a single low dose (11.5 mg/kg bw) oral administration of TBBPA (Viberg and Eriksson 2011). However, there was a decrease in binding sites of the nicotinic ligand cytisine in frontal cortex, but not in the parietal cortex or hippocampus of 17 day old mice. Earlier developmental neurotoxicity studies also did not observe any adverse effects upon neurodevelopment or effects upon behaviour, auditory startle habitutation, learning or memory in perinatal or adult rats (Eriksson et al. 1998, 2001; Schroeder 2002; Hass et al. 2003). As previously mentioned, an acute neurobehavioral study by Nakajima et al. (2009) observed behavioural changes, but these effects were not considered to be treatment related.

The above-mentioned cross-sectional study from Belgium examining neurobehavioural function in adolescents and low level exposure to TBBPA, did not find any consistent associations with performance in neurobehavioural tests and levels of TBBPA measured in blood (Kiciński et al. 2012). Again, this study is limited based on the lack of significant number of samples with levels of TBBPA above the LOQ (See Appendix 8).

Overall, although it was found that TBBPA and its derivative TBBPA bis(allyl ether) were cytoxotic to neuronal cells *in vitro*, the available *in vivo* studies in rodents were negative and there were no permanent adverse effects in brain development.

Immunotoxicity

Limited data were available upon which to assess immunotoxicity of TBBPA. Kibakaya et al. (2009) demonstrated that *in vitro* exposure of TBBPA to human natural killer (NK) cells decreased lytic function that was persistent even after the substance was removed. It must be noted that the concentrations at which function was impaired were high compared to those measured in human serum. Similarly, increases in cytokine mRNA and protein expression were noted at 1 μM (Han et al. 2009), while reactive oxygen species (ROS) production was increased at 2 μM and higher (Reistad et al. 2005), and cell surface proteins were reduced in NK cells at a concentration of 5 μM (Hurd and Whalen 2011) in *in vitro* studies.

The ability of TBBPA to stimulate mouse immune cells was examined *in vitro* using splenocytes and bone marrow-derived dendritic cells (BMDCs) from atopic prone NC/Nga mice (Koike et al. 2012). In this study, TBBPA showed no cytotoxic effect on either splenocytes or BMDCs and did not have any effect on BMDCs, but could stimulate activation marker expression and IL-4 production in splenocytes.

In i*n vivo* studies, Watanabe et al. (2010) exposed BALB/c mice to 1% TBBPA in the diet for 28 days (1887 mg/kg-bw per day). The host immunity to respiratory syncytial virus was mildly affected in lungs and bronchoalveolar lavage (BAL) fluid tested *in vitro* while systemic immunity was not affected. The authors proposed that changes in cytokine production and immune (BAL) cell populations affected the immunity of the mice. Immune parameters were also investigated in a reproductive assay with rats (van der Ven et al. 2008). There was no effect upon the immunization response against sheep red blood cells in male F1 animals. Similarly, the natural killer activity test in spleen cells showed no effect in these animals.

Overall, although there was some indication of perturbation of immune function in *in vitro* studies, there was no evidence for specific effects on immune response and overall systemic immunity was not affected whole animals.

Toxicokinetics

No data are available for the toxicokinetics of TBBPA via the inhalation route, however the EU RAR (2006) predicts that, based on respiratory tract deposition, approximately 70% of particles will be available for absorption through the GI tract and less than 4% through the lungs. No data were available via the dermal route of exposure.

The toxicokinetics of TBBPA via the oral route was examined in male Sprague Dawley rats after a single administration of 2.0 mg/kg-bw of ^{14}C-ring labelled TBBPA (Hakk et al. 2000). The same dose was administered to eight bile-cannulated rats. Urine, bile, and faeces were collected between 0 and 72 hours and tissues were examined at the end of 72 hours. According to the EU RAR (2006), approximately 71% of the administered dose is absorbed from the GI tract and is excreted via the bile/faeces and 26% is not excreted via the bile, but appears in the faeces within 72 hours. It was therefore assumed that 100% of the administered oral dose of TBBPA is absorbed from the GI tract with approximately 50% being excreted in the bile after 24 hours. Examination of the bile at this time point revealed three metabolites of TBBPA: a diglucuronide ether conjugate (24%), a glucuronic acid/sulphate ester diconjugate (14%), and a monoglucuronic acid conjugate (24%) constituting approximately 31% of the total administered dose. After tissue examination, only 2% and 1% of the administered dose was retained in the tissues in the non-cannulated and cannulated rats, respectively. In both groups the highest levels were found in the small and large intestines (contents not emptied prior to measurement). Levels in other tissues were below the LOD in this study (Hakk et al. 2000).

Previous studies performed using rats also reported that the majority of administered TBBPA and/or its metabolites appeared in the faeces and that there was limited tissue distribution and systemic distribution via the blood suggesting that TBBPA does not bioaccumulate (EU RAR 2006). A study using pregnant Wistar rats indicated that there was no significant transfer of TBBPA or its metabolites from the maternal circulation to the foetus at low doses (5 mg/kg bw), although a very small portion of the administered dose was detected in the foetus (0.34%) (Meerts et al. 1999).

Additional data were identified since the European Union assessment. A concurrent study in rats and humans was performed by Schauer et al. (2006). Five human subjects were administered a single oral dose of 0.1 mg/kg TBBPA and rats were administered 300 mg/kg bw TBBPA with urine and blood samples measured for TBBPA and its metabolites in both species. Two major metabolites of TBBPA, TBBPA-glucuronide and TBBPA-sulfate, were found in urine and blood samples in subjects while the parent TBBPA was not present in detectable levels in any of the human plasma samples. TBBPA-glucuronide plasma levels reached peak concentrations between two and six hours after administration and was slowly eliminated in urine to reach the LOD 124 hrs after administration. TBBPA-sulfate (found in 2 of the 5 human subjects) was measured between four and six hrs after administration in plasma and was below the LOD in urine. The authors suggest that the major role of enterohepatic circulation is indicated by the slow elimination of TBBPA-glucuronide in urine in both humans and rats and this, along with efficient hepatic metabolism, would result in low systemic bioavailability of TBBPA in humans (Schauer et al. 2006).

A study by Kuester et al. (2007) examined the effects of repeated dosing and route of administration on the kinetics of radioactive ^{14}C-TBBPA using Fischer 344 rats. Almost all (90% or greater) of single oral doses of 0, 20, or 200 mg/kg-bw of ^{14}C-TBBPA were eliminated after 72 hrs. Tissue deposition was minimal (0.2-0.9%) even at the highest

oral dose administered (tissue distribution studies were not performed in intravenous (*iv*) dose administered animals). Rates of elimination or tissue retention were not affected with repeated daily oral doses of 20 mg/kg-bw for five or ten consecutive days. Following a single *iv* dose of 20 mg/kg, rabiolabelled TBBPA levels decreased rapidly. Furthermore faecal excretion was the major route of elimination of TBBPA regardless of dose or route (oral versus *iv*) of administration although the rate of elimination was somewhat slower when TBBPA was given through *iv* (Kuester et al. 2007).

A study in rats examining the nephrotoxic potential of TBBPA by Kang et al. (2009) suggested that TBBPA produces only transient oxidative stress to the adult kidney, but as it was not present in renal tissue after repeated oral administration of doses as high as 1000 mg/kg-bw, these effects did not appear toxic.

A neurodevelopmental toxicity study measuring levels of ^{14}C-TBBPA in the brain of young mice at 3 h, 24 h, and 7 days post administration observed that TBBPA levels were low and dispersed rapidly (3.7%, 0.9%, and 0.3% respectively) (Viberg and Eriksson 2011).

Characterization of Risk to Human Health

TBBPA has low acute toxicity following all routes of exposure. The evidence from animal studies indicates that TBBPA is not a skin, eye or respiratory irritant. Similarly, it is neither a skin nor a respiratory sensitizer.

In a limited number of generally poorly reported repeated-dose toxicity studies, adverse effects were not observed in rats or rabbits following either inhalation or dermal exposure. In a 14-day gavage study, no effects were observed in mice up to 700 mg/kg-bw per day. In two subchronic studies (diet, gavage), no adverse effects were observed at exposures up to 1000 mg/kg-bw per day.

The EU RAR (2006) concluded that TBBPA was not genotoxic in *in vitro* systems. No *in vivo* data were identified. They noted that there were no structural indications that TBBPA would be genotoxic (no QSAR modelling identified). Furthermore, TBBPA does not appear to be carcinogenic.

Several reproductive and developmental studies were available to the EU RAR (2006). No effects upon fertility or reproduction were observed in a two-generation study in rats, at doses up to 1000 mg/kg-bw per day. In a pilot range-finding study and two standard developmental assays, no developmental effects were observed at doses up to 10 000 mg/kg-bw per day. In developmental neurotoxicity studies in rats, no adverse effects upon neurodevelopment were observed at doses up to 1000 mg/kg-bw per day. In a single exposure protocol with neonatal mice, no effects were observed upon behaviour, learning or memory.

The critical effect level selected by the EU RAR (2006) (NOAEL of 40 mg/kg-bw per day) was from a developmental toxicity study (Fukuda et al. 2004), in which polycystic

lesions associated with kidney tubule dilation was noted at doses of 200 mg/kg-bw or 600 mg/kg-bw per day.

The lowest reported critical effective dose in the database identified since the publication of the EU RAR (2006) assessment is a LOAEL of 1.4 mg/kg-bw per day for calculated increased absolute F1 testes weight in a reproductive toxicity study, while an increased F1 male pituitary gland absolute weight was calculated at a slightly higher dose (2.2 mg/kg-bw per day) (Van der Ven et al. 2008; Lilienthal et al. 2008). A comparison of the relative weights of these organs (Appendix 10) does not indicate a clear dose-response. These effects were not considered critical end points for the purposes of the current risk assessment. Further details of these studies are available in Appendices 9 and 10.

Characterization of risk of TBBPA and its derivatives is therefore based on the lowest LOAEL (140.5 mg/kg-bw per day), based upon liver toxicity in female offspring identified in a reproductive assay with mice, by Tada et al. (2006). This study is considered to be of adequate duration and a very conservative effect level upon which to base risk characaterization for long term exposure to TBBPA and its derivatives. This is a conservative approach, in view of the well-conducted two-generation assay with rats, in which no adverse effects were observed at a dose level of 1000 mg/kg-bw per day where the intakes of the rats in the two-generation study spanned *in utero* exposure, lactation and development into adulthood (MPI Research 2002b, 2003). Similarly, no adverse effects were observed in a subchronic study in which rats were exposed to up to 1000 mg/kg-bw per day (MPI Research 2002a). The critical levels identified for hepatic effects in mice in the reproductive assay by Tada et al. (2006) are congruent with the corresponding levels for adverse effects in the kidneys of newborn rats (Fukuda et al. 2004). The effects in the latter study were attributed to the effects of TBBPA upon animals with immature metabolic capability and/or immature kidneys. As a comparison, risk was also characterized using the NOAEL of 40 mg/kg-bw per day from a developmental toxicity study in newborn rats (Fukuda et al. 2004), similar to the assessment detailed in the EU RAR (2006). This point of departure is also considered protective of any potential transient effects on neurogenesis (increase in reelin-expressing interneurons in the dentate hilus in newborn rats).

The highest upper bounding estimate of exposure of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) by the general population of Canada was determined to be 1.95×10^{-4} mg /kg-bw per day for breast fed infants. This estimate of intake for human breast fed infants was calculated from a known exposure algorithm (Health Canada 2008).

A comparison between the critical effect level identified (140 mg/kg-bw per day for the developing young and for the general public) and the intake of 1.95×10^{-4} mg/kg-bw per day for breast fed infants results in a margin of exposure (MOE) of 717 950. Using the NOAEL of 40 mg/kg-bw per day from a developmental toxicity study (Fukuda et al. 2004), similar to the assessment detailed in the EU RAR (2006) provides a MOE of 205 000. Taking into consideration that exposure estimates were based on conservative assumptions (i.e., upper bounding estimates in breastfed infants when actual

measurements of TBBPA in human breastmilk and maternal blood serum levels of TBBPA were virtually undetected in more recent surveys in North America), and given that these margins are based on both NOAELs and LOAELs, these MOEs are considered adequate to address uncertainties in the health effects and exposure database.

Uncertainties in Evaluation of Risk to Human Health

Confidence in the upper bounding estimate of daily intake is considered to be low to moderate.

No Canadian monitoring data for relevant environmental media (air, water, soil, dust) or food were located for TBBPA or the two derivative substances.

The measurement of TBBPA in ambient air is from the Arctic.

Levels in indoor air are taken from two sources: measured levels in the vapour and particulate matter, as reported from a Michigan, US study.

Food exposure estimates are also based on levels found in food from other countries. Dietary patterns in Canada may differ from the country which provided the data used in the exposure assessment.

The maximum concentration of TBBPA measured in surface water in Germany in an industrial area was used as an estimate of levels in drinking water.

The maximum concentration of TBBPA measured in dust from daycare and school environments in United Kingdom was used. However, significantly higher levels (several orders of magnitude) are reported in Japan from dust from the rear cabinets of television and computers, but which were not used in the assessment. The UK values were used because these levels were consistent with levels found in office buildings and are expected to be similar to those in households and/or in cars.

Although the database is considered adequate to characterize an upper bound estimate considered relevant to the Canadian use pattern at this time, it is noted that exposures to TBBPA and the two derivative substances are reported to have increased in several countries. Exposure will vary throughout the world, depending on usage of the products containing TBBPA and the two derivative substances. Since Canada is a neighbouring country to the United States, a primary producer and consumer of TBBPA and the two derivative substances, exposures reported in US are considered the most relevant. If available, data from the United States was used in the upper bounding estimates, but for some parameters, data from United Kingdom, Belgium, China and Japan were used.

The highest upper bounding estimate of exposure of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) among the general population of Canada was determined to be 1.95×10^{-4} mg/kg-bw per day (0.195 µg/kg-bw per day) for breast fed infants. In the European risk assessment report, the exposure estimate for 0-3 month

infants was 0.05 µg/kg-bw per day with a human milk concentration, 1/3 less than the highest reported value by Cariou et al. (2008). If the concentration in breast milk used in this assessment (37.3 ng/g lipid value) is substituted, an exposure of 0.15 µg/kg-bw per day would be obtained for breast fed infants, which is closer to the value used in this assessment.

Additionally, lack of exposure methodologies to characterize the contribution of exposure from dust particles and particulate matter in indoor air, other than by oral ingestion, is an uncertainty.

There is uncertainty introduced in terms of the actual contributions made by the derivatives. It is reported that the presence of the two derivatives in a polymeric material is expected to comprise no more than 10% to 25% of the amount of TBBPA present in the formulation. Therefore, a conservative approach using an upper-bounding exposure value for TBBPA in the assessment is considered to account for additional exposure resulting from the two derivatives.

Confidence in the health effects database is considered to be moderate. Although no lifetime assays were identified, there were no indications of tumour generation in the repeated dosing studies. TBBPA was negative for genotoxicity in *in vitro* studies (no *in vivo* studies were identified). There is uncertainty regarding the potential of TBBPA to affect the endocrine system, including the thyroid, and the immune system.

The health effects database for TBBPA has been used to characterize the potential health effects of TBBPA and TBBPA bis(allyl ether), based on the two derivatives being structurally similar to TBBPA.

Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from TBBPA and its two derivative substances, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether). It is concluded that TBBPA, TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) do not meet the criteria under paragraphs 64(*a*) or 64(*b*) of CEPA 1999 as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Based on the adequacies of the margins between upper bounding estimates of exposure to TBBPA and critical effect levels, it is concluded that TBBPA does not meet the criteria under paragraph 64(*c*) of CEPA 1999 as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on the information presented in this screening assessment, it is concluded that TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) do not meet the criteria under paragraph 64(*c*) of CEPA 1999 as they are not entering the environment in a quantitiy or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that TBBPA and the derivatives TBBPA bis(allyl ether) and TBBPA bis(2-hydroxyethyl ether) do not meet any of the criteria under section 64 of CEPA 1999.

Consideration for Follow-up

Although there is currently limited exposure in Canada to TBBPA and its concentrations currently in the environment are not indicative of harm to organisms in Canada, there may be concerns if new activities were to occur, including increased volume of manufacture, import or use, which may result in increased exposure to organisms in Canada. Therefore, options on how best to monitor changes in the use of this substance will be investigated, such as addition to the National Pollutant Release Inventory and/or amending the Domestic Substance List to indicate that the Significant New Activity provisions applies with respect to this substance, so that new activities pertaining to the use, manufacture, or import are notified and undergo ecological and human health risk assessment.

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Table 1. Substance identity for TBBPA, TBBPA Bis(2-hydroxyethyl ether), and TBBPA Bis(allyl ether)

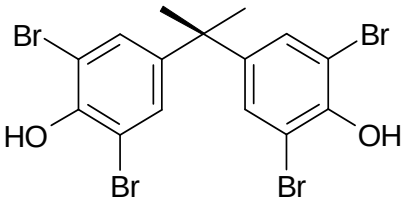
CAS RN	79-94-7
DSL name	Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-
National Chemical Inventories (NCI) names[1]	Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo- (TSCA, DSL, PICCS, ASIA-PAC, NZIoC) 2,2',6,6'-Tetrabromo-4,4'-isopropylidenediphenol (French) (DSL) 2,2',6,6'-tetrabromo-4,4'-isopropylidenediphenol (English, French) (EINECS) 2,2',6,6'-Tetrabrom-4,4'-isopropylidendiphenol (German) (EINECS) 2,2',6,6'-tetrabromo-4,4'-isopropilidendifenol (Spanish) (EINECS) 2, 2-Bis (4'-hydroxy-3',-5'-dibromophenyl) propane (ENCS) Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo- (AICS) 4,4'-(1-Methylethylidene)bis[2,6-dibromophenol] (ECL) BIS(PHENOL, 2,6-DIBROMO), 4,4'-(1-METHYLETHYLIDENE) (PICCS) BISPHENOL A, TETRABROMO- (PICCS) BISPHENOL, 4,4'-(1-METHYLETHYLIDENE)TETRABROMO- (PICCS) TETRABROMOBISPHENOL-A (ABS) (PICCS) Tetrabromobisphenol A (PICCS)
Other names	Tetrabromobisphenol A (TBBPA); 2,2',6,6'-Tetrabromobisphenol A; 3,3',5,5'-Tetrabromobisphenol A; 3,5,3',5'-Tetrabromobisphenol A; 2,2-Bis(3,5-dibromo-4-hydroxyphenyl)propane; 2,2-Bis(4-hydroxy-3,5-dibromophenyl)propane; 4,4'-Isopropylidenebis(2,6-dibromophenol); 4,4'-(1-Methylethylidene)bis(2,6-dibromophenol); Tetrabromodiphenylolpropane; Tetrabromodian; Tetrabromobisphenol A; T 0032; BA 59; BA 59BP; BA 59P; CP 2000; Flame Cut 120G; Flame Cut 120R; GLCBA 59P; NSC 59775; PB 100; RB 100; Bromdian; FR-1524; Fire Guard FG2000; Firemaster BP 4A; Great Lakes BA-59P; Saytex CP-2000; Saytex RB 100; Saytex RB 100PC;
Chemical group	Brominated flame retardant
Chemical subgroup	Brominated aromatic phenol
Chemical formula	$C_{15}H_{12}Br_4O_2$
Chemical structure	
SMILES[1]	Oc(c(cc(c1)C(c(cc(c(O)c2Br)Br)c2)(C)C)Br)c1Br
Mol. Wt.	543.88 g/mol (Ashford 1994)

Table 1. Substance identity continued.

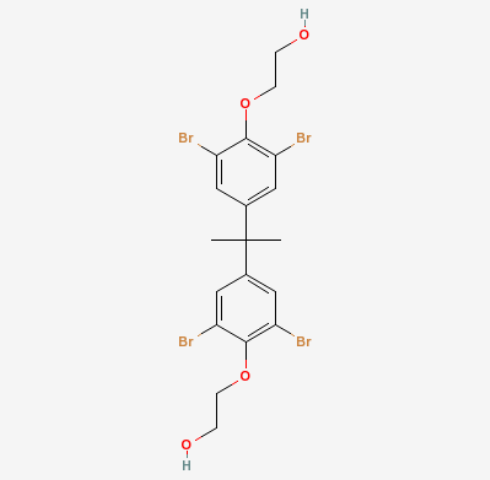
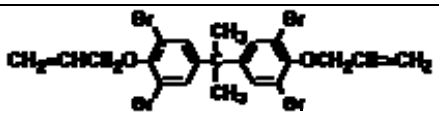
CAS RN	4162-45-2
DSL name	Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-
National Chemical Inventories (NCI) names[1]	Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis- (TSCA, DSL, ENCS, PICCS, ASIA-PAC) 4,4'-Isopropylidenebis(2-(2,6-dibromophenoxy)ethanol) (French) (DSL) 4,4'-isopropylidenebis(2-(2,6-dibromophenoxy)ethanol) (English, French) (EINECS) 4,4'-Isopropylidenbis(2-(2,6-dibromphenoxy)ethanol) (German) (EINECS) 4,4'-isopropilidenobis(2-(2,6-dibromofenoxi)etanol) (Spanish) (EINECS) Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis- (AICS) 2,2'[(1-Methylethylidene)bis[(2,6-dibromo-4,1-phenyleneoxy]]bisethanol (ECL) Tetrabromobisphenol A Bis(2-hydroxyethyl ether) (PICCS)
Other names	2,2'-Isopropylidenebis[(2,6-dibromo-p-phenyleneoxy)diethanol] 2,2-Bis[3,5-dibromo-4-(b-hydroxyethoxy)phenyl]propane 2,2-Bis[3,5-dibromo-4-(2-hydroxyethoxy)phenyl]propane 2,2-Bis[4-(2-hydroxyethoxy)-3,5-dibromophenyl]propane 4,4'-Isopropylidenebis[2-(2,6-dibromophenoxy)ethanol] AFR 1011 BA 50 BA 50P Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-bromo-4,1-phenylene)oxy]bis- Ethanol, 2,2'-[isopropylidenebis[(2,6-dibromo-p-phenylene)oxy]]di- Ethoxylated tetrabromobisphenol A FG 3600 Fire Guard 3600
Chemical group	Brominated flame retardant
Chemical subgroup	Brominated aromatic phenol
Chemical formula	C19H20Br4O4
Chemical structure	
SMILES[1]	OCCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCCO)c(Br)c2
Mol. Wt.	631.98 g/mol (EPISuite 2008)

Table 1. Substance identity continued.

