SCIENTIFIC OPINION

Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

This scientific output, published on 6 December 2013, replaces the earlier version published on 19 December 2011[4].

ABSTRACT

EFSA was asked by the European Commission to deliver a scientific opinion on tetrabromobisphenol A (TBBPA) and its derivatives in food. TBBPA and its derivatives are widely used as flame retardants. TBBPA is primarily used as reactive flame retardant covalently bound to epoxy and polycarbonate resins. TBBPA derivatives are used as either reactive or additive intermediates in polymer manufacture. Data from the analysis of TBBPA in 652 food samples were submitted to EFSA by four European countries (Ireland, Norway, Spain and the UK), covering the period from 2003 to 2010. All analytical results were reported as less than the limit of quantification (LOQ) and the majority of the samples were in the food group "Fish and other seafood" (n=465). Toxicological studies with TBBPA have been carried out using different experimental designs with single or repeated administration during gestation, postnatally or in adulthood. The main target is thyroid hormone homeostasis. TBBPA is not genotoxic. There are no indications that TBBPA might be carcinogenic. The Panel on Contaminants in the Food Chain (CONTAM Panel) identified a lower confidence limit for a benchmark response of 10 % ($BMDL_{10}$) of 16 mg/kg b.w. reported for changes in thyroid hormones as the critical reference point. Due to the limitations and uncertainties in the database, the Panel concluded that it was inappropriate to use this BMDL to establish a health based guidance value, and therefore used a margin of exposure (MOE) approach for the health risk assessment of TBBPA. In view of the large MOEs, the Panel concluded that current dietary exposure to TBBPA in the European Union does not raise a health concern. Also exposure of infants via

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[4] Corrections were made to the abstract, summary, main body of the text and conclusions to include the data submitted by Ireland and the UK through the EFSA BFR call for data. The inclusion of these data does not change the approach taken by the CONTAM Panel, or the conclusions or recommendations.

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human milk does not raise a health concern. Additional exposure, particularly of young children, to TBBPA from house dust is unlikely to raise a health concern.

KEY WORDS

Tetrabromobisphenol A, TBBPA, TBBPA derivatives, occurrence, food, toxicology, human exposure, risk assessment.

SUMMARY

Following a request from the European Commission, the Panel on Contaminants in the Food Chain (CONTAM Panel) was asked to deliver a scientific opinion on tetrabromobisphenol A (TBBPA) and its derivatives in food.

TBBPA and its derivatives are a widely used group of flame retardants. TBBPA is primarily used as a reactive flame retardant, covalently bound to epoxy and polycarbonate resins. It is also used as an additive flame retardant in the manufacture of acrylonitrile butadiene styrene (ABS) resins, high impact polystyrene (HIPS) and phenolic resins. TBBPA derivatives may be used as either reactive or additive intermediates in polymer manufacture. When used as additive flame retardants, TBBPA and/or its derivatives might leach from the products into the environment.

TBBPA is susceptible to photolysis, and reductive debromination has been observed under experimental conditions.

A call for data on brominated flame retardants (BFRs) including TBBPA was issued by EFSA in December 2009. EFSA collected and evaluated the results reported from the analysis of 652 food samples, reported by four European countries (Ireland, Norway, Spain and the UK). These results covered the period from 2003 to 2010. The dominant food category was "Fish and other seafood (including amphibians, reptiles, snails and insects)" (n=465), followed by "Meat and meat products (including edible offal)" (n=49), "Milk and dairy products" (n=40), "Animal and vegetable fats and oils" (n=41) and "Eggs and egg products" (n=27). Less than 10 samples were reported for the remaining food categories. All analytical results on TBBPA were reported as less than the limit of quantification (LOQ) (in general $\leq$ 1 ng/g wet weight). Therefore a meaningful exposure assessment for the general population is not possible. In order to provide some indication of whether there could be a possible health concern with respect to dietary exposure to TBBPA, the CONTAM Panel made a worst case intake estimate for two specific groups of the population, i.e. adult high fish consumers and high cow's milk consumers (toddlers), by substituting the concentration levels of TBBPA in fish and in cow's milk, all reported as not quantified, by the maximum LOQ reported for those food categories of 1 ng/g and 0.65 wet weight, respectively. The resulting "upper bound" intake estimate was 2.6 and 55.7 ng/kg body weight (b.w.) per day, respectively.

Data on levels of TBBPA in human milk are scarce. For 3 months old breast-fed infants with average human milk consumption (800 mL per day) concentrations of TBBPA in human milk (ranging from 0.06 to 37.3 ng/g fat) result in daily exposures of 0.28 to 171 ng/kg b.w. For infants with high human milk consumption (1 200 mL per day) the respective daily exposures range from 0.41 to 257 ng/kg b.w.

The limited toxicokinetics data suggest that oral bioavailability of TBBPA in rats is about 70 %. After absorption, TBBPA is distributed in different tissues and rapidly excreted via the bile in faeces. Glucuronide or sulphate conjugates of TBBPA were identified in the bile. Tribromobisphenol A has been identified in faeces, suggesting that debromination of TBBPA can occur in mammals. The plasma half-life in rats was estimated to be about half a day. In humans, the half-life of TBBPA-glucuronide in plasma appeared to be between 48 and 72 h.

Toxicological studies with TBBPA have been carried out using different experimental designs with single or repeated administration during gestation, postnatally or in adulthood. The main target for TBBPA toxicity is thyroid hormone homeostasis.