CAS RN	25327-89-3
DSL name	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)-
National Chemical Inventories (NCI) names[1]	Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)- (TSCA, DSL, ENCS, PICCS, ASIA-PAC, NZIoC) 1,1'-Isopropylidenebis[4-(allyloxy)-3,5-dibromobenzene] (French) (DSL, EINECS) 1,1'-isopropylidenebis[4-(allyloxy)-3,5-dibromobenzene] (EINECS) 1,1'-Isopropylidenbis[4-(allyloxy)-3,5-dibrombenzol] (German) (EINECS) 1,1'-isopropilidenbis[4-(aliloxi)-3,5-dibromobenceno] (Spanish) (EINECS) Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propenyloxy)- (AICS) 1,1'-isopropylidenebis[4-(allyloxy)-3,5-dibromobenzene] (ECL) Tetrabromobisphenol A Bis(allyl ether) (PICCS)
Other names	2,2-Bis(3,5-dibromo-4-allyloxyphenyl)propane 2,2-Bis(4-allyloxy-3,5-dibromophenyl)propane BE 51 FG 3200 Fire Guard 3200 Flame Cut 122K Propane, 2,2-bis[4-(allyloxy)-3,5-dibromophenyl]- Pyroguard SR 319 See also Brominated flame retardant SR 319 Tetrabromobisphenol A allyl ether Tetrabromobisphenol A diallyl ether Tetrabromobisphenol A, bis(allyl ether) Tetrabromobisphenol-A-bisethoxylate
Chemical group	Brominated flame retardant
Chemical subgroup	Brominated aromatic phenol
Chemical formula	C21H20Br4O2
Chemical structure	
SMILES[2]	C=CCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCC=C)c(Br)c2
Mol. Wt.	624.01 g/mol (EPISuite 2008)

[1] National Chemical Inventories (NCI). 2009: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ELINCS (European List of Notified Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

[2] Simplified Molecular Input Line Entry System

Table 2. Selected measured and predicted physical and chemical properties of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether)

Property	TBBPA	TBBPA bis(2-hydroxyethyl ether)	TBBPA bis(allyl ether)
Physical state (20°C; 101.325 kPa)	Crystalline or powdered white (colourless) solid (WHO 1995)	Crystalline white-coloured powder (WHO 1995)	Crystalline white solid (WHO 1995)
Water solubility (mg/L)	0.240 (25°C, pH 6.7-7.3) (ACCBFRIP 2002b) 0.148–2.34 (25°C; pH 5.0–9.0) (ACCBFRIP 2002b) 0.063 (21°C) (NOTOX 2000) 0.72–4.16 (15–25°C) (Velsicol Chemical Corporation 1978f)	0.03119 (25°C) (WSKOWWIN, version 1.43, within ECOSAR) 0.005 – 0.019 (WATERNT, version 1.01)[9] 0.0001593 (25°C) (WSKOWWIN version 1.34)	2.05×10^{-5} (25°C) (WSKOWWIN, version 1.43, within ECOSAR) 4.07×10^{-6} (25°C) (WSKOWWIN, version 1.41) 3.40×10^{-6} (25°C) (WATERNT, version 1.01) 3.12×10^{-7} (25°C) (WSKOWWIN version 1.34) $7.4 \times 10^{-7} – 2.83 \times 10^{-6}$ (WATERNT, version 1.01)(EVA)[9] 1.12×10^{-3} (ACD/labs v.12.5)
Vapour pressure (Pa)	$< 1.19 \times 10^{-5}$ (20°C) (ACCBFRIP 2001b) 6.24×10^{-6} (25°C) (Watanabe and Tatsukawa 1989) 4.72×10^{-9} (25°C) (Kuramochi et al. 2008) 8.47×10^{-9} (298.15K) (Fu J and Suuberg FM 2012)	1.29×10^{-13} (25°C) (MPBPWIN, version 1.31) 1.53×10^{-8} (25°C) (MPBPWIN, version 1.43) Mackay method	2.9×10^{-9} (25°C) (MPBPWIN, version 1.43) Antoine method 2.00×10^{-8} (25°C) (MPBPWIN, version 1.31) 2.65×10^{-7} (25°C) (MPBPWIN, version 1.43) modified grain method
Henry's law constant (Pa m^3/mole)	< 0.10 0.014–0.054 (EU RAR 2008) 1.47×10^{-5} (Kuramochi et al. 2008)	1.78×10^{-8} (HENRYWIN, version 3.03, bond method) 5.12×10^{-7} (HENRYWIN, version 3.03, VP/Wsol) Incomplete[1] (HENRYWIN, version 3.03, group method)	1.30×10^{-2} (HENRYWIN, version 3.03 and 3.20, bond method) 40.0 (HENRYWIN, version 3.03, and 3.20, VP/Wsol) Incomplete[1] (HENRYWIN, version 3.03 and 3.20, group method)

Property	TBBPA	TBBPA bis(2-hydroxyethyl ether)	TBBPA bis(allyl ether)
Log K_{ow} (Log D)	5.903 (ACCBFRIP 2001a) 4.540 (Velsicol Chemical Corporation 1978b) 6.53– (-1.22)(25°C; pH 3.05 – 11.83) (Kuramochi et al. 2008) 5.1 (WSKOWWIN version 1.41)[2] 5. 7 (WSKOWWIN version 1.41)[3] Species Specific QSAR Estimates (using KOWWIN, version 1.65) $TBBPA^0$ $TBBPA^{-1}$ $TBBPA^{-2}$ 7.2 4.52[4] 3.18[5]	5.48 (KOWWIN, version 1.67, Experimental Value Adjusted (EVA)) 5.995 (ClogP, version, 1.0.0) 6.7842 (KOWWIN, version, 1.65) 7.48 at pH 7 (PALLAS, version 4.0)	8.71 (KOWWIN, version 1.67 (EVA) 8.89 (ClogP, version 1.0.0) 10.02 (KOWWIN, version 1.65) 10.33 (PALLAS, version 4.0)
Log K_{oc}	5.43[6] (KOCWIN, version 2.0, MCI) 4.52[6] (KOCWIN, version 2.0, LogKow derived) 5.02[6] (ASTER) 5.5[7] 4.1[7] Species Specific K_{oc} Estimates[8] $TBBPA^0$ $TBBPA^{-1}$ $TBBPA^{-2}$ 6.8 4.1 2.8	3.24 (KOCWIN, version 2.0, MCI) 3.25 (KOCWIN, version 2.0, LogKow derived)	5.87 (KOCWIN, version 2.0, MCI) 5.85 (KOCWIN, version 2.0, LogKow derived)
pKa	7.5 (1^{st}) and 8.5 (2^{nd}) (Bayer 1990) 9.40 (ACCBFRIP 2002a) 6.79 (1^{st}) and 7.06 (2^{nd}) (Kuramochi et al. 2008)	-3.16 – 14.41 (PALLAS, version 4.0)	

Notes

[1] HENRYWIN, version 3.03, does not define *incomplete*. Information in Meylan and Howard (1991) and Hine and Mookerjee (1975), two publications upon which the model is based, suggests that the term may be used to indicate that an estimate for the Henry's law constant could not be determined using the group estimation method, since activity information was not available for all chemical groups in the molecule.

[2] WSKOWWIN version 1.41, using water solubility (WS) = 0.240 mg/L, pH 6.7-7.3, (ACCBFRIP 2002b)

[3] WSKOWWIN version 1.41, using WS = 0.063 mg/L, pH 7.6 – 8.1, (NOTOX 2000)

[4] Intermediate between ClogP-predicted values of 3.8 (assuming no ion pairing, zero ionic strength) and 6.06 (assuming complete ion pairing, high ionic strength).

[5] Intermediate between ClogP-predicted values of 1.31 (assuming no ion pairing, zero ionic strength) and 5.31 (assuming complete ion pairing, high ionic strength).

[6] Using experimentally measured logKow 5.90.

[7] Using the general equation $K_{oc} = 0.41K_{ow}$ applied to experimentally measured values for Kow.

[8] Using the general equation $K_{oc} = 0.41K_{ow}$ applied to QSAR estimates of K_{ow} for $TBBPA^0$, $TBBPA^{-1}$ and $TBBPA^{-2}$. Based on data from table estimated using KOWWIN, version 1.65.

[9] Experimental Value Adjusted (EVA), using TBBPA water solubility =0.063 - 0.240 mg/L, 21 -25°C

Table 3a. Results of the Level III fugacity modelling for TBBPA (EQC 2003)

	Percentage of substance partitioning into each compartment			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	0.10	0.07	97.6	2.22
Water (100%)	7.42×10^{-4}	2.84	0.75	96.4
Soil (100%)	2.68×10^{-5}	6.85×10^{-3}	99.8	0.23

Table 3b. Results of the Level III fugacity modelling for TBBPA bis(allyl ether) (EQC 2003)

	Percentage of substance partitioning into each compartment			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	0.48	0.31	81.1	18.1
Water (100%)	1.57×10^{-7}	1.7	2.64×10^{-5}	98.29
Soil (100%)	3.74×10^{-9}	0.002	99.9	0.12

Table 3c. Results of the Level III fugacity modelling for TBBPA bis(2-hydroxyethyl ether) (EQC 2003)

	Percentage of substance partitioning into each compartment			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	0.35	0.93	89.8	8.95
Water (100%)	1.99×10^{-6}	9.43	5.03×10^{-4}	90.57
Soil (100%)	8.02×10^{-7}	0.01	99.89	0.10

Table 4. Modelled data for degradation of TBBPA

Fate Process	Model and model basis	Model Result and Prediction	Extrapolated Half-life (days)
AIR			
Atmospheric oxidation	AOPWIN 2008[1]	$t_{1/2}$ = 3.615 days	≥ 2
Ozone reaction	AOPWIN 2008[1]	n/a[2]	n/a
WATER			
Hydrolysis	HYDROWIN 2008[1]	n/a[2]	n/a
Primary biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 4: Expert Survey (qualitative results)	2.37[3] "biodegrades slowly"	< 182
Ultimate biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 3: Expert Survey (qualitative results)	1.35[3] "recalcitrant"	≥ 182
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 5: MITI linear probability	-0.01[4] "biodegrades slowly"	≥ 182
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 6: MITI non-linear probability	0.01[4] "biodegrades very slowly"	≥ 182
Biodegradation (aerobic)	TOPKAT 2004 Probability	0[4] "biodegrades very slowly	≥ 182
Biodegradation (aerobic)	CATABOL 2004-2008 % BOD (biological oxygen demand)	3.5% BOD = "biodegrades very slowly"	≥ 182

[1] EPIsuite 2008
[2] Model does not provide an estimate for this type of structure.
[3] Output is a numerical score from 0 to 5.
[4] Output is a probability score.

Table 5a. Empirical data for bioaccumulation of TBBPA

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Fish *Pimephales promelas*	BCF	1200 [1] 1300 [2]	Brominated Flame Retardants Industry Panel 1989c[3]
Fish *Lepomis macrochirus*	BCF	20 (edible tissue) [1] 170 (visceral tissue)[1]	Velsicol Chemical Corporation 1978d
Fish Carp	BCF	30 – 485 [1]	CITI 1992
Marine Invertebrate *Crassostrea virginica*	BCF	720 [1] 780 [2]	Brominated Flame Retardants Industry Panel 1989b
Freshwater Invertebrate *Chironomus tentans*	BCF	240 -510 high organic carbon (OC), 490 - 1100 medium OC 650 - 3200 low OC	Brominated Flame Retardants Industry Panel 1989h
Terrestrial earthworm, *Eisenia fetida*	BAF study[4]	0.24 - 0.019, 5.1	ACCBFRIP 2003

[1] measured tissue concentration / water concentration
[2] predicted from uptake rate / depuration rate
[3] BCF values include metabolites, BCF for parent compound alone estimated at 160-177 (EU RAR 2008).
[4] measured tissue concentration / soil concentration

Table 5b: Modelled data for bioaccumulation for TBBPA

Test organism	logKow	kM ($days^{-1}$)	BCF (L/kg)	Value wet weight (L/kg)	Reference
Fish	5.9	1.12[1]	BCF	150	BCFBAF 2008; Sub-model 2: Arnot-Gobas mass balance,
Fish	5.9	1.12[1]	BAF	174.1	BCFBAF 2008; Sub-model 3: Arnot-Gobas mass balance.
Fish	5.9	0.07[2]	BCF	347.9	CPOPs 2008; BBM with Mitigating Factors 2008

[1] kM is mean value derived from 3 experimental BCF studies (Brominated Flame Retardants Industry Panel 1989c, Velsicol Chemical Corporation 1978d (assumed wt=2g, T=22°C), and CITI 1992), and normalized for MTL fish (184g, 10°C)
[2] Reported from CPOPs model (CPOPs 2008; BBM with Mitigating Factors 2008)

Table 6. Measured concentrations of TBBPA and TBBPA bis(allyl ether) in the ambient environment and sewage sludge

Medium	Location; year	TBBPA Concentration*	Samples	TBBPA bis(allyl ether) concentration	Reference
Air	United States; 1977	< 0.01–1.8 µg/m^3	8		Zweidinger et al. 1979a
Air	United Kingdom; 2007	8 x 10^{-7} (0.8 pg/m^3)	5		Abdallah et al. 2008
Air	Russian Arctic; 1994 to 1995	0.00007 µg/m^3	in 1 of 4		Alaee et al. 2003
Air	Arctic (northeast Atlantic); 2004	< 4.0 x 10^{-8}–1.7 x 10^{-7} µg/m^3	in 2 of 7		Xie et al. 2007
Air	Wadden Sea; 2005	2.1 x 10^{-7}, 5.0 x 10^{-7} µg/m^3 (vapour) 1.0 x 10^{-7}, 1.9 x 10^{-7} µg/m^3 (particle)	in 2 of 2		Xie et al. 2007
Air	Northern Germany; 2005 and 2006	< 4.0 x 10^{-8}–2.5 x 10^{-7} µg/m^3 (vapour) 1.6 x 10^{-7}–8.5 x 10^{-7} µg/m^3 (particle)	in 6 of 7 in 7 of 7		Xie et al. 2007
Air/Precipitation	The Netherlands; 2000 to 2001	0.0000001–0.000002 µg/m^3 0.0002–0.0041µg/L	n.s. [a]		Duyzer and Vonk 2003
Air	Suburban area, Stockholm, Sweden	n.d.[b]	0/2		Sjödin et al. 2001
Air	Berlin,; Germany	n.d.	Multiple, n.s.		Kemmlein 2000
Air	Southern Arkansas, USA near two organobromine chemical manufacturing facilities	n.d. - 0.028 (facility 1) [n.d. - 1.8] (facility 2)	8, 4 high volume samples at each facility		Zweidinger et al. 1979a
Precipitation	Germany, Belgium, the Netherlands; no year	< 0.0005–0.0026 µg/L	in 8 of 50		Peters 2003
Water	France. Predecelle river near Paris n= 5 stations; June 2008	< 3 x 10^{-5}- 6 x 10^{-5} µg/L (<35-64 pg/L)	n.s.		Labadie et al. 2010
Water	England, Lakes n=9; July –Aug 2008; Nov 2008 andJan 2009	1 x 10^{-4} - 3 x 10^{-3} µg/L (140-3200 pg/L)	3 per site x 9 sites=27		Harrad et al. 2009
Water	Japan, multiple locations; 2000	n.d. (detection limit: 0.09)	0/27		MOE Japan 2003
Water	Japan, multiple locations; 1988	n.d. (detection limit: 0.04)	0/150		MOE Japan 2003
Water	Japan, multiple locations; 1987	0.05. (detection limit: 0.03)	Detected in 1 of 75		MOE Japan 2003
Water	Japan, multiple locations; 1977	n.d. (0.02 to 0.04)	0/15		MOE Japan 2003

Table 6. Measured concentrations of TBBPA and TBBPA bis(allyl ether) in the ambient environment and sewage sludge (continued)

Medium	Location; year	TBBPA Concentration*	Samples	TBBPA bis(allyl ether) concentration	TBBPA Concentration*
Water	Germany; 2000	< 0.0002–0.0204 µg/L (TBBPA) < 0.0002–0.00106 µg/L (Me-TBBPA[c])	in 7 of 30 in 3 of 30		Kuch et al. 2001
Water	Japan; 1977 to 1989	< 0.02–0.05 µg/L	in 1 of 240		Environment Agency Japan 1989, 1991
Water	South China, Liuyang river; 2009		18 samples	n.d. to 0.0491 µg/L (49.1 ng/L) (instrument detection limit:40 pg/L)	Qu et al. 2011
Landfill leachage	Canada; 2009-2010	0.049 µg/L (49 ng/L)	50		CRA 2011
Landfill leachate	Finland; no year	< 0.2–0.9 µg/L	2		Peltola 2002
Landfill leachate (solid phase)	The Netherlands; no year	< 5.5–320 µg/kg dw	in 3 of 9		de Boer et al. 2002
Landfill leachate (solid phase)	The Netherlands; 2002	< 0.3–320 µg/kg dw	11		Morris et al. 2004
Sediment	Lake Ontario; 2003	n.d. to 0.063 µg/kg dw	8		Quade 2003
Sediment	Detroit River; 2000	0.60–1.84 µg/kg dw	8		Quade 2003
Sediment	United States; 1977	< 100–330,000 µg/kg dw	7		Zweidinger et al. 1979b
Sediment	France, Predecelle river near Paris Sediments, n=5 stations	0.07-0.3 µg/kg dw (65-280 pg/g dw)	18		Labadie et al. 2010
Sediment	United Kingdom, English lakes; July –Aug 2008; Nov 2008 and Jan 2009	0.3-3.8 µg/kg dw (330 – 3800 pg/g dw)	7 cores / site= 63		Harrad et al. 2009
Sediment	United Kingdom; 1998	< 1.07–2.3 µg/kg ww	in 1 of 50		CEFAS 2002
Sediment	United Kingdom; no year	< 2.4–9753 µg/kg dw	in 10 of 22		de Boer et al. 2002
Sediment	Ireland; no year	< 0.1–3.7 µg/kg dw	in 4 of 13		de Boer et al. 2002
Sediment	England; 2000 to 2002	< 2.4–9750 µg/kg dw	22		Morris et al. 2004
Sediment	The Netherlands; 2000	< 0.1–6.9 µg/kg dw	28		Morris et al. 2004
Sediment	Belgium; 2001	< 0.1–67 µg/kg dw	20		Morris et al. 2004
Sediment	Sweden; 1988	34–270 µg/kg dw (TBBPA) 24–1500 µg/kg dw (Me-TBBPA[c])	n.s		Sellström and Jansson 1995
Sediment	Finland; 2000	< 0.2–21 µg/kg dw	in 2 of 5		Peltola 2002
Sediment	Germany; 2001	n.d. to 4.6 µg/kg dw	in 7 of 20		Heemken et al. 2001
Sediment	Germany; no year	n.d.to 18.68 µg/kg dw	13		Kemmlein 2000
Sediment	Germany; no year	< 0.2–1.83 µg/kg dw	in 8 of 19		Kuch et al. 2001

Table 6. Measured concentrations of TBBPA and TBBPA bis(allyl ether) in the ambient environment and sewage sludge (continued)

Medium	Location; year	TBBPA Concentration*	Samples	TBBPA bis(allyl ether) concentration	Reference
Sediment	China; 2009-2010 Dongjiang River Zhujiang River Beijiang River Xijiang River Shunde tributaries Dayanhe River Pearl River Estuary	Surface sediment samples n.d.-82.3 µg/kg dw (mean=15.158 µg/kg dw) 0.103-127 µg/kg dw (mean=28.365 µg/kg dw) 0.537-6.20 µg/kg dw (mean=2.804 µg/kg dw) n.d.-1.33 µg/kg dw (mean=0.510 µg/kg dw) 0.264-27.1 µg/kg dw (mean=4.589 µg/kg dw) 0.741-304 µg/kg dw (mean=13.375 µg/kg dw) 0.06-1.39 µg/kg dw (mean=0.471 µg/kg dw)	 42 19 14 13 13 8 12		Feng et al. 2012
Sediment	Qinghe canal in Beijin, China; May-July, 2011	0.3 – 22 µg/kg dw	13		Xu et al. 2012
Sediment	Norway; 2003	0.02–39 µg/kg dw	11		Schlabach et al. 2004
Sediment	Norway; no year	1.92–44.4 µg/kg dw (TBBPA) n.d. [3] to1.23 µg/kg dw (Me-TBBPA[c])	in 12 of 12 in 11 of 12		SFT 2002
Sediment	Norway; no year	1.24 µg/kg dw	n.s.		Fjeld et al. 2004
Sediment	The Netherlands; no year	< 0.1–32 µg/kg ww (TBBPA) < 0.1–0.4 µg/kg ww (Me-TBBPA[c])	in 35 of 47 in 6 of 47		de Boer et al. 2002
Sediment	Japan; 1981	20 µg/kg dw	1		Watanabe et al. 1983
Sediment	Japan; 1981 to 1983	< 0.5–140 µg/kg dw (TBBPA) < 0.5–1.8 µg/kg dw (Me-TBBPA[c])	in 14 of 19 in 5 of 19		Watanabe et al. 1983
Sediment	Japan; 1987	< 2–150 µg/kg dw	in 14 of 66		Watanabe and Tatsukawa 1989
Sediment	Japan; 1988	< 2–108 µg/kg dw	in 20 of 130		Environment Agency Japan 1996
Sediment	Japan; 1999	0.68–12 µg/kg dw	6		Ohta et al. 2002
Sediment	Japan; 2003	0.08–5.0 µg/kg dw	17		Ohta et al. 2004
Sediment	China; October 2006	3.8-230 µg/kg dw	17 (15 surface and 2 cores)		Zhang et al. 2009
Sediment	South China, Liuyang river; 2009		18 samples	143.4 to 10183.41 µg/kg (ng/g) (instrument detection limit:40 pg)	Qu et al. 2011
Soil	China, Beijin; May-July 2011	26 – 104 µg/kg dw (e-waste recycling site) Not detected – 5.6 µg/kg dw (farmlands)	4 11		Xu et al. 2012

Table 6. Measured concentrations of TBBPA and TBBPA bis(allyl ether) in the ambient environment and sewage sludge (continued)

Medium	Location; year	TBBPA Concentration*	Samples	TBBPA bis(allyl ether) concentration	TBBPA Concentration*
Soil	Spain; no year	3.4-32.2 µg/kg dw (industrial)	n.s.		Sanchez-Brunete et al. 2009
Soil	United States; no year	222 000 µg/kg [d]	n.s		Pellizzari et al. 1978
Soil	Israel; no year	450 000 µg/kg [d]	n.s		Arnon 1999
Soil	South China, Liuyang river; 2009		18 samples	n.d. to 41.7µg/kg (ng/g) (instrument detection limit:40 pg)	Qu et al. 2011
Sewage sludge	Canada; 2010 to 2011	53–195 µg/kg dw	in 4 of 40		Smyth 2013
Sewage sludge	Quebec dried sludge; Oct 2003	330 ug/kg dw; 310 µg/kg dw (330 ng/g dw and 310 ng/g dw)	1 sample, 8 analyses (2 mean values with n=3 and 5)		Saint-Louis and Pelletier 2004
Sewage sludge	Canada; 1994 to 2001	< 1–46.2 µg/kg dw	in 34 of 35		Lee and Peart 2002
Sewage sludge	Ontario; 2002	9.04–43.1 µg/kg dw	7		Quade 2003
Sewage sludge	Spain (Catalonia); 2009	nd – 472 µg/kg dw (mean = 104 µg/kg dw; median = 96.7 µg/kg dw)	17	3.00 µg/kg (ng/g) dw	Gorga et al. 2013
Sewage sludge Municipal wastewater treatment plants Industrial wastewater treatment plant	Korea, Busan city; n.s. Korea, Ulsan city; n.s.	67.1 – 618 µg/kg dw 4.01 - 144 µg/kg dw	4 7		Hwang et al. 2012
Sewage sludge	United States; 1999 to 2001	2.98–196 µg/kg dw	7		Quade 2003
Sewage sludge Influent (liquid) Influent (solid)	United Kingdom; no year	54–112 µg/kg dw < 0.015–0.0852 µg/L 21.7 µg/kg dw	in 5 of 5 in 4 of 5 in 1 of 5		de Boer et al. 2002
Sewage sludge Influent (solid) Influent (liquid) Effluent	Southeast England; 2002	15.9–112 µg/kg dw < 3.9–21.7 µg/kg dw 0.0026–0.085 µg/L < 3.9 µg/kg dw	5 5 5 5		Morris et al. 2004
Sewage sludge	Ireland; no year	< 0.1–192 µg/kg dw	in 5 of 6		Morris et al. 2004

Table 6. Measured concentrations of TBBPA and TBBPA bis(allyl ether) in the ambient environment and sewage sludge (continued)

Medium	Location; year	TBBPA Concentration*	Samples	TBBPA bis(allyl ether) concentration	TBBPA Concentration*
Sewage sludge	Sweden; 1988	31–56 µg/kg dw	2		Sellström and Jansson 1995
Sewage sludge	Sweden; 1997 to 1998	3.6–45 µg/kg dw	n.s		Sellström 1999; Sellström et al. 1999
Sewage sludge	Sweden; 1999 to 2000	< 0.3–220 µg/kg ww	57		Öberg et al. 2002
Sewage sludge Influent Effluent	Germany; no year	< 0.2–34.5 µg/kg dw (TBBPA) < 0.2–11.0 µg/kg dw (Me-TBBPA2) 0.00086–0.0174 µg/L (TBBPA) < 0.0002–0.025 µg/L (TBBPA) < 0.0002–0.00145 µg/L (Me-TBBPAc)	in 11 of 12 in 7 of 12 in 5 of 5 in 10 of 19 in 5 of 19		Kuch et al. 2001
Sewage sludge	Germany; no year	0.6–62 µg/kg dw	32		Metzger and Kuch 2003
Wastewater Influent (filtered) Influent raw (unfiltered) Effluent	South Africa, Vereeniging region; n.s.	 6,629 µg/L (TBBPA) 6.806 µg/L (TBBPA) 3.269 µg/L (TBBPA)	 1 (250 mL) 1 (250 mL) 1 (250 mL)		 Chokwe et al. 2012
Sewage sludge Effluent (solid phase)	The Netherlands; no year	2.8–600 µg/kg dw (TBBPA) < 0.1–5.5 µg/kg dw (Me-TBBPAc) 37–62 µg/kg dw (TBBPA) < 0.1–0.6 µg/kg dw (Me-TBBPAc)	in 10 of 10 in 3 of 10 in 5 of 5 in 3 of 5		de Boer et al. 2002
Sewage sludge Influent Effluent	The Netherlands; 2002	2–600 µg/kg dw < 6.9 µg/kg dw 3.1–63 µg/kg dw	8 5 5		Morris et al. 2004

Notes
* "<" values represent method detection limit (MDL) for sample
[a] Number of samples not specified.
[b] Not detected; detection limit not specified.
[c] Dimethylated derivative of TBBPA.
[d] Dw or ww not specified.

Table 7. Measured concentrations of TBBPA and TBBPA bis(allyl ether) in biota

Organism	Location; year	TBBPA Concentration*	Samples	TBBPA bis(allyl ether) concentration	Reference
Bottlenose dolphin Bull shark Atlantic sharpnose shark	Florida; 1991 to 2004	0.056–8.48 µg/kg lw 0.035–35.6 µg/kg lw 0.495–1.43 µg/kg lw	in 15 of 15 in 13 of 13 in 3 of 3		Johnson-Restrepo et al. 2008
Harbour porpoise	United Kingdom; 1996 to 2000	3.9–376 µg/kg ww	4		Law et al. 2003
Starfish Whiting Cormorant	United Kingdom; 1999 to 2000	4.5 µg/kg ww < 4.8–3.3 µg/kg ww [1] 0.07–0.28 µg/kg ww	1 in 1 of 2 in 5 of 5		de Boer et al. 2002
Harbour porpoise Cormorant	United Kingdom; no year	0.05–376 µg/kg ww 0.07–10.9 µg/kg ww	in 8 of 25 in 7 of 28		CEFAS 2002
Harbour porpoise Cormorant Sea star Hake	United Kingdom; 1998 to 2001	0.1–418 µg/kg lw 2.5–14 µg/kg lw 205 µg/kg lw < 0.2 µg/kg lw	5 5 1 1		Morris et al. 2004
Cod Whiting Hermit crab Sea star Whelk Harbour porpoise	North Sea; 1999 to 2000	< 0.1–0.8 µg/kg ww < 97–245 µg/kg lw < 1–35 µg/kg lw < 1–10 µg/kg lw 5–96 µg/kg lw 0.05–376 µg/kg ww	in 1 of 2 in 2 of 3 in 5 of 9 in 2 of 3 in 3 of 3 in 5 of 5		de Boer et al. 2002
Whelk Hermit crab Whiting Cod Harbour porpoise Harbour seal	North Sea; 1999	5.0–96 µg/kg lw < 1–35 µg/kg lw < 97–245 µg/kg lw < 0.3–1.8 µg/kg lw < 11 µg/kg lw < 14 µg/kg lw	3 9 3 2 4 2		Morris et al. 2004
Baltic salmon	Finland; 1993 to 1999	2.0–5.0 µg/kg ww	in 2 of 10		Peltola 2002
Predatory birds' eggs	Norway; 1992 to 2002	< 0.004–0.013 µg/kg ww	in 8 of 8		Herzke et al. 2005
Eel	Norway; 2003	0.3 µg/kg lw	n.s [2]		Schlabach et al. 2004
Blue mussel Cod Moss	Norway; no year	0.01–0.03 µg/kg ww 0.08–0.16 µg/kg ww 0.019–0.89 µg/kg ww	in 6 of 6 in 6 of 6 in 11 of 11		SFT 2002
Atlantic cod	Norway; no year	0.5–2.5 µg/kg lw	2		Fjeld et al. 2004
Eel Perch Pike	Germany; 1998 to 1999	0.045–0.10 µg/kg ww 0.033 µg/kg ww 0.021 µg/kg ww	2 1 1		Kemmlein 2000
Eel	Belgium; 2000	< 0.1–13 µg/kg ww	19		Morris et al. 2004
Common tern eggs Eel	The Netherlands; 1999 to 2000	ND [3] (TBBPA) 0.4–0.8 µg/kg ww (Me-TBBPA [4]) < 0.1–2.6 µg/kg ww (TBBPA) < 0.1–2.5 µg/kg ww (Me-TBBPA [4])	10 in 4 of 10 in 6 of 18 in 7 of 18		de Boer et al. 2002
Common tern Eel	The Netherlands; 1999 to 2001	< 2.9 µg/kg ww < 0.1–1.3 µg/kg ww	10 11		Morris et al. 2004

Mussel (*Mytilus edulis*)	Japan; 1981	n.d. [3] (TBBPA) 5 µg/kg ww (Me-TBBPA[4])	n.s [2]		Watanabe et al. 1983
Fish and shellfish	Japan; 1983	n.d. [3] to 4.6 µg/kg ww (Me-TBBPA[4])	in 2 of 19		Watanabe and Tatsukawa 1989
Sea bass	Japan; 1986 to 2000	3.4–23 µg/kg lw	n.s [2]		Ohta et al. 2004
Lake trout	Lake Ontario; 1997 to 2004		in 5 of 30	0.2 – 1.7 µg/kg ww (ng/g ww)	Ismail et al. 2006
Gull herring eggs	Eastern Great lakes and St. Lawrence River; 2008 to 2009		83% of samples (concentrations reported for 8 samples)	0.08 – 0.56 µg/kg ww (ng/g ww)	Letcher and Chu 2010

[1] The detection limit reported for the study exceeded the measured concentration.
[2] Number of samples not specified.
[3] Not detected; detection limit not specified.
[4] Dimethylated derivative of TBBPA.

Table 8. Representative input values used for estimating aquatic concentrations resulting from industrial releases of TBBPA

Input	Value Scenario #1	Value Scenario #2	Justification and reference
Quantity (kg)	1,000,000	10,000 - 100,000	Lower and upper range of mass in commerce
Loss to wastewater (%)	No water discharge	0.21%	Loss to water based on company activities. ESD on Plastic Additives, Chapter 15 (OECD 2004)
Wastewater system removal efficiency (%)	Not Applicable	93%	Standard sewage treatment plants in Canada have primary or secondary treatment in place.
Number of annual release days (days)	Not Applicable	250	Site specific information (Environment Canada 2013)
Dilution factor (–)	Not Applicable	10	Site specific information (Environment Canada 2013)

Table 9. Representative input values used for estimating aquatic concentrations resulting from industrial releases of TBBPA bis(allyl ether)

Input	Value Scenario #1	Value Scenario #2	Justification and reference
Quantity (kg)	1,000,000	100,000	Upper and lower range of mass in commerce
Loss to wastewater (%)	0.21%	0.21%	Loss to water based on company activities. ESD on Plastic Additives, Chapter 15 (OECD 2004)
Wastewater system removal efficiency (%)	59.8	93	Standard sewage treatment plants in Canada have primary or secondary treatment in place.
Number of annual release days (days)	250	250	250 days considered "worst case" for HPV substance. (European Commission 2003)
Dilution factor (–)	10	10	

Table 10. Summary of key toxicity studies used in the ecological effects assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether)

Species, life stage	Test material	Study design	Effect leve (endpoint and value)	Reference
Crassostrea virginica, eastern oyster	TBBPA: 100% active ingredient	• 96-hour flow-through using natural, unfiltered seawater • measured concentrations: 0, 0.018, 0.032, 0.051, 0.087 and 0.15 mg/L • 40 oysters per treatment • 19–20°C, pH 7.9–8.1, DO 6.3–7.9 mg/L, 33–34 ppt • GLP; in-house protocol based on US EPA 1985a, b	• 96-hour EC_{50} (95% CI) (shell deposition) = 0.098 (0.020–0.210) mg/L • 96-hour LOEC (shell deposition) = 0.018 mg/L (mean measured) • 96-hour NOEC could not be determined, since an effect was seen at the lowest concentration tested; estimated NOEC = 0.0026 mg/L	Brominated Flame Retardants Industry Panel 1989a
Mytilus edulis, common mussel	TBBPA: purity 99.2%	• 70-day flow-through using filtered, natural seawater • measured concentrations: 0, 0.017, 0.032, 0.062, 0.126 and 0.226 mg/L • 30 mussels per treatment • 15±1°C, pH 7.9–8.1, DO 7.2–8.2 mg/L, 34.5–35.5 ppt • GLP	• 70-day LOEC (shell length) = 0.032 mg/L • 70-day NOEC (shell length) = 0.017 mg/L • 70-day LOEC (wet tissue weight) = 0.126 mg/L • 70-day NOEC (wet tissue weight) = 0.062 mg/L • 70-day LOEC (dry tissue weight) = 0.032 mg/L • 70-day NOEC (dry tissue weight) = 0.017 mg/L • dry tissue weight data not strictly dose-responsive	ACCBFRIP 2005b, c
Daphnia magna, water flea (less than 24 hours old at test initiation)	TBBPA: 100% active ingredient	• 21-day flow-through using well water • measured concentrations: 0, 0.056, 0.10, 0.19, 0.30 and 0.98 mg/L • 40 daphnids per treatment • 20 ± 1°C, pH 8.1–8.2, DO 8.0–8.7 mg/L, conductivity 498 μmhos/cm, hardness 170 mg/L as $CaCO_3$, alkalinity 120 mg/L as $CaCO_3$ • GLP; in-house protocol based on US EPA 1985c	• 21-day LOEC (survival, growth) > 0.98 mg/L • 21-day NOEC (survival, growth) ≥ 0.98 mg/L[1] • 21-day LOEC (reproduction) = 0.98 mg/L • 21-day NOEC (reproduction) = 0.30 mg/L • 21-day LOEC (overall study) = 0.98 mg/L • 21-day NOEC (overall study) = 0.30 mg/L • 21-day MATC (overall study) = 0.54 mg/L	Brominated Flame Retardants Industry Panel 1989g
Daphnia magna, water flea (less than 24 hours old at test initiation)	TBBPA: composition from 3 manufacturers; purity 99.17%	• 48-hour flow-through using well water • 10 per replicate, 2 replicates per treatment • 20 °C, pH 8.1-8.2, hardness 131 mg/L, DO ≥ 8.6 mg/L • measured concentrations: 1.2 and 1.8 mg/L • OECD 202 limit test	• Immobility 48-h NOEC ≥ 1.8 mg/L	Wildlife International 2003
Acartia tonsa, copepod (adults used for acute test; eggs and juveniles used for chronic test)	TBBPA: composition and purity not given	• 2-day acute and 5-day larval development static renewal tests using saltwater • concentration series not specified • 30–40 eggs per beaker, number of replicates per treatment not provided • 20±0.5°C, 18 ppt • acute test performed according to	• 2-day LC50 (95% CI) = 0.40 (0.37–0.43) mg/L • 5-day EC50 for larval development rate (95% CI) = 0.125 (0.065–0.238) mg/L	Wollenberger et al. 2005; Breitholtz et al. 2001

Species, life stage	Test material	Study design	Effect leve (endpoint and value)	Reference
		ISO 1999		
Skeletonema costatum, Thalassiosira pseudonana, marine algae	TBBPA: composition and purity not given	• 72-hour static test • concentration series not specified • six nutrient media • pH 7.6–8.2, 30 ppt • population density estimated by cell counts using a haemocytometer	• 72-hour EC50 = 0.09–0.89 mg/L for S. costatum • 72-hour EC50 = 0.13–1.00 mg/L for T. pseudonana	Walsh et al. 1987
Pimephales promelas, fathead minnow (embryos and larvae)	TBBPA: 100% active ingredient	• 35-day flow-through using well water • 5-day embryo and 30-day larval exposure • measured concentrations: 0, 0.024, 0.040, 0.084, 0.16 and 0.31 mg/L • 120 embryos, 60 larvae per treatment • 24°C, pH 7.0–8.2, DO 8.1–8.6 mg/L, hardness 28–29 mg/L as CaCO3, alkalinity 23–24 mg/L as CaCO3, conductivity 120–140 µmhos/cm • GLP; in-house protocol based on US EPA Final Test Rule Fed. Reg. Vol. 52, No. 128	• 35-day LOEC (overall study, based on embryo survival) = 0.31 mg/L • 35-day NOEC (overall study) = 0.16 mg/L • MATC = 0.22 mg/L	Brominated Flame Retardants Industry Panel 1989i
Oncorhynchus mykiss, rainbow trout (juvenile)	TBBPA: composition and purity not given	• 1-, 4-, 14- and 28-day tests • concentration series not specified • endpoints: hepatic detoxification and antioxidant enzymes, liver somatic index, blood plasma vitellogenin	• EROD-activity significantly inhibited after 4 days at doses of 100 and 500 mg/kg • trend towards EROD inhibition when injected together with EROD-inducer β-aphthoflavone • glutathione reductase activity decreased after 1 day at 100 mg/kg but significantly increased after 4, 14 and 28 days at same dose, suggesting TBBPA is possible inducer of oxidative stress • no elevation of vitellogenin levels; no detectable estrogenicity • no significant effect on LSI	Ronisz et al. 2001
Oncorhynchus mykiss, rainbow trout (immature, 80–120 g)	TBBPA: composition and purity not given	• 18-day flow-through • dose: 50 mg/kg fish • 10 fish per treatment • 11–14°C • dose delivered on days 0, 6 and 12 • blood samples collected prior to and 6 days following last injection • vitellogenin quantification by ELISA (enzyme-linked immunosorbant assay)	• no induction of vitellogenin synthesis • authors reported TBBPA tested positive for estrogenic activity in vitro using another monitoring method, the E-screen (Körner et al. 1998)	Christiansen et al. 2000

Table 10. Summary of key toxicity studies used in the assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (continued)

Species, life stage	Test material	Study design	Effect level (endpoint and value)	Reference
Danio rerio, zebrafish (adults and eggs)	TBBPA: 99.17% purity	• adults: 30-day semi-static • 47-day and 3-day egg exposure • nominal concentrations: 0, 0.047, 0.094, 0.188, 0.375, 0.750, 1.5, 3.0 and 6.0 µM • 3 male and 3 female adult fish per treatment with duplicate controls • 100 eggs per treatment for 47-day exposure; 12 eggs per treatment for 3-day exposure • 27±2°C, pH 7.2–8.4, DO ≥ 5 mg/L, 14:10-hour light:dark cycle	• 30-day LOEC (acute) = 3.0 µM (1.63 mg/L) • 30-day NOEC (acute) = 1.5 µM (0.816 mg/L) • 30-day LOEC (egg production) = 0.047 µM (0.026 mg/L) • 30-day NOEC (egg production) = 0.023 µM (0.013 mg/L) • 47-day LOEC (hatching) = 0.023 µM (0.013 mg/L) • 47-day NOEC (hatching) < 0.023 µM (0.013 mg/L) • 3-day LOEC (development) = 3.0 µM (1.63 mg/L) • 3-day NOEC (development) = 1.5 µM (0.816 mg/L)	Kuiper et al. 2007
Lumbriculus variegatus, oligochaete (adult)	TBBPA: 98.91% active ingredient	• 28-day flow-through using filtered well water, hardness 127–128 mg/L as $CaCO_3$ • nominal concentrations: 0, 90, 151, 254, 426, 715 and 1200 mg/kg dw of sediment • 80 animals per treatment • Two trials with different artificial sediments: (i) 83% sand, 9% clay, 8% silt, 2.5% OC, water-holding capacity 10.7%, 23 ± 2°C, pH 6.8–8.3, DO 3.8–8.0 mg/L, gentle aeration from day 6 to test end (ii) 80% sand, 14% silt, 6% clay, 5.9% OC, water-holding capacity 13.9%, 23±2°C, pH 7.5–8.3, DO 4.2–7.9 mg/L, gentle aeration from day 7 to test end • GLP, protocol based on Phipps et al. 1993, ASTM 1995 and US EPA 1996a	For 2.5% OC sediment: • 28-day EC_{50} (survival and reproduction) = 294 mg/kg sediment dw • 28-day LOEC (survival and reproduction) = 151 mg/kg sediment dw • 28-day NOEC (survival and reproduction) = 90 mg/kg sediment dw • LOEC/NOEC for growth could not be determined as no clear dose-response was obtained For 5.9% OC sediment: • 28-day EC_{50} (survival and reproduction) = 405 mg/kg sediment dw • 28-day LOEC (survival and reproduction, growth) = 426 mg/kg sediment dw • 28-day NOEC (survival and reproduction, growth) = 254 mg/kg sediment dw	ACCBFRIP 2002c, d
Chironomus tentans, midge (second instar larvae at test initiation)	TBBPA: 99.15% active ingredient	• 14-day flow-through using well water • measured concentrations: 0, 0.07, 0.12, 0.20, 0.41 and 0.85 mg/L • 50 larvae per treatment • 21–22°C, pH 6.9–7.8, DO 7.7–8.6 mg/L, conductivity 120–130 µmhos/cm, hardness 29–30 mg/L as $CaCO_3$, alkalinity 25–28 mg/L as $CaCO_3$ • water-only testing with thin (~2 mm) sediment layer • GLP; in-house protocol based on Adams et al. 1985 and ASTM 1988	• 14-day LC_{50} (95% CI) = 0.13 (0.11–0.15) mg/L • 14-day LOEC (survival) = 0.20 mg/L • 14-day NOEC (survival) = 0.12 mg/L • 14-day LOEC (growth) = 0.07 mg/L • 14-day NOEC (growth) could not be determined as an effect was seen at the lowest concentration tested	Brominated Flame Retardants Industry Panel 1989h

Table 10. Summary of key toxicity studies used in the assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (continued)

Species, life stage	Test material	Study design	Effect level (endpoint and value)	Reference
Chironomus tentans, midge (second instar larvae at test initiation)	TBBPA: 99.15% active ingredient	• 14-day flow-through using well water and streambed sediment • measured concentrations: 6.8% OC: 0, 16, 44, 66, 110 and 340 mg/kg dw; 2.7% OC: 0, 16, 31, 65, 130 and 240 mg/kg dw; 0.25% OC: 0, 15, 24, 52, 110 and 230 mg/kg dw • 50 larvae per treatment • hardness 27–29 mg/L as $CaCO_3$, alkalinity 23–26 mg/L as $CaCO_3$; conductivity 120–130 µmhos/cm • 3 tests; (i) 92% sand, 6% silt, 2% clay, 6.8% OC, 16% soil moisture, 22°C, pH 6.4–8.3, DO 5.2–6.7 mg/L (ii) 93% sand, 1% silt, 6% clay, 2.7% OC, 6.8% soil moisture, 22°C, pH 6.4–7.9, DO 6.2–7.3 mg/L (iii) 94% sand, 2% silt, 4% clay, 0.25% OC, 1.7% soil moisture, 22°C, pH 6.9–7.8, DO 7.0–8.0 mg/L • GLP; in-house protocol based on Adams et al. 1985 and ASTM 1988	• survival negative controls: 44–64% (6.8% OC), 8–24% (2.7% OC), 4–24% (0.25% OC) • survival solvent controls: 60–76% (6.8% OC), 72–76% (2.7% OC), 76–92% (0.25% OC) • based on comparison with solvent controls, midge survival and growth was not significantly different in any treatment • no-effect concentrations based on solvent controls: 340 mg/kg (6.8% OC), 240 mg/kg (2.7% OC) and 230 mg/kg (0.25% OC)	Brominated Flame Retardants Industry Panel 1989h
Chironomus riparius, midge (first instar larvae at test initiation)	TBBPA: 99.2% purity	• 28-day static-renewal using filtered well water and artificial sediment • nominal concentrations: 0, 63, 125, 250, 500 and 1000 mg/kg sediment dw • 80 larvae per treatment • 19.0–21.3°C, pH 7.7–8.6, DO 5.9–8.9 mg/L, NH_3 < 0.017–0.290 mg/L • GLP; in-house protocol based on OECD 2001b	• 28-day EC_{50} (emergence) = 235 mg/kg dw with 95% CI of 207 and 268 mg/kg dw • 28-day LOEC (emergence ratio, development rate, development time) = 250 mg/kg dw • 28-day NOEC (sediment ratio, development rate, development time) = 125 mg/kg dw	ACCBFRIP 2005d

Table 10. Summary of key toxicity studies used in the assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (continued)

Species, life stage	Test material	Study design	Effect level (endpoint and value)	Reference
Hyalella azteca	TBBPA: composition with a purity of 99.2%	• 28-day flow-through using well water • artificial sediment: 5.7% OC; 0.01% humic acid, 0.5% dolomite, 13% alpha cellulose, 10% kaolin clay and 77% industrial quartz sand • dilution water: 23°C, pH 7.7-8.2, DO ≥67%, NH_3 <0.17 mg/L, hardness 116-132 mg/L • measured concentrations: 63, 125, 250, 500 and 1000 mg/kg dry weight • 80 amphipods per treatment (8 replicates of 10 each) • GLP, protocol based on USEPA (2000) ASTM Standard E 1706-00 and USPEA OPPTS 850.1735	• 28-day NOEC (survival) = 250 mg/kg sediment dw • 28-day NOEC (growth) ≥1000 mg/kg sediment dw	Wildlife International 2006c
Eisenia fetida, earthworm (adult)	TBBPA: 98.91% active ingredient	• 56-day test • measured concentrations: study 1: 0, 326, 640, 1250, 2430 and 4840 mg/kg soil dw; study 2: 0, 0.562, 1.16, 2.11, 4.50, 9.01, 16.7 and 35.4 mg/kg soil dw • 80 per control, 40 per treatment • artificial soil: 78–79% sand, 8–10% silt, 12–13% clay, 4.5–4.7% OC, pH 5.8–7.5, 18.5–21.9°C, soil moisture 14.6–45.3% • GLP, protocol based on OECD 1984a, 2000 and US EPA 1996d	• 28-day LOEC (survival) > 4840 mg/kg soil dw • 28-day NOEC (survival) ≥ 4840 mg/kg soil dw[1] • 28-day EC10, 28-day EC50 (survival) > 4840 mg/kg soil dw • 56-day LOEC (reproduction) = 4.50 mg/kg soil dw • 56-day NOEC (reproduction) = 2.11 mg/kg soil dw • 56-day EC_{10} (reproduction) = 0.12 mg/kg soil dw • 56-day EC_{50} (reproduction) = 1.7 mg/kg soil dw	ACCBFRIP 2003
Eisenia fetida, earthworm (adult)	TBBPA: 99.2% purity	• 56-day test • nominal concentrations: 0, 0.31, 0.63, 1.3, 2.5, 5.0, 10 and 20 mg/kg soil dw • 80 per control, 40 per treatment • artificial soil: 77% sand, 6% silt, 17% clay, 4.4% OC, pH 5.8–7.3, 19.5–21.7°C, soil moisture 20.5–32.7% • GLP, in-house protocol based on OECD 1984a, 2000, US EPA 1996d and ISO 1998	• 28-day NOEC (survival) ≥ 20 mg/kg soil dw1 • 28-day EC10, 28-day EC50 (survival) > 20 mg/kg soil dw • 56-day LOEC (reproduction) = 0.63 mg/kg soil dw • 56-day NOEC (reproduction) = 0.31 mg/kg soil dw • 56-day EC10 (reproduction) = < 0.31 mg/kg soil dw • 56-day EC50 (reproduction) = 0.91 mg/kg soil dw	ACCBRIP 2005a

Table 10. Summary of key toxicity studies used in the assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (continued)

Species, life stage	Test material	Study design	Effect level (endpoint and value)	Reference
Zea mays, corn *Allium cepa*, onion *Lolium perenne*, ryegrass *Cucumis sativa*, cucumber *Glycine max*, soybean *Lycopersicon esculentum*, tomato	TBBPA: 99.17% active ingredient	• 21-day test • nominal concentrations: 0, 20, 78, 313, 1250 and 5000 mg/kg dw of soil • 40 seeds per treatment • artificial soil: 49% sand, 30% silt and 21% clay, 2.1% OM, pH 7.79 • watering with well water using sub-irrigation, 14:10 light:dark photoperiod, 16–32°C, relative humidity 32–70% • GLP, in-house protocol based on OECD 1998 and US EPA 1996b,c	• no apparent treatment-related effects on emergence and seedling condition • 21-day LOEC (growth) > 5000 mg/kg soil dw and 21-day NOEC (growth) ≥ 5000 mg/kg soil dw[1] for soybean • 21-day LOEC (growth) = 1250 mg/kg soil dw; 21-day NOEC (growth) = 313 mg/kg soil dw for corn, onion and tomato • 21-day LOEC (growth) = 313 mg/kg soil dw; 21-day NOEC (growth) = 78 mg/kg soil dw for ryegrass • 21-day LOEC (growth) = 78 mg/kg soil dw; 21-day NOEC (growth) = 20 mg/kg soil dw for cucumber • 21-day EC_{25} (growth) > 5000 mg/kg soil dw for corn and soybean; 460 mg/kg for onion; 422 mg/kg for tomato; 73 mg/kg for cucumber, 49 mg/kg for ryegrass • 21-day EC_{50} (growth) > 5000 mg/kg soil dw for corn, soybean and tomato, 4264 mg/kg for onion. 1672 mg/kg for cucumber, 459 mg/kg for ryegrass	ACCBFRIP 2002e
Trifolium pratense, red clover	TBBPA: composition and purity not given (purchased from Fluka, Germany)	• 21-day test • nominal concentrations: 0, 1, 3, 10, 100, 300 and 1000 mg/kg dw soil • 20 seeds per treatment • Danish agricultural soil: 38.4% coarse sand, 23.6% fine sand, 12.7% coarse silt, 12.3% fine silt and 13.0% clay, 1.6% OC • 15–25°C, soil pH 6.2, soil moisture 65% of water-holding capacity, 16:8 light:dark photoperiod • OECD 1984b	• no apparent treatment-related effects on seedling emergence or growth • 21-day LOEC > 1000 mg/kg dw • 21-day NOEC ≥ 1000 mg/kg dw[1]	Sverdrup et al. 2006
Enchytraeus crypticus, earthworm (sexually mature adult)	TBBPA: composition and purity not provided (purchased from Fluka, Germany)	• 21-day test • nominal concentrations: 0, 1, 3, 10, 100, 300 and 1000 mg/kg dw soil • 40 worms per treatment • Danish agricultural soil: 38.4% coarse sand, 23.6% fine sand, 12.7% coarse silt, 12.3% fine silt and 13.0% clay, 1.6% OC • 20±1°C, soil pH 6.2, soil moisture 65% of water-holding capacity • ISO 2002	• 21-day LOEC (survival) > 1000 mg/kg dw • 21-day NOEC (survival) ≥ 1000 mg/kg dw1 • 21-day LOEC (reproduction) = 10 mg/kg dw • 21-day NOEC (reproduction) = 3 mg/kg dw • 21-day EC10 (95% C.) = 2.7 (0.7–5.4) mg/kg dw	Sverdrup et al. 2006

Table 10. Summary of key toxicity studies used in the assessment of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) (continued)

Species, life stage	Test material	Study design	Effect level (endpoint and value)	Reference
Soil nitrifying bacteria	TBBPA: composition and purity not provided (purchased from Fluka, Germany)	• 28-day test • nominal concentrations: 0, 1, 3, 10, 100, 300 and 1000 mg/kg dw soil • Danish agricultural soil: 38.4% coarse sand, 23.6% fine sand, 12.7% coarse silt, 12.3% fine silt and 13.0% clay, 1.6% OC • 20°C, soil pH 6.2, soil moisture 57% of water-holding capacity, incubation in the dark • based on ISO 1997	• 28-day LOEC (nitrification) = 1000 mg/kg dw • 28-day NOEC (nitrification) = 300 mg/kg dw • 28-day EC_{10} (95% CI) = 295 (210–390) mg/kg dw	Sverdrup et al. 2006
Soil microorganisms	TBBPA: composition, >99% purity	• 28-day test • Nominal concentrations: 10, 32, 100, 316, 1000 mg/kg dw soil, 3 replicates per treatment • sand 69%, silt 12%, clay 19%, OC 1.3%, microbial biomass 127 mg/kg dw • 20°C, pH 6.9, soil moisture 50% of water-holding capacity, pre-incubation in the dark for 24 days, incubation in the dark for the 28-day test • OECD 216	• 28-day EC_{10} >1000 mg/kg dw	Wildlife International 2005
Coturnix japonica, Japanese quail *Gallus domesticus*, domestic chicken (fertilized eggs)	TBBPA: > 99% active ingredient	• single exposure with analysis at 12 days (quail) or 15 days (chicken) • 15 or 45 mg/kg injected into egg • exposure of fertilized eggs at day 3 of incubation for quail and day 4 for chicken • minimum 24 embryonated eggs per dose • analysis 2 days before anticipated hatch (day 15 for quail, day 19 for chicken) • endpoints: mortality, malformation of Müllerian ducts, feminization of left testis	• significant embryo mortality at 45 mg/kg egg dose (80% in quail and 96% in chicken) • mortality at 15 mg/kg egg dose not statistically different from control • no significant effect on Müllerian duct formation or left testis histology	Berg et al. 2001
Giardia lamblia, parasitic protozoan	TBBPA: 98.91% active ingredient	• activated sludge from a waste water treatment plant receiving maily domestic sewage • 20-22°C, SSC 3.640 mg/L, pH 7.8 • test concentration: 15 mg/L in triplicate • OECD Guideline 209	• 3-hour NOEC $\geq$15 mg/L	Wildlife International 2002
Oryzias latipes, orange-red killifish	TBBPA bis(2-hydroxyethyl ether): composition and purity not given	• 48-hour test duration • no other study details available •	• LC_{50} = 30 mg/L	CITI 1992

[1] Study identified that the highest concentration tested did not result in statistically significant results. Since the NOEC or NOAEL could be higher, the NOEC or NOAEL is described as being greater than or equal to the highest concentration tested.

Table 11. Predicted ecotoxicity data for TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether)

Organism	Effect level (endpoint and value)	TBBPA (Log K_{ow}= 5.9)*	TBBPA bis(2-hydroxyethyl ether) (Log K_{ow} = 5.48)*	TBBPA bis(allyl ether) (Log K_{ow} = 8.71)*	Model
Fish	96-hour LC50 14-day LC50 chronic no-effect level	0.140 mg/L[1,2] – 0.21 mg/L	0.389 mg/L[1, 2] 0.477 mg/L[2] 0.056 mg/L[2]	0.000483 mg/L[1,2] – 0.000098 mg/L[1, 2] –	ECOSAR 2011, version 1.10
Daphnid	48-hour LC50 chronic no-effect level	0.156 mg/L[2] 0.030 mg/L	0.302 mg/L[1, 2] 0.073 mg/L[2] –	0.000912 mg/L[1, 2] – 0.000278 mg/L[1, 2]	ECOSAR 2011, version 1.10
Mysid shrimp	96-hour LC50	–	0.035 mg/L[1, 2]	–	ECOSAR 2011, version 1.10
Green algae	96-hour EC50 chronic no-effect level	0.148 mg/L[2] 0.220 mg/L[2]	0.377 mg/L[1, 2] 0.459 mg/L[1, 2] – –	0.000879 mg/L[1, 2] 0.005 mg/L[1, 2] –	ECOSAR 2011, version 1.10
Fish	96-hour LC50	–	1.614 mg/L	–	ASTER 1999
Fish	96-hour LC50	0.0115 mg/L	4.29 mg/L	1.05 mg/L	AIEPS (2003–2007)
Daphnid	48-hour LC50	2.85 mg/L	0.041 mg/L	0.154 mg/L	AIEPS (2003–2007)
Green algae	72-hour EC50	5.51 mg/L	11.25 mg/L	4.01 mg/L	AIEPS (2003–2007)
Fish	96-hour LC50	0.1413 mg/L	0.0015 mg/L	0.0097 mg/L[3]	TOPKAT 1998, Fathead Minnow LC50 v3.2
Daphnid	EC50	0.6803 mg/L	21.2 mg/L	0.0000102 mg/L[3]	TOPKAT 2004, Daphnia EC50 v3.1
Fish	96-hour LC50	0.194 mg/L	0.3919 mg/L[4]	2.0163 mg/L[4]	OASIS Forecast 2005 (CPOPs 2008) -Acute Toxicity v.01
Daphnid	48-hour LC50	0.1225 mg/L	0.2180 mg/L[4]	3.4868 mg/L[4]	OASIS Forecast 2005 (CPOPs 2008) -Acute Toxicity v.01
Earthworm	14-day LC50	–	478.664 mg/L[2]	–	ECOSAR 2011, version 1.10

Notes
[1] ECOSAR warning: the log K_{ow} value used in calculating the predicted toxicity value exceeded the log K_{ow} cut-off for the model.
[2] ECOSAR warning: chemical may not be soluble enough to measure the predicted value.
[3] TOPKAT provides warning that computed logP (logKow) value exceeds the range spanned by the training set. The substance appears to be outside model domain.
[4] CPOPs provides warning that value may exceed water solubility of substance. The substance does not appear to be within the domain of the models (<60% of structure within domain).
* Identified logKow values were input only for ECOSAR and OASIS (CPOPs) models. LogKow could not be specified for AIEPS and TOPKAT models.

Table 12. Summary of data used in the ecological risk quotient analysis of TBBPA

	Pelagic organisms	Benthic organisms	Soil organisms	Fish-consuming Wildlife
Predicted exposure concentration (PEC)	0.000719 – 0.00719[1] mg/L	42.08 – 420.75 mg/kg (normalized 100% OC)[4]	0.000057 mg/kg dw[8]	0.007 mg/kg bw-day[11]
Critical toxicity value (CTV)	0.31 mg/L[2]	151 mg/kg dw[5]	0.12 mg/kg dw[9]	1.64 mg/kg bw-day[12]
Application factor	100[note 3]	100 [note 6]	100 [note 6]	10 [note 13]
Predicted no-effects concentration (PNEC)	0.0031 mg/L	60.4 mg/kg dw (normalized 100% OC) [7]	0.0005 mg/kg dw[10]	0.164 mg/kg bw-day
Risk quotient (PEC/PNEC)	**0.23 – 2.3**	**0.7 – 7.0**	**0.11**	**0.043**

Notes:

[1] Due to the lack of adequate measured data, PECs were estimated using the IGETA industrial release model.

[2] Brominated Flame Retardants Industry Panel (1989i).

[note 3] Application Factor of 100 applied to account for interspecies and intraspecies variations in sensitivity and extrapolation from laboratory to field conditions..

[4]Due to the limited measured sediment values for North America, PECs for sediment were predicted using the equilibrium approach based on Equation R.16-35 of the REACH guidance document (ECHA 2010):

$PEC_{local\ sed} = K_{susp\text{-}water}/RHO_{susp} \times PEC_{local\ water} \times 1000$

where:

$PEC_{local\ sed}$ = PEC for sediment (mg/kg)

$K_{susp\text{-}water}$ = suspended matter-water partitioning coefficient (m^3/m^3); $K_{susp\text{-}water}$ =26915.3 as determined from equation R16-7 and Table R.16-9 (ECHA 2010), assuming a log Koc= 5.43 and Henry's law constant = 0.1 Pa m^3/mol.

RHO_{susp} = bulk density of suspended matter (kg/m^3); default = 1150 from equation R16-16 (ECHA 2010)

$PEC_{local\ water}$= PEC for surface water during a release episode (mg/L), determined from IGETA model results.

In the sediment partitioning equation, the OC fraction (Foc) =10%, representing surface sediment; however to allow comparison with the PNEC, the PEC was standardized to represent sediment with 100% OC.

[5] ACCBFRIP (2002d).

[note 6] Application Factor of 100 applied to account for extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity.

[7] The CTV of 151 mg/kg dw was obtained using sediments containing 2.5% OC. To allow comparison between the PNEC and PECs, the PNEC was normalized to represent sediment with 100% OC.

[8] Due to the lack of measured data, PEC was calculated using the BASL4 model. To examine potential impacts from long-term application, an application time period of 10 consecutive years was considered. The calculation considered a maximum application rate of 8300 kg dw/ha per year (based on the highest existing provincial regulatory limit; Environment Canada 2006a) with a mixing depth of 0.1 m (default value for BASL4) and a soil density of 1487 kg/m^3 (default value for BASL4). A sludge concentration reported by Smyth (2013) of 0.195 mg/kg dw (OC estimated at 38.5% based on the fraction of volatile solids x 1.8 (Adams et al. 1951) was used as the C_{sludge} in the calculation. PEC is normalized to 2% OC andrepresents the maximum concentration predicted by the BASL4 model at day 56 to coincide with the duration of the study from which the PNEC was derived.

[9] ACCBFRIP (2003).

[10] The CTV of 0.12 mg/kg dw was obtained using a soil with 4.5% OC. The PNEC was normalized to 2% OC.

[11] Based on Total Daily Intake (TDI) for mink (*Mustela vison)* consuming fish, determined from Wildlife Exposure Model, where

$$TDI = \left[FMR\left(\frac{C_i \cdot E_D \cdot P_i}{GE_i \cdot AE_i} \right) + \left(C_s \cdot IR_s \right) + \left(C_w \cdot IR_w \right) \right] \cdot Pt$$

where:

TDI = total daily intake (mg/kg bw/day)
FMR = free-living metabolic rate of wildlife receptor of interest; In this assessment, it is assumed FMR=181 kcal/kg bw/day for mink.
Ci = concentration of contaminant in the ith prey species (mg/kg); determined as Ci =Cw x BCF; where BCF=485(CITI 1992).
Pi = proportion of the ith prey species in the diet (unitless); It is assumed that approximately only 30-35% of the diet of mink is fish: Pi=0.35.
GEi = gross energy of the ith prey species (850 kcal/kg prey) 5th percentile used for conservative value; GEi=1200.
AEi = assimilation efficiency of the ith prey species by the wildlife receptor; AEi=0.91. Default value.
Cs = concentration of contaminant in the sediments (mg/kg dw); It is assumed that TBBPA exposure via sediment is negligible; Cs=0.
IRs = intake rate of sediments (kg dw/kg bw/day); It is assumed that incidental sediment ingestion is zero IRs=0.
Cw = concentration of contaminant in the water (mg/L); 0.05 ug/L, which is the highest measured TBBPA concentration in Table 6, was selected to represent a potential regional water concentration (Table 6, Environment Agency Japan 1989,1991); Cw=0.05 ug/L
IRw = intake rate of water (L/day); Assumed to be 10%; IRw=0.1.
Pt = proportion of the time the receptor spends in the contaminated area. Assumed to 50%; Pt=0.5.
A description and definition of each variable in the above equation can be found in US EPA (1993).

[12] Due to the lack of data for wildlife species, the CTV is based on a Wildlife Toxicity Reference Value (TRV) (Sample et al. 1996), determined from the Wildlife Exposure Model, where potential effects in rodents (Tada et al. 2006) are normalized to typical body weight of mink, *Mustela vison*, a surrogate wildlife species:

$TRV =_s MATC_{ts} \times (BW_{ts}/BW_{fs})$

where:

TRV_e = wildlife tissue residue value (mg/kg bw/day)
$MATC_{ts}$ = maximum allowable toxicant concentration for test species (mg/kg bw/day), MATC= Geomean of NOAEL and LOAEL for test species. A LOAEL of 140.5 mg/kg bw/d and NOAEL of 15.7 mg/kg bw/d (Tada et al. 2006), were selected to determine a TRV for the evaluation of potential effects in wildlife. This endpoint was considered relevant, based upon liver toxicity in female offspring in a reproductive assay with mice (see Health Assessment Section (Tada et al. 2006)).
BW_{ts} = mean body weight of test species (kg); BW_{ts} = 0.0383 kg (mean for NOAEL and LOAEL mouse weight, Tada et al. 2006)
BW_{fs} = body weight of focal species (kg); =1.1 (US EPA 1993).

note [13]Application factors: 10 applied to account for extrapolation from laboratory to field conditions.

Table 13. Summary of data used in the risk quotient analysis of TBBPA bis(allyl ether)

	Pelagic organisms	Benthic organisms	Fish-consuming Wildlife
Predicted exposure concentration (PEC)	0.0000204 mg/L[1]	3.29 mg/kg (normalized 100% OC)[4]	0.00005[7] mg/kg bw day
Critical toxicity value (CTV)	0.000098 mg/L[2]	151 mg/kg dw[5]	1.635 mg/kg bw day[8]
Application factor	1 note3	100 note 6	10 note 9
Predicted no-effects concentration (PNEC)	0.000098 mg/L	60.4 mg/kg dw (normalized 100% OC)[g]	0.1635 mg/kg bw day[10]
Risk quotient (PEC/PNEC)	**0.21**	**0.054**	**0.00031**

Notes:
[1] Due to the lack of adequate measured data, the highest predicted water solubility limit and therefore theoretical maximum PEC for water was used (Table 2).
[2] ECOSAR 2011 v.1.10, chronic value for fish.
note 3 Application Factor was not used. The selected chronic CTV was the lowest predicted pelagic toxicity result by a wide margin; therefore, it was assumed that a factor of 10 to account for interspecies and intraspecies variations in sensitivity was not required. It is assumed that the predicted value is conservative enough to account for foreseeable uncertainties relating to laboratory to field extrapolation. All other predicted toxicity values (within the domain of models used) exceeded the substance water solubility limit by greater than a factor of 10, and therefore, indicated no effects at saturation.
[4] Due to the limited measured sediment values for North America, PECs for sediment were predicted using the equilibrium approach based on Equation R.16-35 of the REACH guidance document (ECHA 2010):

$$PEC_{local\ sed} = K_{susp\text{-}water}/RHO_{susp} \times PEC_{local\ water} \times 1000$$

where:

$PEC_{local\ sed}$ = PEC for sediment (mg/kg)
$K_{susp\text{-}water}$ = suspended matter-water partitioning coefficient (m^3/m^3); $K_{susp\text{-}water}$ =74131 as determined from equation R16-7 and Table R.16-9 (ECHA 2010), assuming a log Koc= 5.87 and Henry's law constant = 0.01 Pa m^3/mol.
RHO_{susp} = bulk density of suspended matter (kg/m^3); default = 1150 from equation R16-16 (ECHA 2010)
$PEC_{local\ water}$= PEC for surface water during a release episode (mg/L); predicted water solubility limit (0.0000204 mg/L).

.In the sediment partitioning equation, the OC fraction (Foc) =10%, representing surface sediment; however to allow comparison with the PNEC, the PEC was standardized to represent sediment with 100% OC

[5]ACCBFRIP (2002d). Due to lack of sediment organism data, TBBPA was used as an analogue.
note 6 Application Factor of 100 applied to account for extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity.
[7]The CTV of 151 mg/kg dw was obtained using sediments containing 2.5% OC. To allow comparison between the PNEC and PECs, the PNEC was normalized to represent sediment with 100% OC.

[8] Based on Total Daily Intake (TDI) for mink (*Mustela vison)* consuming fish, determined from Wildlife Exposure Model, where

$$TDI = \left[FMR\left(\frac{C_i \cdot E_D \cdot P_i}{GE_i \cdot AE_i} \right) + \left(C_s \cdot IR_s\right) + \left(C_w \cdot IR_w\right) \right] \cdot Pt$$

where:

TDI = total daily intake (mg/kg bw/day)
FMR = free-living metabolic rate of wildlife receptor of interest; In this assessment, it is assumed FMR=181 kcal/kg bw/day for mink.
Ci = concentration of contaminant in the ith prey species (mg/kg); determined as Ci = 0.0017 mg/kg, from lake trout samples collected in Lake Ontario (Ismail et al. 2006).
Pi = proportion of the ith prey species in the diet (unitless); It is assumed that approximately only 30-35% of the diet of mink is fish: Pi=0.35.
GEi = gross energy of the ith prey species (850 kcal/kg prey) 5th percentile used for conservative value; GEi=1200.
AEi = assimilation efficiency of the ith prey species by the wildlife receptor; AEi=0.91. Default value.
Cs = concentration of contaminant in the sediments (mg/kg dw); It is assumed that TBBPA exposure via sediment is negligible; Cs=0.
IRs = intake rate of sediments (kg dw/kg bw/day); It is assumed that incidental sediment ingestion is zero IRs=0.
Cw = concentration of contaminant in the water (mg/L);Cw=0.0000204 mg/L, the highest predicted water solubility for TBBPA bis(allyl ether) (Table 2).
IRw = intake rate of water (L/day); Assumed to be 10%; IRw=0.1.
Pt = proportion of the time the receptor spends in the contaminated area. Assumed to 50%; Pt=0.5
A description and definition of each variable in the above equation can be found in US EPA (1993).

note [9] Due to the lack of data for wildlife species, TBBPA was used as an analogue. The CTV is based on a Wildlife Toxicity Reference Value (TRV) (Sample et a.l 1996), determined from the Wildlife Exposure Model, where potential effects in rodents (Tada et al. 2006) are normalized to typical body weight of mink, *Mustela vison*, a surrogate wildlife species:

$TRV =_s MATC_{ts} \; x \; (BW_{ts}/BW_{fs})$

where:

TRV_e = wildlife tissue residue value (mg/kg bw/day)
$MATC_{ts}$ = maximum allowable toxicant concentration for test species (mg/kg bw/day), MATC= Geomean of NOAEL and LOAEL for test species. A LOAEL of 140.5 mg/kg bw/d and NOAEL of 15.7 mg/kg bw/d (Tada et al. 2006), were selected to determine a TRV for the evaluation of potential effects in wildlife. This endpoint was considered relevant, based upon liver toxicity in female offspring in a reproductive assay with mice (see Health Assessment Section (Tada et al. 2006)).
BW_{ts} = mean body weight of test species (kg); BW_{ts} = 0.0383 kg (mean for NOAEL and LOAEL mouse weight, Tada et al. 2006)
BW_{fs} = body weight of focal species (kg); =1.1(US EPA 1993).

[10]Application factors: 10 applied to account for extrapolation from laboratory to field conditions.

APPENDICES:

Appendix 1a. PBT Model Inputs Summary Table- TBBPA

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	BASL4 Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
SMILES Code	Oc(c(cc(c1)C(c(cc(c(O)c2Br)Br)c2)(C)C)Br)c1Br							Oc(c(cc(c1)C(c(cc(c(O)c2Br)Br)c2)(C)C)Br)c1Br	Oc(c(cc(c1)C(c(cc(c(O)c2Br)Br)c2)(C)C)Br)c1Br
Molecular weight (g/mol)		x (1, 2, 3)	543.88 (I,II)	x (I,II)	x		543.88		
Melting point (ºC)			181 (I)	x (I)					
Boiling point (ºC)									
Data temperature (ºC)			20 (I,II)	x (I,II)					
Density (kg/m^3)		x (2)					1487[3]		
Vapour pressure (Pa)		x (1, 3)	1.19 × 10^{-5} (I)	x (I)			1.19 x 10^{-5}		
Henry's Law constant (Pa·m^3/mol)		x (3)							
Log K_{aw} (air-water partition coefficient; dimensionless)		x (2)	x (II)	x (II)	x				
Log K_{ow} (octanol-water partition coefficient; dimensionless)	5.9	x (1)	5.9 (I)	x (I)	x	5.9	5.9	5.9	5.9
K_{ow} (octanol-water partition coefficient; dimensionless)		x (2, 3)							
Log K_{oc} (organic carbon-water partition coefficient – L/kg)							5.43		
Water solubility (mg/L)		x (1, 3)	0.063[a] (I)	x			0.063		

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	BASL4 Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
Log K_{oa} (octanol-air partition coefficient; dimensionless)									
Soil-water partition coefficient (L/kg)[1]			x (II)	x (II)					
Sediment-water partition coefficient (L/kg)[1]			x (II)	x (II)					
Suspended particles-water partition coefficient (L/kg)[1]		x (2)	x (II)	x (II)					
Fish-water partition coefficient (L/kg)[2]			x (II)	x (II)					
Aerosol-water partition coefficient; dimensionless[3]			x (II)	x (II)					
Vegetation-water partition coefficient; dimensionless[1]				x (II)					
Enthalpy (K_{ow})				-20 (3)					
Enthalpy (K_{aw})				55 (3)					
Half-life in air (days)			3.615 (I,II)	x (I,II)	x				
Half-life in water (days)			4166 (I,II)	x (I,II)	x				
Half-life in sediment (days)			4166 (I,II)	x (I,II)					
Half-life in soil (days)			4166 (I,II)	x (I,II)	x		182		
Half-life in vegetation (days)[4]				x (I,II)					
Metabolic rate constant (1/days)						1.12			
Biodegradation rate constant (1/days) or		x (3, 1/hr) (2,							

	Phys-Chem/Fate	Fate	Fate	Fate	Fate	Fate	Fate	PBT Profiling	Ecotoxicity
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	BASL4 Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
(1/hr)–specify		1/days)							
Biodegradation half-life in primary clarifier ($t_{1/2\text{-}p}$) (hr)		x (1)							
Biodegradation half-life in aeration vessel ($t_{1/2\text{-}s}$) (hr)		x (1)							
Biodegradation half-life in settling tank ($t_{1/2\text{-}s}$) (hr)		x (1)							

[1] derived from $\log K_{oc}$
[2] derived from BCF data
[3] default value
[4] derived from half-life in water

Appendix 1b. PBT Model Inputs Summary Table- TBBPA bis(2-hydroxyethyl ether)

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
SMILES Code	OCCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCCO)c(Br)c2						OCCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCCO)c(Br)c2	OCCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCCO)c(Br)c2
Molecular weight (g/mol)		x (1, 2, 3)	631.98 (I,II)	x (I,II)	x			
Melting point (ºC)			247.21 (I)	x (I)				
Boiling point (ºC)								
Data temperature (ºC)			25 (I,II)	x (I,II)				
Density (kg/m^3)		x (2)						
Vapour pressure (Pa)		x (1, 3)	1.29×10^{-13} (I)	x (I)				
Henry's Law constant ($Pa \cdot m^3/mol$)		x (3)						
Log K_{aw} (air-water partition coefficient; dimensionless)		x (2)	x (II)	x (II)	x			
Log K_{ow} (octanol-water partition coefficient; dimensionless)	5.48	x (1)	5.48 (I)	x (I)	x	5.48	5.48	5.48
K_{ow} (octanol-water partition coefficient; dimensionless)		x (2, 3)						
Log K_{oc} (organic carbon-water partition coefficient – L/kg)								
Water solubility (mg/L)		x (1, 3)	0.031 (I)	x				

	Phys-Chem/Fate	Fate	Fate	Fate	Fate	Fate	PBT Profiling	Ecotoxicity
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
Log K_{oa} (octanol-air partition coefficient; dimensionless)								
Soil-water partition coefficient (L/kg)[1]			x (II)	x (II)				
Sediment-water partition coefficient (L/kg)[1]			x (II)	x (II)				
Suspended particles-water partition coefficient (L/kg)[1]		x (2)	x (II)	x (II)				
Fish-water partition coefficient (L/kg)[2]			x (II)	x (II)				
Aerosol-water partition coefficient; dimensionless[3]			x (II)	x (II)				
Vegetation-water partition coefficient; dimensionless[1]				x (II)				
Enthalpy (K_{ow})				-20 (3)				
Enthalpy (K_{aw})				55 (3)				
Half-life in air (days)			0.418 (I,II)	x (I,II)	x			
Half-life in water (days)			180 (I,II)	x (I,II)	x			
Half-life in sediment (days)			720 (I,II)	x (I,II)				
Half-life in soil (days)			180 (I,II)	x (I,II)	x			
Half-life in vegetation (days)[4]				x (I,II)				
Metabolic rate constant (1/days)						13.8		
Biodegradation rate constant (1/days) or (1/hr)–specify		x (3, 1/hr) (2, 1/days)						

	Phys-Chem/Fate	Fate	Fate	Fate	Fate	Fate	PBT Profiling	Ecotoxicity
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
Biodegradation half-life in primary clarifier ($t_{1/2\text{-}p}$) (hr)		x (1)						
Biodegradation half-life in aeration vessel ($t_{1/2\text{-}s}$) (hr)		x (1)						
Biodegradation half-life in settling tank ($t_{1/2\text{-}s}$) (hr)		x (1)						

[1] derived from $\log K_{oc}$
[2] derived from BCF data
[3] default value
[4] derived from half-life in water

Appendix 1c. PBT Model Inputs Summary Table- TBBPA bis (allyl ether)

	Phys-Chem/Fate	Fate	Fate	Fate	Fate	Fate	PBT Profiling	Ecotoxicity
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
SMILES Code	C=CCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCC=C)c(Br)c2						C=CCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCC=C)c(Br)c2	C=CCOc1c(Br)cc(cc1Br)C(C)(C)c2cc(Br)c(OCC=C)c(Br)c2
Molecular weight (g/mol)		x (1, 2, 3)	624.01 (I,II)	x (I,II)	x			
Melting point (ºC)			216.64 (I)	x (I)				
Boiling point (ºC)								
Data temperature (ºC)			25 (I,II)	x (I,II)				
Density (kg/m^3)		x (2)						
Vapour pressure (Pa)		x (1, 3)	2.9 x10-9 (I)	x (I)				
Henry's Law constant (Pa·m^3/mol)		x (3)						
Log K_{aw} (air-water partition coefficient; dimensionless)		x (2)	x (II)	x (II)	x			
Log K_{ow} (octanol-water partition coefficient; dimensionless)		x (1)	8.71 (I)	x (I)	x	8.71	8.71	8.71
K_{ow} (octanol-water partition coefficient; dimensionless)		x (2, 3)						
Log K_{oc} (organic carbon-water partition coefficient – L/kg)								
Water solubility (mg/L)		x (1, 3)	0.000020 (I)	x				
Log K_{oa} (octanol-air partition coefficient;								

	Phys-Chem/Fate	Fate	Fate	Fate	Fate	Fate	PBT Profiling	Ecotoxicity
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
dimensionless)								
Soil-water partition coefficient (L/kg)[1]			X (II)	x (II)				
Sediment-water partition coefficient (L/kg)[1]			x (II)	x (II)				
Suspended particles-water partition coefficient (L/kg)[1]		x (2)	x (II)	x (II)				
Fish-water partition coefficient (L/kg)[2]			x (II)	x (II)				
Aerosol-water partition coefficient; dimensionless[3]			x (II)	x (II)				
Vegetation-water partition coefficient; dimensionless[1]				x (II)				
Enthalpy (K_{ow})				-20 (3)				
Enthalpy (K_{aw})				55 (3)				
Half-life in air (days)			0.159 (I,II)	x (I,II)	x			
Half-life in water (days)			180 (I,II)	x (I,II)	x			
Half-life in sediment (days)			360 (I,II)	x (I,II)				
Half-life in soil (days)			180 (I,II)	x (I,II)	x			
Half-life in vegetation (days)[4]				x (I,II)				
Metabolic rate constant (1/days)						0.0018		
Biodegradation rate constant (1/days) or (1/hr)–specify		x (3, 1/hr) (2, 1/days)						
Biodegradation half-life in primary clarifier		x (1)						

	Phys-Chem/Fate	Fate	Fate	Fate	Fate	Fate	PBT Profiling	Ecotoxicity
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF, BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type I vs. Type II chemical)	OECD POPs Tool	Arnot-Gobas BCFBAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER)
($t_{1/2\text{-}p}$) (hr)								
Biodegradation half-life in aeration vessel ($t_{1/2\text{-}s}$) (hr)		x (1)						
Biodegradation half-life in settling tank ($t_{1/2\text{-}s}$) (hr)		x (1)						

[1] derived from $\log K_{oc}$
[2] derived from BCF data
[3] default value
[4] derived from half-life in water

Appendix 2. Robust Study Summaries

Description of the reliability evaluation

To evaluate the reliability of studies for key ecological endpoints (i.e., inherent toxicity to aquatic organisms, bioaccumulation potential, persistence), an approach analogous to that of Klimisch et al. (1997) has been developed. It involves the use of a standardized Robust Study Summary form, including a scoring system to quantitatively evaluate the studies. The Robust Study Summary (RSS) is an adaptation of the OECD Robust Study Summary templates (OECD 2009). It consists of a checklist of items or criteria (column 2 of the RSS) relating to identity of the substance, experimental protocol or method, test organism, specific test design/conditions, ecological relevance, and results. Most items are weighted according to their criticality to the quality and reliability of the study (column 3). The most important or critical items (which describe parameters/factors that have the most direct influence on the quality of the study) have been given a higher weight (3 points), while the less critical items have been given a lower score (1 or 2 points). For each item, the evaluator must indicate whether the item has been addressed appropriately in the study by answering "yes", "no" or "non-applicable (n/a)" (column 4). Specific information relating to the items is provided in column 5 of the RSS.

Once answers to all the items have been provided in column 4, an overall Robust Study Summary score for the study is calculated as:

$$\textbf{Overall Study Score (\%)} = \frac{\sum W_{Yes}}{\sum W_{Yes+No}} \times \textbf{100\%}$$

Where:
W_{Yes} = weight of applicable "Yes" answers;
W_{Yes+No} = weight of applicable "Yes" and "No" answers.

The overall score's corresponding reliability code and category is determined using the four categories adapted from the Klimisch approach and based on the score ranges as described in Table A.

Table A: Scoring Grid for Overall Study Reliability

Reliability Code	Reliability Category	Overall Study Score Range
1	High confidence	≥ 80%
2	Satisfactory confidence	60 – 79%
3	Low confidence	40 – 59%
4	Not acceptable	< 40%

References

Klimisch HJ, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25:1-5

[OECD] Organisation for Economic Co-operation and Development. 2009. Manual for the Assessment of Chemicals. Annex 1: Guidance for Completing a SIDS Dossier. [Internet]. Paris (FR): OECD, Environment Directorate. [cited July, 2011].Available from http://www.oecd.org/dataoecd/13/17/36045066.pdf

Robust Study Summary Forms For Key Ecotoxicological Studies

Item	Yes	No
***Reference*:** Springborn Laboratories Inc. 1989. Determination of the Biodegradability of Tetrabromobisphenol A in a Soil Under Aerobic Conditions. *SLS Report: 88-11-2848; Study No.: 1199-1287-6103-760* p. 40. (Reference: Brominated Flame Retardants Industry Panel 1989d).		
Test Substance (CAS # and name): 79-94-7 (phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-] / TBBPA)		
Chemical composition of the substance (including purity, by-products)	X	
Method		
References		X
OECD, EU, national, or other standard method?		X
Justification of the method/protocol if not a standard method was used		
***GLP* (Good Laboratory Practice)**	X	
Test design / conditions		
Study type (photodegradation, hydrolysis, biodegradation, other –specify, do **not** assess): Biodegradation		
Test type (aerobic or anaerobic - specify, do **not** assess): Aerobic		
Test medium (air, water, soil, sediment - specify, do **not** assess): Soil		
Information on stability of the substance in the media of concern is reported?		X
Controls (positive or negative): Not mentioned		X
Number of replicates (including controls)	X	
Temperature	X	
Duration of the experiment	X	
For photodegradation only		
Light source (specify):		
Light spectrum and relative intensity based on sunlight intensity:		
For hydrolysis only		
Measured concentrations reported?		
Basic water properties (pH, hardness, etc.)		
For biodegradation only		
Ready or inherent biodegradation (specify): Inherent	X	
Inoculum (concentration and source): Not mentioned		X
Results		
Endpoints: half-life (preferred); degradation, %; etc. (do **not** assess this item): 78.1% remaining ($k \cong 0.0039$; $t_{1/2} \cong 179$ days) (64-days - MASDLM); 42.2% remaining ($k \cong 0.013$; $t_{1/2} \cong 51.3$ days) (64-days - Clay Loam); 38% remaining ($k \cong 0.015$; $t_{1/2} \cong 45.8$ days) (64-days - Silty Loam). **Average $t_{1/2} \cong 92$ days**		
Information on breakdown products (do **not** assess this item): No		
Overall score: 6/**11 = 55 %**		
***EC Reliability code*:** 3		
Reliability category *(high, satisfactory, low)*: Low		
Comments: Score = 55%; Chemical purity – '99%'. Method as per "Protocol for Determining the Inherent Biodegradability in Soil under Aerobic Conditions" – in-house protocol. Temperature = 20-25°C. 64-day study; chemical measured by liquid scintillation counting. Maintained in darkness. Solvent – Acetone. 3 different soil types – Massachusetts Sandy Loam (MASDLM); Clay Loam; Silty Loam. "Only a limited amount (<6%) of the applied radioactivity was recovered in the CO_2 traps, suggesting merely partial biodegradation to unidentified products". The absence of reported controls is a concern. Further, there is no mention of controls in the in-house protocol, thus the confidence that the reported percentages are a result of biodegradation ***only*** is low. It is hard to distinguish what factors cause the differences in biodegradation rates (e.g. OC content, pH etc) since there is also no documentation on inoculum. Low confidence; reliability code = 3.		

Summary Table

Soil Type	Organic Carbon (%)	pH	Field Moisture Capacity (%)	Sand (%)	Silty (%)	Clay (%)	Remaining TBBPA in Soil (%)	½ life (d) (estimated by evaluator)
MASDLM	4.4	7.0	74.8	83	13	4	74.3-81.9	179
Clay Loam	0.8	6.2	43.9	16	58	26	41.1-43.2	51.3
Silty Loam	1.8	7.6	75.9	43	24	33	35.9-40.1	45.8

ROBUST STUDY SUMMARY - Persistence

Item	Yes	No
***Reference*:** Springborn Laboratories Inc. 1989. (Tetrabromobisphenol A) – Determination of the Biodegradability in a Sediment/Soil Microbial System. *SLI Report: 89-8-3070; Study No.: 1199-1287-6102-785* p. 69. (Reference: Brominated Flame Retardants Industry Panel 1989f).		
Test Substance (CAS # and name): 79-94-7 (phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-] / TBBPA)		
Chemical composition of the substance (including purity, by-products)	X	
Method		
References	X	
OECD, EU, national, or other standard method?		X
Justification of the method/protocol if not a standard method was used		
***GLP* (Good Laboratory Practice)**	X	
Test design / conditions		
Study type (photodegradation, hydrolysis, biodegradation, other –specify, do **not** assess): Biodegradation		
Test type (aerobic or anaerobic - specify, do **not** assess): Aerobic		
Test medium (air, water, soil, sediment - specify, do **not** assess): Water and **Sediment**		
Information on stability of the substance in the media of concern is reported?	X	
Controls (positive or negative): Negative control	X	
Number of replicates (including controls)	X	
Temperature	X	
Duration of the experiment	X	
For photodegradation only		
Light source (specify):		
Light spectrum and relative intensity based on sunlight intensity:		
For hydrolysis only		
Measured concentrations reported?		
Basic water properties (pH, hardness, etc.)		
For biodegradation only		
Ready or inherent biodegradation (specify): Not specified		X
Inoculum (concentration and source): Natural assemblages of microorganisms from sediment. 10^3 – 10^5 colony forming units per ml (final)	X	
Results		
Endpoints: half-life (preferred); degradation, %; etc. (do **not** assess this item): (10 *u*g/L) $t_{1/2}$ = 48 days (k = 0.0145 day^{-1}), r^2 = 0.67; **(100 *u*g/L) $t_{1/2}$ = 69 days (k = 0.0101 day^{-1}), r^2 = 0.87**; (1,000 *u*g/L) $t_{1/2}$ = 84 days (k = 0.00829 day^{-1}), r^2 = 0.79.		
Information on breakdown products (do **not** assess this item): No		
Overall score: 9/**11 = 82 %**		
***EC Reliability code*:** 2		
Reliability category *(high, satisfactory, low)*: satisfactory		
Comments: Score = 82%; Chemical purity – '96%'. Method as per "Protocol for Determining the Biodegradation of a Test Material in a Sediment/Water Microbial System Following Proposed TSCA Guidelines" – in-house protocol, but the ***actual reference*** is not provided. Temperature = 25°C. Stability of chemical monitored throughout the 56-day study by HPLC. Maintained in darkness. Solvent – Acetone. pH range 5.2 – 6.6. Sediment characteristics – total carbon=6.8%, sand=92%, silt=6%, clay=2%, field moisture capacity=15.9%. 3 concentrations of test chemical used – high (1,000 *u*g/L); medium (100 *u*g/L); and low (10 *u*g/L). Three replicates per sample time. "Only a limited amount (<8%) of the applied radioactivity was recovered in the CO_2 traps, suggesting merely partial biodegradation to unidentified products". Although experiment conducted in water/sediment, half-lives and rates should be applied to sediment compartment, as this is where the majority of the chemical was detected. The increased concentration of test chemical appears to inhibit biodegradation rates perhaps by some effect on microbial populations. This was further investigated but was generally inconclusive (according to methods of OECD 209). Satisfactory confidence; reliability code = 2. Value could be selected based on concentration of chemical to align with these rates or suggested bold value.		

ROBUST STUDY SUMMARY - Persistence

Item	Yes	No
***Reference*:** Ronen, Z. and A. Abeliovich. 2000. Anaerobic-Aerobic Process for Microbial Degradation of Tetrabromobisphenol A. *Applied and Environmental Microbiology 66:2372-2377*.		
Test Substance (CAS # and name): 79-94-7 (phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-] / TBBPA)		
Chemical composition of the substance (including purity, by-products)		X
Method		
References	X	
OECD, EU, national, or other standard method?		X
Justification of the method/protocol if not a standard method was used		
***GLP* (Good Laboratory Practice)**	n/a	n/a
Test design / conditions		
Study type (photodegradation, hydrolysis, biodegradation, other –specify, do **not** assess): Biodegradation		
Test type (aerobic or anaerobic - specify, do **not** assess): **Anaerobic** / Aerobic		
Test medium (air, water, soil, sediment - specify, do **not** assess): **Sediment**		
Information on stability of the substance in the media of concern is reported?		X
Controls (positive or negative): Negative control	X	
Number of replicates (including controls)		X
Temperature	X	
Duration of the experiment	X	
For photodegradation only		
Light source (specify):		
Light spectrum and relative intensity based on sunlight intensity:		
For hydrolysis only		
Measured concentrations reported?		
Basic water properties (pH, hardness, etc.)		
For biodegradation only		
Ready or inherent biodegradation (specify): Not specified (~Inherent)		X
Inoculum (concentration and source): Natural assemblages of microorganisms from sediment.	X	
Results		
Endpoints: half-life (preferred); degradation, %; etc. (do **not** assess this item): ***ESTIMATED*** Anaerobic – $t_{1/2}$ = 11.5 days (based on rate constant of 0.06/day estimated from graph from reviewer). No graphs or rates presented for aerobic degradation of BPA (this is also not the primary chemical).		
Information on breakdown products (do **not** assess this item): No		
Overall score: 5/**10 = 50 %**		
***EC Reliability code*:** 3		
Reliability category *(high, satisfactory, low)*: low		
Comments: Score = 50%; Chemical purity – not determined. No standard methods mentioned. Temperature = 30°C. Two experiments conducted from contaminated site sediment. (i) Anaerobic degradation of TBBPA and (ii) aerobic degradation of BPA. Medium for anaerobic conditions include peptone, tryptone, glucose and yeast extract. TBBPA is biodegradable under anaerobic conditions; however, BPA (primary degradation product - 88%) is not biodegradable under anaerobic conditions. BPA requires aerobic conditions to be degraded. pH range adjusted to 7.7. Rate and half-life estimated from a graph by reviewer. This rate is for the anaerobic biodegradation of TBBPA to BPA only. Low confidence; reliability code = 3.		

ROBUST STUDY SUMMARY - Inherent Toxicity

Item	Yes	No
***Reference*:** Surprenant, D.C. 1989. The toxicity of tetrabromobisphenol A (TBBPA) to Fathead Minnow *(Pimphales promelas)* embryos and larvae. *Springborn Life Sciences, Inc. Report No: 89-2-2937. Study No: 1199-1287-6108-120.* 52 pp..(Reference: Brominated Flame Retardants Industry Panel 1989i).		
Test Substance (CAS # and name): 79-94-7 (Tetrabromobisphenol A (TBBPA))		
***Chemical composition of the substance (including purity, by-products)**	X	
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method**?	**X**	
Justification of the method/protocol if not a standard method was used		
***GLP (Good Laboratory Practice)**	**X**	
Test organisms (specify common and Latin names): *Fathead Minnow (Pimphales promelas)*		
Latin or both Latin and common names reported?	X	
Life cycle age / stage of test organism	X	
Sex		X
Length and weight of test organisms	X	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation/during test)	X	
Test design / conditions		
Test type – acute or chronic (specify, but do **not** assess this item): 35 day, partial life cycle, chronic endpoints		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls (specify)? Negative control	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**	**X**	
Exposure media conditions (temperature, pH, electrical conductivity, hardness, TOC, DOC, DO, major cations and anions; other)	X	
Was pH within 6-9 range? (do **not** assess this item)	X	
Was temperature within 5-28 °C range? (do **not** assess this item)	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators / solubilizers (especially for poorly soluble / unstable substances)	X	
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50} - specify, do **not** assess this item): 35 d LOEC=0.31 mg/L, 35 d NOEC = 0.16 mg/L		
Other endpoints reported - BCF/BAF, LOEC/NOEC (specify, do **not** assess this item): No		
***Was toxicity value below the chemical's water solubility**?	**X**	
Other adverse effects (carcinogenicity, mutagenicity, etc. Do **not** assess this item)		X
Score: major items – 5/**5**; overall score – **(97%)**		
***EC Reliability code*:** 1		
Reliability category (high, satisfactory, low): high		
Comments: The test was well-conducted and followed an established protocol based on EPA methods. Observations, both biotic and abiotic, were recorded daily and all WQ was within acceptable limits. Test concentrations were measured radiometrically throughout the test, with HPLC used to check the accuracy of the radiometric technique. Analysis of the test concentrations indicates they were reasonably well maintained. Control performance was good and there was a definitive dose-response.		

Item	Yes	No
***Reference*:** Krueger, H.O., Kendall, T.Z. and M. Jaber. 2002. Tetrabromobisphenol A – A Prolonged Sediment Toxicity Test with *Lumbriculus variegatus* Using Spiked Sediment with 2% Total Organic Carbon. *Wildlife International, Ltd, Easton Maryland Project No.: 439A-115*, p. 103. (Reference: ACCBFRIP 2002c).		
Test Substance (CAS # and name): 79-94-7 (Tetrabromobisphenol A (TBBPA))		
***Chemical composition of the substance (including purity, by-products)**	**X**	
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method**?	**X**	
Justification of the method/protocol if not a standard method was used		
***GLP (Good Laboratory Practice)**	**X**	
Test organisms (specify common and Latin names): Oligochaete (*Lumbriculus variegatus*)		
Latin or both Latin and common names reported?	X	
Life cycle age / stage of test organism	X	
Sex		X
Length and weight of test organisms	X	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation/during test)	X	
Test design / conditions		
Test type – acute or chronic (specify, but do **not** assess this item): chronic		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls (specify)? Negative control	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**		**X**
Exposure media conditions (temperature, pH, electrical conductivity, hardness, TOC, DOC, DO, major cations and anions; other)	X	
Was pH within 6-9 range? (do **not** assess this item)	X	
Was temperature within 5-28 °C range? (do **not** assess this item)	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators / solubilizers (especially for poorly soluble / unstable substances)		X
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50} - specify, do **not** assess this item): EC_{50} = 294 mg/Kg dry weight sediment (28 day)		
Other endpoints reported - BCF/BAF, LOEC/NOEC (specify, do **not** assess this item): Yes, LOEC = 151 mg/Kg dry weight sediment (statistically different than control ($p < 0.05$)); NOEC = 90 mg/Kg dry weight sediment.		
***Was toxicity value below the chemical's water solubility**?	**X**	
Other adverse effects (carcinogenicity, mutagenicity, etc. Do **not** assess this item)		X
Score: major items – 4/**5**; overall score – 22/**25 (88%)**		
***EC Reliability code*:** 1		
Reliability category (high, satisfactory, low): high		
Comments: Four major items reported "yes"; overall score 88%. Methods as per "A prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked sediment with 5% total organic carbon" –in-house protocol based on ASTM E 1706-95b (1995) and OPPTS 850.1735 Guideline (US EPA 1996a). Flow through test design. Chemical purity – '98.91%'. Temperature 23ºC. 95% C.L. = 140 - 391 mg/Kg dry wt. sediment. Effect – 'survival/reproduction'. Hydrophobic chemical (log Kow ~4.5-7.0). Good documentation of test organism and conditions. The water, sediment and pore water are sampled during test to verify test concentrations but nominal concentrations used to determine endpoints. High confidence; reliability code = 1.		

Summary Table

Soil Type	Organic Matter (%)	Organic Carbon (%)	pH	Water Holding Capacity (%)	Sand (%)	Silt (%)	Clay (%)
Artificial Sediment	4.4	2.5	8.1	10.7	83	8	9

ROBUST STUDY SUMMARY - Inherent Toxicity

Item	Yes	No
***Reference*:** Krueger, H.O., Kendall, T.Z. and M. Jaber. 2002. Tetrabromobisphenol A – A Prolonged Sediment Toxicity Test with *Lumbriculus variegates* Using Spiked Sediment with 5% Total Organic Carbon. *Wildlife International, Ltd, Easton Maryland Project No. 439A-116,* p. 104. (Reference: ACCBFRIP 2002d).		
Test Substance (CAS # and name): 79-94-7 (Tetrabromobisphenol A (TBBPA))		
***Chemical composition of the substance (including purity, by-products)**	**X**	
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method**?	**X**	
Justification of the method/protocol if not a standard method was used		
***GLP (Good Laboratory Practice)**	**X**	
Test organisms (specify common and Latin names): Oligochaete (*Lumbriculus variegatus*)		
Latin or both Latin and common names reported?	X	
Life cycle age / stage of test organism	X	
Sex		X
Length and weight of test organisms	X	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation/during test)	X	
Test design / conditions		
Test type – acute or chronic (specify, but do **not** assess this item): chronic		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls (specify)? Negative control	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**		**X**
Exposure media conditions (temperature, pH, electrical conductivity, hardness, TOC, DOC, DO, major cations and anions; other)	X	
Was pH within 6-9 range? (do **not** assess this item)	X	
Was temperature within 5-28 °C range? (do **not** assess this item)	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators / solubilizers (especially for poorly soluble / unstable substances)		X
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50} - specify, do **not** assess this item): EC_{50} = 405 mg/Kg dry weight sediment (28 day)		
Other endpoints reported - BCF/BAF, LOEC/NOEC (specify, do **not** assess this item): Yes, LOEC = 426 mg/Kg dry weight sediment (statistically different than control ($p < 0.05$)); NOEC = 254 mg/Kg dry weight sediment.		
***Was toxicity value below the chemical's water solubility**?	**X**	
Other adverse effects (carcinogenicity, mutagenicity, etc. Do **not** assess this item)		X
Score: major items – 4/**5**; overall score – 22/**25 (88%)**		
***EC Reliability code*:** 1		
Reliability category (high, satisfactory, low): high		
Comments: Four major items reported "yes"; overall score 88%. Methods as per "A prolonged sediment toxicity test with *Lumbriculus variegatus* using spiked sediment with 5% total organic carbon" –in-house protocol based on ASTM E 1706-95b (1995) and OPPTS 850.1735 Guideline (US EPA 1996a). Flow through test design. Chemical purity – '99%'. Temperature 23°C. 95% C.L. = 314 - 869 mg/Kg dry wt. sediment. Effect – 'survival/reproduction'. Hydrophobic chemical (log Kow ~4.5-7.0). Good documentation of test organism and conditions. The water, sediment and pore water are sampled during test to verify test concentrations but nominal concentrations used to determine endpoints. High confidence; reliability code = 1.		

Summary Table

Soil Type	Organic Matter (%)	Organic Carbon (%)	pH	Water Holding Capacity (%)	Sand (%)	Silty (%)	Clay (%)
Artificial Sediment	10.1	5.9	8.0	13.9	80	14	6

Item	Yes	No
***Reference*:** Aufderheide, J., Kendall, T. Z. and W.B. Nixon. 2003. Effect of Tetrabromobisphenol A on the Survival and Reproduction of the Earthworm, *Eisenia fetida*. *ABC Study No. 47014 and Wildlife International, Ltd Project No. 439C-131*, p. 109. (Reference: ACCBFRIP 2003).		
Test Substance (CAS # and name): 79-94-7 (Tetrabromobisphenol A (TBBPA))		
***Chemical composition of the substance (including purity, by-products)**	**X**	
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method**?	**X**	
Justification of the method/protocol if not a standard method was used		
***GLP (Good Laboratory Practice)**	**X**	
Test organisms (specify common and Latin names): Earthworm (*Eisenia fetida*)		
Latin or both Latin and common names reported?	X	
Life cycle age / stage of test organism	X	
Sex		X
Length and weight of test organisms	X	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation/during test)	X	
Test design / conditions		
Test type – acute or chronic (specify, but do **not** assess this item): chronic		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls (specify)? Negative control	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**	**X**	
Exposure media conditions (temperature, pH, electrical conductivity, hardness, TOC, DOC, DO, major cations and anions; other)	X	
Was pH within 6-9 range? (do **not** assess this item)	X	
Was temperature within 5-28 °C range? (do **not** assess this item)	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators / solubilizers (especially for poorly soluble / unstable substances)	n/a	n/a
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50} - specify, do **not** assess this item): Reproduction - EC_{50} = 1.7 mg/Kg dry weight soil (56 day); EC_{10} = 0.12 mg/Kg dry weight soil (56 day). Survival - EC_{50} = > 4,840 mg/Kg dry weight soil (28 day); EC_{10} = 0.12 mg/Kg dry weight soil (28 day).		
Other endpoints reported - BCF/BAF, LOEC/NOEC (specify, do **not** assess this item): Yes, NOEC = 2.11 mg/Kg dry weight soil (reproduction); NOEC = 4,840 mg/Kg dry weight soil (survival).		
***Was toxicity value below the chemical's water solubility**?	**X**	
Other adverse effects (carcinogenicity, mutagenicity, etc. Do **not** assess this item)		X
Score: major items – 5/**5**; overall score – 23/**24 (96%)**		
***EC Reliability code*:** 1		
Reliability category (high, satisfactory, low): high		
Comments: Five major items reported "yes"; overall score 96%. Methods as per "US EPA OPPTS guideline 850.6200, OECD guideline No. 207, OECD proposed guideline "Earthworm Reproduction Test (*Eisenia fetida*)". Two studies conducted (i) 28-d survival and (ii) 56-d reproduction. Initial mean weight of worms 450 – 520 mg/worm. Chemical purity – '99%'. Temperature 19.4 – 21.3°C. 95% C.L. = 0.46 – 3.7 mg/Kg dry wt. soil (56 day reproduction EC_{50}). Effect – 'reproduction'. Good documentation of test organism and conditions. High confidence; reliability code = 1.		

Summary Table (Initial Study - Survival)

Soil Type	Organic Matter (%)	Organic Carbon (%)	pH	Moisture @ 60% of water holding capacity (%)	Sand (%)	Silt (%)	Clay (%)
Artificial Sandy Loam	8.1	4.7	6.0 – 6.9	26	79	8	13

Summary Table (Definitive Study - Reproduction)

Soil Type	Organic Matter (%)	Organic Carbon (%)	pH	Moisture @ 60% of water holding capacity (%)	Sand (%)	Silt (%)	Clay (%)
Artificial Sandy Loam	7.7	4.5	5.8 – 7.5	22.3	78	10	12

Appendix 3. Upper-bounding estimates of daily intake of TBBPA, TBBPA bis(2-hydroxyethyl ether) and TBBPA bis(allyl ether) by Canadians

Route of exposure	Estimated intake (- x 10^{-3} mg/kg-bw per day) of TBBPA 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 fed	formula fed	not formula fed					
Ambient air[9]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Indoor air[10]	0.002	0.002	0.002	0.005	0.004	0.002	0.002	0.002
Drinking water[11]	0.187	0.002	0.001	0.001	0.001	<0.00001	<0.0001	<0.0001
Food [12]			0.081	0.050	0.030	0.017	0.011	0.009
Soil/ Dust[13]	0.006	0.006	0.006	0.009	0.002	0.001	0.001	0.001
Total intake	0.195	0.010	0.090	0.065	0.038	0.020	0.014	0.012

[1] 0.187 µg/kg-bw/day (1.87 x 10^{-4} mg/kg bw/day) based on the highest concentration of TBBPA detected in human breast milk of 37 µg/kg lipid, n=34/77 Cariou et al. 2008. Breast-fed infants consume on average of 742 ml milk per day and the fat content of the milk was 5.08 g per 100 ml milk. Estimated intake of TBBPA for breast fed infants was calculated (Health Canada 2008).

[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 (fed solid food) 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 TBBPA in water of used to reconstitute formula was based on Kuch et al. 2001. No data were identified on levels of TBBPA in formula in Canada or elsewhere. Approximately 50% of not formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990 in Health Canada 1998).

[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 data were available. TBBPA was found in ambient air at 70 pg/m^3 (7 x 10^{-8} mg/m^3) in the Russian Arctic at Dunai (Alaee et al. 2003). This was the value selected. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[10] In the absence of Canadian data, a measurement of 9.8 x 10^{-6} mg/m^3 found in Michigan, US indoor air (computed as summation of both TBBPA in vapour as well as particulate matter) (Batterman et al. 2010) was used. Canadians are assumed to spend 21 h indoors each day (Health Canada 1998). The critical data were selected from a dataset of indoor air studies, with consideration given to a reasonable worst case scenario (see NOTE below).

[11] No data on levels of TBBPA in Canadian drinking water were identified. A value of 0.02 µg/L (2 x 10^{-5} mg/L) measured in surface water in Germany was used as a surrogate (Kuch et al. 2001).

[12] No data were identified for TBBPA levels in foods in Canada. Selected food levels of TBBPA included those of a market survey in China (Shi et al. 2009b). Highest values of 1.3 µg/kg (1.3 x 10^{-3} mg/kg) for meat, 0.7 µg/kg (7 x 10^{-4} mg/kg) for eggs, 2.0 µg/kg (2 x 10^{-3} mg/kg) for aquatic food and 0.8 µg/kg (8 x 10^{-4} mg/kg) for milk. This data was chosen as China is a large consumer of aquatic foods and Asia is a leading manufacturer of TBBPA and TBBPA flame retardant products (e.g. epoxy laminated electric circuit boards). To the dairy value, 0.1 µg/kg (1 x 10^{-4} mg/kg) was added for TBBPA found in hard cheese (de Winter-Sorkina et al. 2003).

[13] Highest level in dust was from the rear of television cabinets in a Japanese study (Takigami et al. 2008). The next highest value is from floor dust of child daycare centers and primary school classrooms in United Kingdom at 1.4 mg/kg (1400 ng/g reported by Harrad et al. 2010). This value is used as a surrogate to approximate a reasonable worst case scenario for a Canadian population, in which children would be exposed continually to such levels indoor. As well, these levels can also approximate a work environment in which adults would be exposed to. Other values considered were: a value of 511 ug/kg (0.511 mg/kg) from a 2008 study which conservatively includes a high standard deviation on the mean value reported (146+/-365 ug/kg or 0.146 +/- mg/kg) of 18 residences and 2 offices from Flanders, Belgium (Geens et al. 2009); dust concentrations of 20 to 938 ng/g (2 x 10^{-4} mg/kg to 0.938 mg/kg) in Michigan, US offices (Batterman et al. 2010); residential house dust at 141 ng/g (0.141 mg/kg) and office dust at 212 ng/g (0.212 mg/kg) in Belgium (D'Hollander et al. 2010). A conservative approach is being taken since it is recognized that there is widespread increase in usage of TBBPA and its derivatives in polymeric materials found in the home and that combined with the increasing time spent indoors, especially in the winter.

NOTE: As there is no quantitative data available (Canadian or otherwise) for the TBBPA bis(2-hydroxyethyl ether) derivative and the bis(allyl ether), an overestimate of the TBBPA value used in the exposure assessment is expected to compensate for any additional amounts contributing to the exposure from the derivatives. It should also be noted here that the quantitative exposure assessments of TBBPA in the literature often refer to a collective group of Brominated Flame Retardants, which may or may not include ALL derivatives of TBBPA, including the TBBPA bis(2-hydroxyethyl ether) and bis(allyl ether).

Appendix 4. TBBPA Levels in Indoor Air

Location	Sampling Period	Number of Samples	Detection Limit (mg/m^3)	Mean Concentration[1] (mg/m^3)	Reference
United Kingdom	2007	5	LOQ n.s.	1.6×10^{-8} ($16\ pg/m^3$)	Abdallah et al. 2008
Apartment and houses, Tokyo, Japan	March – May, 2003	48	1.0×10^{-7} ($0.1\ ng/m^3$)	[3×10^{-7} – 8×10^{-7}] ($0.3 – 0.8\ ng/m^3$)	Inoue et al. 2003
Offices and Classrooms					
USA	2006-2007	10 buildings 18 samples	n.s.	Vapor Range = [$1.2 – 8.6 \times 10^{-8}$] ($12\text{-}86\ pg/m^3$) Particulate matter range–$1.1\text{-}1.2 \times 10^{-8}$ ($11\text{-}12\ pg/m^3$)	Batterman et al. 2010
United Kingdom	2007	5	LOQ n.s.	1.6×10^{-8} ($16\ pg/m^3$)	Abdallah et al. 2008
United Kingdom, public micro-environments	2007	4	LOQ n.s.	2.6×10^{-8} (26 pg/m3)	Abdallah et al. 2008
Offices, Sweden	1 working day in offices with 2 or 3 computers	4	n.s.	3.6×10^{-8} ($0.036\ ng/m^3$) [$1.0 \times 10^{-8} – 7.0 \times 10^{-8}$] ($0.01\text{-}0.07\ ng/m^3$)	Sjödin et al. 2001
Computer teaching hall, Sweden	1 working day in hall with 20 computers	2	n.s.	3.5×10^{-8} and 1.5×10^{-7} (0.035 and $0.15\ ng/m^3$)	Sjödin et al. 2001
Computer room, Germany	3 weeks	1	n.s.	8.0×10^{-9} ($8.0\ pg/m^3$)	Kemmlein 2000
Computer School room Germany	3 weeks 8 computers several printers	1	n.s.	2.9×10^{-8} ($29\ pg/m^3$)	Kemmlein 2000
Electronic Recycling Plants (point sources)	-	-	-	[3 to 15×10^{-5}]	Tollback et al. 2006 Sjödin et al. 2001 Morf et al. 2005 as cited in Xie et al. 2007

[1] Values in [brackets] indicate range of concentrations when available
n.s. = not specified

Appendix 5. TBBPA Levels in Dust

Location	Sampling Period	No. of Samples	Detection Limit (mg/kg)	Mean Concentration (mg/kg)	Reference
Belgium	2008	43 homes 10 offices	3 x 10^{-4} to 5 x 10^{-4}	[<0.003 to 0.419][1]	D'Hollander et al. 2010
United States	2006-2007	10 buildings	n.s.	[0.020 – 0.938]	Batterman et al. 2010
United Kingdom	2007-2008	45 homes 28 offices 20 cars	n.s.	[0.017– 1.4]	Harrad et al. 2010
Japan	n.s. TVs used until 2005-Manufactured from 1989-1998	Dust 5/5 Circuit board 5/5 Front cabinet 5/5 Rear cabinet 5/5	n.s.	Dust= 240 [5.5-680] Circuit board= 280 [7.9-1300] Front cabinet= 20 [0.24 -67] Rear cabinet= 1.9 x 10^4 [0.12-9.7 x 10^4]	Takigami et al. 2008
United Kingdom, dust, public micro-environments, 3 pubs and 1 restaurant	2006-2007	4	LOQ n.s.	0.220	Abdallah et al. 2008
United Kingdom, House dust	2006-2007	34/35	LOQ n.s.	0.087	Abdallah et al. 2008
United Kingdom, Office dust	2006-2007	24/28	LOQ n.s.	0.049	Abdallah et al. 2008
United Kingdom, Car dust	2006-2007	10/20	LOQ n.s.	0.006	Abdallah et al. 2008
Belgium, Flanders, House and office dust	Spring 2008	20 (18 houses 2 offices)	LOQ n.s.	0.146+/-0.365 0.073+/-0.039	Geens et al. 2009
House dust 10 regions of UK mainland	October – November, 2002	70 (pooled into 10 final samples) Detected in 4 of 10 pooled samples	0.5 to 3 x 10^{-3}	0.116 [<0.010 – 0.340]	Santillo et al. 2003
Finland	2002	1	0.5 to 3 x 10^{-3}	0.025	Santillo et al. 2003
Denmark	2002	1	0.5 to 3 x 10^{-3}	0.400	Santillo et al. 2003
Parliament The Hague, Netherlands	June 2000	1	0.5 to 3 x 10^{-3}	0.005	Santillo et al. 2001

Location	Sampling Period	No. of Samples	Detection Limit (mg/kg)	Mean Concentration (mg/kg)	Reference
Computer room and offices, Netherlands	June 2000	3	0.5 to 3 x 10^{-3}	<0.0005 - <0.001	Santillo et al. 2001
Parliament, Helsinki, Finland	May 2000	1	0.5 to 3 x 10^{-3}	<0.003	Santillo et al. 2001
Parliament, Stockholm, Sweden	May 2000	1	0.5 to 3 x 10^{-3}	<0.002	Santillo et al. 2001
Senato and Palazzo Marini, Italy	July 2000	2	0.5 to 3 x 10^{-3}	<0.001	Santillo et al. 2001
Eigtved Pakhus and Parliament, Copenhagen, Denmark	July 2000	2	0.5 to 3 x 10^{-3}	<0.001	Santillo et al. 2001
Parliament, Vienna, Austria	October 4, 2000	2	0.5 to 3 x 10^{-3}	0.015 and 0.033	Santillo et al. 2001
Reichstag, Berlin, Germany	September and October, 2000	2	0.5 to 3 x 10^{-3}	0.046 and 0.20	Santillo et al. 2001
Parliament, London, England	January 2001	2	0.5 to 3 x 10^{-3}	0.012 and 0.047	Santillo et al. 2001

[1] Values in [brackets] indicate range of concentrations when available
n.s. = not specified

Appendix 6. TBBPA Levels in Food

Item Sampled	Sampling Period	No. of Samples	Detection Limit (µg/kg lipid)	Mean Concentration (µg/kg lipid)	Reference
Fish, England	Summer 2008	30	0.29	(<0.29-1.7) [1] [<0.29-1.7 ng/g]	Ha.rrad et al. 2009
Fish, Scotland	2006	n.s.	0.3 wet wt.	< LOQ	Russell et al. 2008
Bull shark muscle, USA, East Coast of Florida	1993-1994 2002-2004	6 7	n.s.	5.17 [4.17-8.07] 13.2 [0.035-35.6]	Johnson-Restrepo et al. 2008
Atlantic sharpnose shark muscle, USA, Florida	2004	3	n.s.	0.9 [0.5-1.4]	Johnson-Restrepo et al. 2008
Harbor porpoise blubber, United Kingdom	1994-2003	18/68	n.s.	6-35 (w.wt)	Law et al. 2006
Harbor porpoise blubber, United Kingdom	2003-2006	0/138	n.s.	n.d.	Law et al. 2008
Fish, Japan	-	29/45	-	[0.01-0.11 w.wt] (0.01-0.11 ng/g wet wt)	Ashizuka et al. 2008
Fish, Japan, Marine products from food market stores of 3 regions (Nagoya, Seto Inland Sea, Kyushu)	2004-2005	45	n.d.	0.02 [n.d.-0.11]	Nakagawa et al. 2006
UK 2004 Total Diet Survey Data, Shellfish, oysters, mussels, scallops, Scotland	2004	0/35	0.05	n.d.	Driffield et al. 2008
Food- Fourth Total Diet Study, China n=12 Provinces	2007	48	n.s.	[< LOD- 2.0] (< LOD- 2044 pg/g lipid)	Shi et al. 2009b
Cow's milk, Ireland	2006	0/5 composite samples of 3 individual milk samples each	0.2	n.d.	Grümping et al. 2007

Item Sampled	Sampling Period	No. of Samples	Detection Limit (µg/kg lipid)	Mean Concentration (µg/kg lipid)	Reference
Whole fish, fish muscle, Norway	2003	16	n.s.	[n.d.-9.0] (n.d.-9.0 ng/g lipid)	Fjeld et al. 2004
Cod liver, Norway	2003	6	n.s.	n.d. – 3.0 (n.d.-3.0 ng/g lipid)	Fjeld et al. 2004
121 Food categories, UK	2001	0/n.s., but expected to be hundreds	1.4 to 30	n.d.	Food Standards Agency 2004
Eel, hatched and imported	2002	3	0.1 ng/g wet wt	0.2-3.4 ng/g wet wt	de Winter-Sorkina et al. 2003
Herring	2001	2	0.12 ng/g wet wt	nd and 0.6 ng/g wet wt	de Winter-Sorkina et al. 2003
Whiting fish, North Sea	1999	3	0.5	136 [<0.97 -245]	Morris et al. 2004
Eel, rivers in Netherlands	1999	11	0.5	0.3 [<0.1-1.3]	Morris et al. 2004
Eel, Scheldt basin, Belgium	2000	19	0.5	1.6 [<0.1-13]	Morris et al. 2004
Harbour porpoise blubber, North Sea	n.s.	4	0.5	<11	Morris et al. 2004
Harbour porpoise blubber, UK	1998	5	0.5	83 [0.1-418]	Morris et al. 2004
Blue mussel, Norway	2002	6	n.s.	0.021 ng/g wet wt 0.01-0.03 ng/g wet wt	Schlabach et al. 2002
Cod liver, Norway	2002	6	n.s.	0.11 ng/g wet wt 0.08-0.16 ng/g wet wt	Schlabach et al. 2002
Fish, 24 areas in Japan	1987 – 2000	0/237	1 and 20,000 (0.001 and 20 µg/g)	n.d.	MOE Japan 2003
Hard cheese	2002	2	0.1 ng/g cheese	0.06 and 0.09 ng/g cheese	de Winter-Sorkina et al. 2003
Cow's milk from Oslo, Norway	2001	1	5×10^{-4} (0.5 pg/g milk)	0.013 (13 pg/g)	Thomsen et al. 2002a

Item Sampled	Sampling Period	No. of Samples	Detection Limit (µg/kg lipid)	Mean Concentration (µg/kg lipid)	Reference
Porpoises, multiple locations, UK	1999-2001	4/8	1.1 µg/kg wet weight	(n.d. – 376 µg/kg wet weight)	Law et al. 2003
Freshwater fish, Germany	1998-1999	2	8.5 pg/µl for diacetyl TBBPA	0.91 and 1.12 (0.91 and 1.12 ng/g)	Kemmlein 2000
Eel, Germany	1998-1999	2/8	8.5 pg/µl for diacetyl TBBPA	0.47 and 0.78 (0.47 and 0.78 ng/g)	Kemmlein 2000

[1] Values in brackets indicate range of concentrations when available
n.s. = not specified
n.d. = not detected

Appendix 7: TBBPA Levels in Human Milk

Location	Sampling Period	No. of Samples	Detection Limit	Mean concentration (ng/g lipid)	Reference
Boston, MA (USA)	2004-2005	43	LOQ 30 pg/g lipid weight	Not reported due to low detection frequency	Carginan et al. 2012
China	2007	24 pooled	n.s	[<LOD-5.1] Levels in 75% of samples were < 1 ng/g lw	Shi et al. 2009b
France	2004-2006	34/77	LOQ <0.05	4.1 [0.06-37.3]	Cariou et al. 2008
France, mother/newborn dyads	2005	23	n.s.	0.17 (median) 0.03-9.4	Antignac et al. 2006
Pooled samples, Norway	2001	1	5×10^{-4}	0.067 (67 pg/g lipid)	Thomsen et al. 2002a
Pooled and single samples, Germany	1998-1999	2/10	8.5 pg/µl for diacetyl TBBPA	[0.29 -0.94]	Kemmlein 2000
Pooled samples, Germany	Archived 1990	0/5	8.5 pg/µl for diacetyl TBBPA	n.d.	Kemmlein 2000
Single sample, Faroe Islands, Denmark	Archived 1990	1	8.5 pg/µl for diacetyl TBBPA	11.0 ng/g lipid	Kemmlein 2000

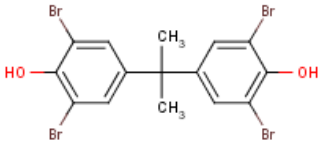
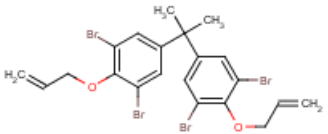
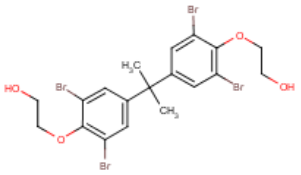
Appendix 8. TBBPA Levels in Human Serum and Adipose Tissue

TBBPA in Human Blood					
Location	**Sampling Period**	**No. of Samples**	**Detection Limit**	**Mean concentration (ng/g lipid)**	**Reference**
Belgium	2008-2-11	515	0.015 ng/ml	Mean: <LOQ P95: 0.022 ng/ml Max: 0.186 ng/ml	Kiciński et al. 2012
Alberta's Biomonitoring Program	Jan-Dec 2005	0/50,599	0.03 ng/g serum	n.d.	Alberta Health and Wellness 2008
Canadian Arctic, Nunavik (Northern Quebec)	Aug. to Oct. 2004	771	0.01 ng/ml	< 0.01-0.48 ng/mL	Dallaire et al. 2009[2]
Belgium	7 in 2007, 14 pooled samples in 1999	7 14	0.05 ng/ml	0.08 +/-0.02 ng/mL 0.09+/-0.03 ng/mL	Dirtu et al. 2008[2]
France, Mothers	2004-2006	29/91	<0.05	19.9 +/-24.15 (0.23-93.22)	Cariou et al. 2008
France, Newborns	2004-2006	27/90	<0.05	103.5+/-149.73 (2.1- 649.45)	Cariou et al. 2008
France n=26 mother/newborn dyads	2005	26	n.s.	maternal serum mean=0.054) 30.4 ng/g lipid (cord serum mean= 0.152)	Antignac et al. 2006
Members of European Parliament	2003	27/40 samples	n.s.	0.33 ng/g whole blood (n.d. -330 pg/g whole blood)	WWF 2004
Computer technicians Sweden	1999	8/10	n.s.	[<0.54-1.8] (<1-3.4 pmol/g lipid)	Jakobsson et al. 2002
Pooled samples, Norwegian men, aged 40-50 yrs	1977-1999	6	LOQ: 0.0004 ng/g plasma	[n.d. – 0.65]	Thomsen et al. 2002b
Pooled samples, Norwegians aged birth to >60 yrs	1998	8	LOQ: 0.0004 ng/g plasma	[0.31 - 0.71]	Thomsen et al. 2002b
Electronics dismantlers, Norway	n.s.	39	0.0004 ng/g plasma	1.3 [0.64 - 1.8]	Thomsen et al. 2001

TBBPA in Human Blood					
Location	**Sampling Period**	**No. of Samples**	**Detection Limit**	**Mean concentration (ng/g lipid)**	**Reference**
Circuit board producers, Norway	n.s.	50	LOQ: 0.0004 ng/g serum	0.54 [n.d. – 0.80]	Thomsen et al. 2001
Laboratory personnel	n.s.	46	0.08 ng/g lipid (LOQ: 0.0004 ng/g serum)	0.34 [n.d. – 0.52] [1]	Thomsen et al, 2001
Electronics dismantlers, Sweden	1998	4	n.s.	[0.41-1.3] (2.2 -7 pmol/g lipid)	Hagmar et al. 2000
Japanese men and women, aged 37- 49 yrs	1998	8/14	n.s.	median: 0.92 (920 pg/g lipid) [n.d. – 3.7] (n.d. – 3,700 pg/g lipid)	Nagayama et al. 2000
Adipose Tissue					
France n=26 mother/newborn dyads	2005	0/26	n.s.	n.d.	Antignac et al. 2006
France	2004-2006	0/44	<0.05	n.d.	Cariou et al. 2008
U.S.A. New York	2003-2004	14/20	0.0033	0.048 +/- 0.102 ng/g l.wt [<0.0033 – 0.464]	Johnson-Restrepo et al. 2008

[1] Values in brackets indicate range of concentrations when available
n.s. = not specified
n.d. = not detected
[2] These results are not converted to a lipid basis.

Appendix 9. Summary of health effects information for TBBPA and Derivatives

Endpoint	Lowest Effect Levels		
	TBBPA **(CAS RN 79-94-7)**	**TBBPA bis(allyl ether)** TBBPA diallyl ether **(CAS RN 25327-89-3)**	**TBBPA bis (2-hyrdoxyethyl ether)** TBBPA ethoxylated **(CAS RN 4162-45-2)**
% Similarity (ChemID)	100%	75%	80%
Structure			
Acute toxicity	**LD50 (oral, rat)** > 50 000 mg/kg bw (International Bio-Research. Inc. 1967). **LD50 (oral, mouse) =** 3200 mg/kg (Gustafsson and Wallen 1988) **LC50 (inhalation, rat)** > 10,920 mg/m^3 after 4 hr (Velsicol Chemical Corporation 1978e) (Decreased motor activity, eye squint, slight dyspnea and erythema). **LC50 (inhalation, mouse)** > 50 mg/L (50 000 mg//m^3) after 8 hr with no signs of toxicity (Great Lakes Chemical Corp 1967a). **LD50 (dermal, rabbit)** > 10 000 mg/kg bw (Hill Top Research, Inc. 1966).	**LD50 (oral, rat)** > 5000 mg/kg bw (Abbott et al. 1981). **LD50 (dermal, rabbit)** > 2000 mg/kg (Abbott et al. 1981). Slight to moderate erythema and edema. The skin reaction decreased in severity and area over time. No gross pathological findings were observed.	**LD50 (oral, rat)** > 5000 mg/kg bw (Goldenthal and Dean 1974a) **LC50 (inhalation, rat)** > 12.5 mg/L (12500 mg/m^3) (Goldenthal and Dean 1974a) **LD50 (dermal, rabbit)** > 2000 mg/kg (Goldenthal and Dean 1974a)

Short-term Toxicity	**Lowest oral LOAEL = 700 mg/kg-bw per day** based on slight enlargement of hepatocytes, inflammatory cell infiltration and focal necrosis of hepatocytes at this dose and higher (Tada et al. 2007). Male ICR mice were administered 0, 350, 700 or 1400 mg/kg-bw per day TBBPA via gavage for 14 consecutive days. Absolute and relative liver weight was significantly increased at the highest dose. **Other oral NOAEL (rats, 28 days)** = 250 mg/kg-bw per day. A gavage study with Wistar rats showed no significant hepatic effects in the liver (Szymańska et al. 2000). The EU RAR (2006) noted that most of the few repeated-dose studies by oral exposure were limited or poorly reported (IRDC 1972; Sato et al. 1996; Szymańska 1995; Frydrych and Szymańska 2001). More recent studies by Germer et al. (2006) reported no effects upon hepatic mRNA or microsomes in Wister rats when exposed to dietary concentrations equivalent to intakes of 0, 30, 100 or 300 mg/kg-bw per day for 28 days. **Lowest inhalation LOAEC (rats, 14 days)** = 18 000 mg/m^3 based on observations of local irritation in the upper respiratory tract (IRDC 1975). There were no toxicologically significant systemic effects (IRDC 1975). **Lowest dermal NOAEL (rabbits, 3 weeks)** = 2500 mg/kg-bw per day. No adverse effects were observed (IRDC 1979).	No studies identified.	**Lowest oral LOAEL** = 1000 mg/kg/day based on increased bromine content in the liver. CD Rats (10/sex/group) were fed a diet containing 0, 100, or 1000 mg TBBPA bis (2-hydroxyethyl ether)/kg for 28 days. No changes in organ weights, pathological lesions, or histopathological changes were observed in liver, kidney, or thyroid of any animal (Goldenthal and Geil 1974b).

Sub-chronic toxicity	**Lowest oral NOAEL (rats, 90 days)** = 100 mg/kg bw per day (The Dow Chemical Company 1975). No gross or histopathological lesions were observed in rats exposed by diet to 0, 0.3, 3, 30 or 100 mg/kg-bw per day for 90 days. **Other oral NOAEL (rats, 90 days)** = 1000 mg/kg-bw per day (MPI Research 2002a). In a 13-week gavage study, rats were exposed to 0, 100, 300 or 1000 mg/kg-bw per day. There were no effects observed in either the functional observational battery or motor activity tests, no adverse histopathological changes in liver, thyroid, parathyroid or pituitary and no changes in serum levels of T3 or TSH. Although there was a significant decrease in serum T4 in both sexes, in the absence of any other relevant thyroid-related effects, this was not considered adverse.	No studies identified.	No studies identified.
Chronic toxicity/ carcinogenicity	No studies identified.	No studies identified.	No studies identified.
Genotoxicity and related endpoints: *in vitro*	**Negative**: *S.typhimurium* strains (TA1535, TA 1537, TA1538, TA92 TA98, TA100) 0 to 10,000 µg/plate with and without metabolic activation (Litton Bionetics Inc 1976; Velsicol Chemical Corporation 1978a; Israel Institute for Biological Research 1978; Ethyl Corporation 1981; The Dow Chemical Company 1985; Mortelmans et al. 1986; Great Lakes Chemical Corporation 1986). **Negative**: in Yeast strains *Saccharomyces cerevisiae* D3 and D4 at TBBPA concentrations of 0 to 500 µg/plate with or without metabolic activation (Velsicol Chemical Corporation 1978a; The Dow Chemical Company 1985).	**Negative:** *Salmonella and Saccharomyces* at 0.1 to 500 µg BE-51 applied per plate with and without metabolic activation (Brusick 1977).	**Negative**: *S.typhimurium* strains (TA1535, TA 1537, TA1538, TA98, TA100) 0 to 1000 µg/plate with and without metabolic activation (Jagannath and Brusick 1979).

Genotoxicity: ***in vivo***	No studies identified.	No studies identified.	No studies identified.
Developmental/ Reproductive toxicity (post 2006)	**Lowest oral LO(A)EL (mice) = 140.5-379.9 mg/kg-bw per day** based upon enlargement of hepatocytes, very slight focal necrosis of hepatocytes, and decreased serum triglyceride (quantitative data not presented) levels in female offspring at this dose (Tada et al. 2006). There was also an increase in total serum cholesterol (quantitative data not presented) in male offspring at this dose. Pregnant ICR mice fed a diet of 0%, 0.01%, 0.1%, or 1.0% TBBPA (0, 15.7-42.1, 140.5-379.9, or 1639.7-4155.9 mg/kg bw) from GD 0 to weaning at PND 27. Serum concentrations of total-cholesterol and triglycerides were also affected in dams and offspring. No effects upon litter size, litter weight, total number of offspring male or female offspring weight. **The lowest benchmark dose, BMDL** = 0.5 mg/kg-bw per day for increased F1 testis weight (critical effect dose of 1.4 mg/kg-bw per day) and increased F1 male pituitary weight (critical effect dose, 2.2 mg/kg-bw per day; BMDL, 0.6 mg/kg-bw per day). Wistar rats were administered TBBPA with calculated intakes of 0, 3, 10, 30, 100, 300, 1000 or 3000 mg/kg-bw per day in diet for 70 days (male) or 14 days (female) prior to mating and continuing during mating and throughout gestation and lactation (van der Ven et al. 2008; Lilienthal et al. 2008). There were no effects upon endpoints of reproduction. Other effects noted included delayed sexual development in females, and effects upon brainstem auditory evoked potentials. There were no exposure-related histopathological changes in the organs of the F1 animals. There were no effects upon sperm counts or morphology. There was no effect upon the immunisation response against sheep red blood cells in F1 males. Another "major effect" was the developmentally induced increase of hearing latency at low frequency, with BMDLs of 7.8 and 8.4 mg/kg-bw per day for males and females, respectively**. It is noted that concerns have been**	No studies identified.	No studies identified.

	published concerning the methodology employed in this assay (Banasik et al. 2009; Strain et al. 2009; Lilienthal et al. 2009; van der Ven et al. 2009). A previous study was performed on male Wistar rats which were administered TBBPA with calculated intakes of 0, 30, 100, or 300 mg/kg-bw per day in diet for 28 days. The only effects were a decrease in circulating T4 and increased T3 levels in male rats. **Lowest oral LOAEL (rats) = 200 mg/kg bw per day** based on polycystic lesions associated with the dilation of the tubules in the kidneys of 2 of 6 males at this dose (Fukuda et al. 2004). Newborn rats were dosed by gavage from days 4 to 21 after birth, at doses of 0, 40, 200 or 600 mg/kg-bw per day. Effects on the kidney were observed at the two highest doses. Diarrhea observed in some male and some females treated with 200 and 600 mg/kg bw. In the same study, five-week old rats were dosed at levels of 0, 2000 or 6000 mg/kg-bw per day for 18 days. No similar histopathological renal effects were observed. The EU RAR (2006) selected the NOAEL of 40 mg/kg bw per day for the purpose of risk characterization. However, it is considered that the effect on the kidneys is the result of "unconventional direct gavage administration of very high doses of TBBPA to such young animals and the immature metabolic capability and/or immature kidneys. Therefore, the relevance to human health of this isolated finding is considered questionable". **Other oral LOEL** = 100 mg/kg-bw per day based on a decrease in serum T4 levels in F0 and F1 offspring at this does and higher (MPI Research 2002b, 2003). Sprague Dawley rats were administered 0, 100, 200 or 1000 mg/kg-bw per day gavage for 10 weeks premating, 2 weeks mating and for females, throughout gestation and lactation. Serum T3 levels decreased significantly in F0 males in the 1000 mg/kg-bw dose group. No effects in either the F1 or F2 pups with regard to body weight, clinical findings, sex ratios, survival to weaning, macroscopic findings or organ weights. It was concluded that the effects in T3 and T4 levels were not toxicologically significant, as there was little impact on other parameters (MPI Research 2002b, 2003). **Other oral LOEL** = 818.9-2129.2 mg/kg-bw per day based on decreased relative uterine weight in female offspring at post-natal week 11 at this		

	dose (Saegusa et al. 2009). No other histopathological changes were observed in the uterus or any other organs examined. Pregnant Sprague-Dawley rats were exposed to dietary levels of 0, 100 ppm (9.5 – 22.9 mg/kg-bw per day), 1000 ppm (86.8 – 202.1 mg/kg-bw per day) or 10,000 ppm (818.9 – 2129.2 mg/kg-bw per day) from gestational day 10 to post natal day 20 after delivery (weaning). TBBPA did not alter normal brain development. Relative kidney weights decreased significantly at 1000 ppm dose level, but not at the higher dose in female offspring. There were no significant dose-related effects on T3, T4 or TSH. No effects upon number of implantation sites, number of live offspring or sex ratio (Saegusa et al. 2009). A prepubertal exposure study examined the effects of TBBPA on susceptibility to thyroid tumours induced by a further exposure to DHPN or DMBA in Fisher 344 rats. Although the results of a complex exposure scenario are not taken into consideration in the assessment of TBBPA alone, the initial administration of 1% (1249 mg/kg-bw) TBBPA to dams from parturition to weaning (3 weeks) showed a statistically significant increase in thyroid weights and a decrease in relative liver weights (Imai et al. 2009). However, no histopathological changes were found in the liver and only one dam in 6 had diffuse follicular cell hyperplasia in the thyroid. No developmental or neurotoxicological effects were observed at doses up to 10,000 mg/kg-bw per day and 1000 mg/kg bw per day, respectively in various studies (Velsicol Chemical Corporation 1978c; Noda et al. 1985; Eriksson et al. 1998, 2001; MPI Research 2001, 2002b, 2003; Hass et al. 2003).		

Neurotoxicity *in vivo*	**Acute oral LOEL** = 11.5 mg/kg bw based on a decrease in binding sites of the nicotinic ligand cytisine in frontal cortex, but not in the parietal cortex or hippocampus in male neonate mice. Male NMRI mice (n=6-8) were given 11.5 mg TBBPA/kg bw (21 µmol) or 20% fat-emulsion vehicle/kg bw on PND 10 via a metal gastric-tube, as one single oral dose. The animals were killed 7 days after treatment and protein levels of CaMKII, GAP-43, synaptophysin and tau in hippocampus and cortex were measured using slot-blot analysis. [^{3}H]-QNB binding (all subtypes of muscarinic receptors), [^{3}H]-AFDX 384 binding (M2/M4 muscarinic receptors) and [^{3}H]-cytisine binding (α4β2 nicotinic receptors) were assessed in the hippocampus, parietal and frontal cortex. The statistical evaluation was made using one-way ANOVA and pairwise testing using Newman–Keul's post hoc test. TBBPA did not appear to affect the levels of proteins involved in maturation of the brain, neuronal growth or synaptogenesis in neonate mice. However, there was a decrease in binding sites of the nicotinic ligand cytisine in frontal cortex, (35.9 ± 10.4 pmol/g protein compared to 47.2 ± 7.7 pmol/g protein in controls), but not in the parietal cortex or hippocampus (Viberg and Eriksson 2011). **Oral LOEL** = 86.8-202.1 mg/kg bw/day based on a transient increase in reelin-expressing interneurons in the dentate hilus at this dose and above in offspring at PND 20, but not at PND 77.	No studies identified.	No studies identified.

	Pregnant Sprague–Dawley rats (n = 8/group) were exposed to 0, 100, 1000, or 10 000 ppm (0, 9.5 – 22.9, 86.8 – 202.1, 818.9 – 2129.2 mg/kg-bw per day) TBBPA in the diet from GD 10 through to day 20 after delivery (PND77). No major treatment-related changes were observed in dams during gestation and lactation. There were no dose-related changes in thyroid serum levels (See reproductive/developmental section above; Saegusa et al. 2009) and no effects on organ to body weight changes in the brain or the thyroid of offspring. A slight increase in apoptotic bodies in offspring (n ~ 20/sex/group) was observed at 818.9 – 2129.2 mg/kg-bw per day at PND 20, but this effect appeared reversible as there were very few apoptotic bodies at PND 77. An increase in reelin-expressing interneurons in the dentate hilus was observed at the mid and high doses of TBBPA, but again, these effects returned to control levels at PND77. There was an excess of mature neurons in the hilus later stages, but these effects were reversible. No changes were observed in the number of GAD67- immunoreactive cells in the highest dose groups compared with the untreated controls at both PND 20 and PND 77 nor any changes in EphA5- and Tacr3-immunoreactive cells in the hippocampal CA1 region (Saegusa et al. 2012). Behavioural changes were observed in the two lowest dose groups of exposed male mice to 0, 0.1, 5 or 250 mg/kg-bw once by gavage, but were not considered to be treatment related. It is noted that the authors proposed that a compensation mechanism may account for the lack of a dose-response relationship (Nakajima et al. 2009).		

Neurotoxicity *in vitro*	**Cytotoxicity**: TBBPA appeared to be cytotoxic at low micromolar concentrations (LC_{50} = 15 ± 4 µM) on SH-SY5Y human neuroblastoma cells, however the authors stated that it is unclear from this study if these results showed that TBBPA is neurotoxic (Al-Mousa and Michelangeli 2012). TBBPA caused activation of caspases (3/7) after the cells were exposed to TBBPA for 12 hours at a 1 to 5 µM concentration range. There was also a transient increase in intracellular [Ca2+] levels and reactive-oxygen-species (ROS) within these neuronal cells. Furthermore, TBBPA also caused rapid depolarization of the mitochondria and cytochrome c release in these neuronal cells (at 10 µM). Application of 3 and 10 µM of TBBPA for 12hrs caused increased b-amyloid peptide (Ab-42) processing and release from these cells with a few hours of exposure (Al-Mousa and Michelangeli 2012). TBBPA was also found to be acutely cytotoxic in primary cultures of rat cerebellar granule cells after 30 minute exposures to 10-50 µM of TBBPA (significant at 25 uM). According to the authors, TBBPA also induced an increase in intracellular Ca^{2+} concentrations, depolarization of mitochondria, and activation of ROS production (Ziemińska et al. 2012).	**Cytotoxicity**: Environmental fractions of TBBPA bis(allyl ether) induced high cytotoxicity in neuronal cells of primary cultured cerebellar granule cells from 7 day old Sprague Dawley pups. Neurotoxicity was measured as cell viability compared to the positive control of paraquat. Liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOFMS) and gas chromatography coupled electron capture negative ionization mass spectrometry (GC-ECNI-MS) was optimized to confirm TBBPA bis(allyl ether) as the key neurotoxicant. Human liver carcinoma Hep G2, human breast cancer MCF-7, and mouse leukemic monocyte macrophage RAW 264.7 cell lines were also used to investigate the non-neurotoxic potencies. Results showed that none of the sediment fractions or pure TBBPA bis(allyl ether) standard significantly affected the activity of these cell lines (For details see Qu et al. 2011).	No studies identified.

Endocrine effects *in vivo* (post 2006)	Kitamura et al. (2005b) exposed ovariectomized B6C3F1 mice to 0, 20, 100, 300 and 500 mg/kg bw of TBBPA by *ip* injection for three days. Although the uterus to body weight ratio was significantly increased in all exposed groups, there was a poor dose-response. **Other oral LOEL**: 150 mg/kg bw/day based on a decrease in T3-independent transcription activation of both *Trh* and *Mc4r* promoter genes in the hypothalamus of offspring on PND 2 (n > 10/group). Pregnant Swiss wild-type mice (n > 10/group) were administered 150 mg/kg bw of TBBPA daily via oral gavage from day 13 post conception for 7 days. The activity of *Trh* and *Mc4r* promoters was measured in the pup hypothalami using a reporter gene assay and TBBPA significantly reduced ($P < 0.001$) T3-independent transcription from both *Mc4r* and *Trh* reporter constructs in pups. When pups were administered TBBPA in acute doses with one or two 2.1 g/kg injections of TBBPA, opposite effects were observed on T3-independent transcriptional activity of both promoters. In protocol no. 1, a single injection 48 h before sacrifice decreased Mc4r and Trh transcription in absence of T3 by 32.4% and 33.6% respectively. In contrast, administering TBBPA injections 48 and 24 h before sacrifice significantly increased transcription from both promoters: 28.7% and 37.5% for *Mc4r* and *Trh* constructs, respectively (Decherf et al. 2010).	No studies identified.	No studies identified.

	Other oral NOEL: 1000 mg/kg bw/day based on the lack of change in uterine weight in adult female mice. TBBPA was administered daily via oral gavage and subcutaneous injection for 7 days using C57BL/6J ovariectomized adult female mice (n = 6) in accordance with OECD Test Guideline No. 440. For detection of agonistic activity, control, 4 doses at a half-log ratio, and EE as a positive control were tested. For antagonistic activity, a control and the same 4 doses were administered with a reference dose of EE. The LOEL was defined as the lowest dose that induced significant change in uterine weight. Results from this study showed that TBBPA was negative for agonistic and antagonistic estrogenic responses by both routes of exposure using concentrations up to 1000 mg/kg bw/day (Ohta et al 2012).		

Endocrine effects *in vitro* (post 2006)	**Strong PR antagonist/Weak ERα agonist**: Li et al. (2010) measured ER and PR-mediated transcription of β-galactosidase *in vitro* in reporter yeasts. TBBPA also exhibited the ability to reverse the estrogen-related receptor (ERR) inhibition induced by 4-hydrooxytamoxifen. Yeast strains were tested with increasing concentrations of TBBPA (1×10^{-9} to 1×10^{-4} mol per L) for 2hrs. Estrogenic activity of TBBPA was evident using ERE-luciferase reporter assay in MCF-7 breast cancer cells at $1x10^{-6}$ to $1x10^{-4}$ M. Anti-estrogenic acitivty was also measured in an E2 assay sysem in MCF-7 cells at $1x10^{-5}$ M (Kitamura et al. 2005b). **Negative PR antagonist/ Negative ER agonist**: No detectable antiprogestagenic or ER agonistic potency was measured in ER- and PR-CALUX assays in human breast cancer (ER) and human osteoblast (PR) cells at 10 and 12.5 μM concentrations, respectively (Hamers et al. 2006). No ER agonistic/antagonistic effects were found by Riu et al. (2011) using HGELN, HGELN-ERα, HGELN-ERβ reporter cell lines (10^{-9} to 10^{-5} M). No effect was observed on cell growth in an E-screen assay in MCF-7 breast cancer cells even at a maximum concentration of 20 μM TBBPA did not induce estrogen receptor-mediated TFFl gene expression *in vitro* (Dorosh et al. 2010). TBBPA did not show any estrogenic activity at the estrogen receptor alpha (ERα) ligand at concentrations between 10^{-10} and 10^{-5} M in an OECD guideline stably transfected transcriptional activation (STTA) assay (Lee et al. 2012).		

	Positive Inhibitor of E2 Sulfation: Hamers et al. (2006) reported that TBBPA was a potent inhibitor of E_2 (estradiol) sulfation (IC = 0.016 uM) in an E2SULT assay. **Positive competitor of T4 binding to TTR**: TBBPA was a potent T4 competitor in a TTR-binding assay (IC_{50} < 0.1 μM) with a 1.6 times higher TTR-binding potency than the natural ligand T4 (Hamers et al. 2006). **Conflicting Thyroid Hormone agonist/antagonist**: An increase in growth hormone-releasing activity was observed from GH3 cells after addition of TBBPA at $1x10^{-6}$ to $1x10^{-4}$ M (Kitamura et al. 2005b). No antagonistic activity was found. Further work using GH3 cells (GH3.TRE-Luc) has shown that TBBPA acts as a very weak agonist (5% of T_3-max) up to a concentration of 1 μM, but a slight antagonist at concentrations above 5 μM in the presence of 0.25 nM of T_3 after only 24 hours of exposure (Freitas et al. 2010).		

	Administration of 25 μM TBBPA significantly suppressed TRβ activity (IC_{50} of 2.95 x 10^{-5} M). Authors developed a TRβ-1 mediated reporter gene assay by transiently transfecting Gal4-fused thyroid hormone receptor (TR) expressing vector and the Gal4 response reporter structure pUAS-tk-luc into HepG2 cells (1, 10, 25, 50 and 100 μM). When treated alone, TBBPA could not induce the expression of luciferase which indicated that it could not activate TR (Sun et al. 2009). Another TH-responsive luciferase–based reporter gene assay using the human hepatocarcinoma cell line HepG2 showed that TBBPA displayed agonistic effects at 10 μM, but was antagonistic when coincubated with T3 at 1 μM (concentrations ranged from 10^{-4} to 10 μM for 24 h; Hofman et al. 2009). TBBPA bound to the human TRα-LBD, activating transcription when applied alone (without T3) at 3 and 10μM. Further, TBBPA displaced physiological concentrations of T3 from TRα binding in HeLA cells using a reporter system based on fusion of the ligand-binding domain (LBD) from TRα to a GAL4 DNA–binding domain at 10 μM (Fini et al. 2012). TBBPA prevented binding (or induced dissociation) of NcoRp, but failed to promote SRC2p binding, and even inhibited T3-induced SRC2p binding in a coactivator/corepressor peptide binding assay. Increasing concentrations (2–50 μM) of TBBPA were incubated with GST-LBD and FITC-labeled corepressor peptide (NcoRp) or coactivator peptide (SRC2p) in the presence and absence of T3 (cell-free) (Lévy-Bimbot et al. 2012).		

	At concentrations as high as 10 μM, TBBPA did not affect transcriptional activities of TRα and TRβ in any of the species studied (three frog species (*Xenopus laevis, Silurana tropicalis* and *Rana rugosa*), a fish (*Oryzias latipes*), an alligator (*Alligatormississippiensis*) and human (*Homo sapiens*). In order to examine whether T3-stimulated activity was inhibited by TBBPA, T3 was added at a concentration that generated an EC_{50} value for each receptor type (TRα: $4x10^{-10}$ M and TRb: $2x10^{-9}$ M). Results indicated that TBBPA inhibited T3-stimulated activation of TRα and TRβ from *S. tropicalis* and human cells at concentrations higher than 10 μM (however, the cell viability after treatment with TBBPA was compromised at doses higher than 10 μM). Therefore, TBBPA can be evaluated at this concentration or less in this assay, which showed no effects on activity in human cells *in vitro*. Using this approach, authors noted that T3-induced transactivity of the *O. latipes* TRα was inhibited by 10 μM TBBPA, but this compound at this concentration did not antagonize TRβ activity (Oka et al. 2012). **Deiodinase Inhibition:** Almost complete inhibition of DI activity was observed at the highest dose tested (2.1μM) for TBBPA. A dose-response relationship was shown for TBBPA in inhibition of the formation of rT3 from T4. Inhibition of 3,3'-T2 formation was also observed at 1.9 μM. Thyroxine (T4) and reverse triiodothyronine (rT3) deiodination kinetics were measured by incubating pooled human liver microsomes with T4 or rT3 and monitoring the production of T3, rT3, 3,3'-diiodothyronine, and 3-monoiodothyronine by liquid chromatography tandem mass spectrometry (Butt et al. 2011).		

	Equivocal AR antagonist: Weak antiandrogenic activity in MDA-kb2 cells *in vitro* between 10 and 50 μM for 24 hrs followed by a luciferase assay (Christen et al. 2010). Li et al. (2010) and Hamers et al. (2006) did not find any effect on AR activity in yeast cells (concentration not listed) or in human osteoblast cells at 10 μM concentrations using an AR-CALUX assay, respectively, after administration of TBBPA. No antiandrogenic activity was found in an AR responsive luciferase reporter gene system in NIH3T3 cells at $1x10^{-11}$ to $1x10^{-9}$ M concentration range (Kitamura et al. 2005b). **Negative aromatase activity**: TBBPA did not inhibit or induce aromatase (CYP19) activity and was not cytotoxic at concentrations of 2.5 μM and 7.5 μM in H295R human adrenocortical carcinoma cells after 24 hr incubation (Cantón et al. 2005).		

Sensitization	The EU RAR (2006) concluded that TBBPA is neither a skin nor a respiratory sensitizer.	No studies identified.	No studies identified.
Irritation	**Not irritating**: In skin (Hill Top Research 1966; Pharmakon Laboratories 1981a; Israel Institute for Biological Research 1978; IRDC 1979; EU RAR 2006) or eyes (Pharmakon Laboratories 1981b; Israel Institute for Biological Research 1978; Hill Top Research 1966; EU RAR 2006).	**Mildly irritating**: In eyes and skin of New Zealand Albino rabbits after applications of 100 mg and 500 mg of BE-51, respectively (Abbott et al. 1981).	**Not irritating**: In eyes or skin of New Zealand Albino rabbits after applications of 100 mg and 500 mg of TBBPA bis (2-hydroxyethyl ether), respectively (Goldenthal and Dean 1974a).
Special Studies	**Immunotoxicity *in vitro*:** Exposure of 0 to 10 µM of TBBPA to human natural killer cells decreases the lytic function at concentrations as low as 0.5 µM after 24 hrs exposure and 1.0 µM after 1 hr exposure to TBBPA (Kibakaya et al. 2009). A follow up study showed that the expression of cell-surface proteins CD2, CD11a, CD16, CD18 needed for attachment of NK cells to target cells was decreased after exposure to 5 µM TBBPA for 24 hr (Hurd and Whalen 2011). NK cells were exposed to TBBPA (0, 1, 2.5, 5 and 10 µM) for 24h, 48h, and 6 days or for 1 hr followed by 24h, 48 hr, and 6 days without TBBPA. Each experiment was completed four times using cells prepared from different blood donors. CD16 expression was decreased by >35%, CD11a by 16%, and CD18 and CD56 by ~ 20%. Expression of CD18 was also decreased (14%) at 2.5 µM. Cell viability was compromised at 10 µM TBBPA (at all timepoints) and at 5 µM after 48 hrs and not evaluated. Expression of CD16 and CD56 proteins were similar at 24 and 48 hrs at 2.5 µM (Hurd and Whalen 2011). Han et al. (2009) reported that exposure to TBBPA (0- 50 µM) induced COX-2 transcription and proinflammatory cytokine expression through the P13-K/Akt/MAPK signalling pathway mediated via increased NF-κB and AP-1 activation in murine macrophages *in vitro*.	**Immunotoxicity *in vitro*:** Mice splenocytes incubated with a TBBPA allyl ether (10 µmol/L) exhibited significantly reduced expression of the interleukin-2 receptor α chain (CD25), an antigen necessary for the production of activated T cells during an immune response (Pullen et al. 2003).	

	Exposure of 2 uM and higher concentrations of TBBPA to human neutrophil granulocytes enhanced reactive oxygen species (ROS) production in a concentration dependent manner (Reistad et al. 2005). Mice splenocytes incubated with a TBBPA (3 μmol/L) exhibited significantly reduced expression of the interleukin-2 receptor α chain (CD25), an antigen necessary for the production of activated T cells during an immune response (Pullen et al. 2003). TBBPA showed no cytotoxic effect on either splenocytes or bone marrow-derived dendritic cells (BMDCs) from atopic prone NC/Nga mice. After exposure to TBBPA, cell surface molecule expression and cytokine production was measured using WST-1 assay, FACS and ELISA (three individual cultures obtained from three animals and two or three independent experiments were repeated). Spenocytes were exposed to 0.01–10 μg/ml TBBPA for 24 hrs and BM cells were exposed to 0.001 – 1 μM TBBPA for 6 days and BMDCs were collected. TBBPA did increase MHC class II and CD86 expression, and T-cell receptor (TCR) expression in splenocytes (1 and 10 μg/ml) and increased interleukin (IL)-4 production (but a chemical-dependent impact pattern was observed). There was no effect on expression of MHC class II, CD80, CD86, CD11c and DEC205) and chemokine production after 24-h exposureafter TBBPA exposure in BMDCs (Koike et al. 2012). **Immunotoxicity *in vivo*:** Exposure in mice to 1% TBBPA in the diet for 28 days (1887 mg/kg-bw per day) demonstrated that host immunity to respiratory syncytial virus was affected in lung and BALF samples while systemic immunity was not affected when spleen samples were examined (Watanabe et al. 2010).		

	Hepatoxicity *in vitro*: TBBPA competitively inhibited the binding of [3H]-rosiglitazone to PPARγ with a half maximal inhibitory concentration (IC_{50}) of 0.7 μM. HeLa cells transiently transfected with (GALRE)5-βglobin-luciferase and pSG5-GAL4-PPARγ (human and zebrafish) or (PPRE)3-TK-luciferase and pSG5-PPARγ (*Xenopus laevis*) plasmids were incubated with 10 μM TBBPA or 1 μM rosiglitazone (Rosi) to assess their agonist potential on PPARγ. The binding affinities to PPARγ by competitive binding assays with [^{3}H]-rosiglitazone were measured (0.001–30 μM) and the impact of TBBPA on adipocyte differentiation using NIH3T3-L1 cells was investigated. At 10 μM, TBBPA also induced adipogenesis, whereas co-treatment with CD5477 inhibited the adipogenic action of TBBPA, indicating that TBBPA mediates adipogenesis via PPARγ (Riu et al 2011). Alternatively, when the ability of TBBPA was tested to activate human PXR or mouse PXR using a transfection assay, results were negative (Siu et al. 2012). HepG2 cells were transfected with either full-length hPXR together with CYP3A4-luc reporter or full-length mPXR together with (CYP3A2)3-luc reporter and CMX-ß-galactosidase control plasmid. Cells were treated with DMSO (control) or TBBPA for 24 h at 0-20 μM concentrattions.		

Human Studies			
Sensitization/ Irritation	Not sensitizing: TBBPA did not result in skin sensitization with humans in a multiple insult test after approximately 3 to 5 mg of TBBPA (50-70% concentration) was applied to 54 volunteers (IRDC 1978).	No studies identified.	No studies identified.
Toxicokinetics	Blood serum levels ranged from >0.5 to 3.8 µg/kg lipid in various occupational groups in several studies in Sweden and Norway (EU RAR 2006). Levels in breast milk ranged from 0.01 to as high as 11 µg/kg lipid in one case in the Faroe Islands (EU RAR 2006). Five human subjects were administered a single oral dose of 0.1 mg/kg TBBPA. Two major metabolites of TBBPA, TBBPA glucuronide (5 of 5 subjects) and TBBPA-sulfate (2 of 5 subjects), were found in urine and blood samples while the parent TBBPA was not present in detectable levels in any of the human plasma samples. TBBPA-glucuronide plasma levels reached peak concentrations between 2 and 6 hrs after administration and was slowly eliminated in urine to reach the LOD 124 hrs after administration. TBBPA-sulfate (found in 2 of the 5 human subjects) was measured between 4 and 6 hrs after administration as was below the LOD in urine. The authors suggest that the major role of enterohepatic circulation is indicated by the slow elimination of TBBPA-glucuronide in urine in both humans and rats and this, along with efficient hepatic metabolism, would result in low systemic bioavailability of TBBPA in humans (Schauer et al. 2006).	No studies identified.	No studies identified.

Appendix 10: Supplementary Data from van der Ven et al. (2008)

A. Organ weight data, F1 male rats

Group (mg/kg-bw per day)	**Body weight (g)**	**Testis weight (g)**	**Organ to body weight ratio (presented by Health Canada)**
Control	414	3.01	0.0073
3	433	3.25	0.0075
10	453	3.48	0.0077
30	461	3.50	0.0076
100	478	3.55	0.0074
300	454	3.56	0.0078
1000	461	3.41	0.0074
3000	472	3.32	0.0070

Critical effect dose, 1.4 mg/kg-bw per day (BMDL, 0.5 mg/kg-bw per day)

Group (mg/kg-bw per day)	**Body weight (g)**	**Pituitary weight (g)**	**Organ to body weight ratio (presented by Health Canada)**
Control	414	0.011	0.000027
3	433	0.012	0.000028
10	453	0.014	0.000031
30	461	0.016	0.000035
100	478	0.014	0.000029
300	454	0.017	0.000037
1000	461	0.013	0.000028
3000	472	0.016	0.000034

Critical effect dose, 2.2 mg/kg-bw per day (BMDL, 0.6 mg/kg-bw per day)

B. Endocrine parameters

Group (mg/kg-bw per day)	TT4 (nmol/L) (females)	TT4 (nmol/L) (males)
Control	34.3	53.4
3	33.5	40.7
10	38.0	45.7
30	41.2	47.6
100	27.1	43.0
300	23.2	31.5
1000	22.2	26.5
3000	18.4	27.9

Critical effect dose females: 35.6 mg/kg-bw per day (BMDL, 16.1 mg/kg-bw per day)

Critical effect dose, males: 99.5 mg/kg-bw per day (BMDL, 30.8 mg/kg-bw per day)