The limited studies available do not indicate reproductive or teratogenic effects of TBBPA.

The available *in vitro* data indicate that TBBPA is not genotoxic. There are no long-term toxicity/carcinogenicity studies for TBBPA. However, based on the weight of evidence (absence of genotoxicity *in vitro*, no indications for proliferative changes or cytotoxicity in studies with up to 90 days repeated administration, no immunosuppression, except possibly at high doses), the CONTAM Panel concluded that there are no indications that TBBPA might be carcinogenic.

The CONTAM Panel identified a lower confidence limit for a benchmark response of 10 % ($BMDL_{10}$) of 16 mg/kg b.w. reported for changes in thyroid hormone levels (decrease in circulating T4) as the critical reference point. The CONTAM Panel concluded, however, that due to the limitations and uncertainties in the current database, the derivation of a health based guidance value for TBBPA was not appropriate. Therefore, the Panel used a margin of exposure[5] (MOE) approach for the risk characterisation of TBBPA.

Comparison of the "upper bound" dietary exposure estimate of 2.6 ng/kg b.w. per day for the specific group of adult high fish consumers with the $BMDL_{10}$ of 16 mg/kg b.w. resulted in an MOE of 6×10^6. In the case of high cow's milk consumers (i.e. toddlers), it resulted in an MOE of 3×10^5.

Usually an MOE of 100 is sufficient to cover uncertainties and variability with respect to kinetic and dynamic differences between animal species and humans and within the human population, and to conclude that there is no health concern. In the case of TBBPA, the CONTAM Panel noted that an additional factor would be needed to cover deficiencies in the database. The MOEs of 6×10^6 and 3×10^5 reported for the "upper bound" exposure scenario for adult high fish consumers and high cow's milk consumers (i.e. toddlers) are, however, sufficiently large that the CONTAM Panel concluded that the current dietary exposure to TBBPA for these specific population groups with potential high exposure does not raise a health concern.

The limited data for other food groups, all reported as less than the LOQs, did not facilitate a hypothetical exposure assessment. However, since the reported LOQs for these food groups are in general below those reported for milk and fish, and given the large MOEs for adult high fish consumers and high cow's milk consumers (i.e. toddlers), the CONTAM Panel concluded that it is unlikely that current dietary exposure of the general population to TBBPA raises a health concern.

For breast-fed infants with average or high human milk consumption, MOEs ranging from 6×10^7 to 9×10^4 and 4×10^7 to 6×10^4 have been estimated, respectively. Because of these large MOEs, the CONTAM Panel concluded that exposure via human milk also does not raise a health concern.

Dust in homes, classrooms and cars can be an additional source of exposure to TBBPA, particularly for children. Considering the 95th percentile TBBPA concentration in dust of 460 ng/g, the exposure based on a typical or high end exposure scenario would be 1.2 or 4.6 ng/kg b.w. per day, respectively. The CONTAM Panel concluded that the 'typical' exposure scenario provided the most realistic estimate of exposure to TBBPA from dust. Comparing the exposure resulting from this scenario (1.2 ng/kg b.w.) with the $BMDL_{10}$ of 16 mg/kg b.w. results in an MOE of about 1.3×10^7. This MOE also indicates that exposure of children to TBBPA from dust does not raise a health concern.

Based on the large MOEs derived for both dietary exposure and exposure through dust, the CONTAM Panel concluded that it is unlikely that combined exposure through food and dust would result in a health concern.

For TBBPA derivatives no occurrence data had been submitted to EFSA and no information on their toxicity was identified.

[5] The margin of exposure (MOE) is the ratio between a defined point on the dose-response curve for the adverse effect and the human intake.

The CONTAM Panel recognised that there is a need for information on production rates, use, chemical characteristics, occurrence in food, especially for food categories other than fish, and toxicity of TBBPA derivatives.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Brominated flame retardants (BFRs) are anthropogenic chemicals that are added to a wide variety of consumer/commercial products in order to improve their fire resistance. There are 5 major classes of BFRs: brominated bisphenols, diphenyl ethers, cyclododecanes, phenols and phthalic acid derivatives.

Concern has been raised because of the occurrence of several chemical compounds from the group of BFRs in the environment, including feed and food, and in human biota. This has led to bans on the production and use of certain formulations of polybrominated diphenyl ethers (PBDEs).

EFSA concluded in its advice on a request from the Commission related to relevant chemical compounds in the group of brominated flame retardants for monitoring in feed and food of 24 February 2004 that the available occurrence data on brominated flame retardants in feed and food did not allow a comprehensive assessment of contamination in all feeds and foods and identified the following compounds as the most important ones to be monitored based on the analytical feasibility to measure the chemical compounds routinely in accredited laboratories, the production volumes, the occurrence of the chemical compounds in food and feed, their persistence in the environment and their toxicity:

- polybrominated diphenyl ethers (PBDEs): BDE congeners #28, 47, 99, 100, 153, 154, 183 and 209.
- hexabromocyclododecane (HBCD): total amount (isomer specific analysis of a limited number of samples and/or pools in case of significantly elevated levels or increasing trends).
- polybrominated biphenyls (PBBs): BB congener #153.

Optionally, the following brominated flame retardants were recommended to be monitored:

- TBBP-A and other phenols
- decabromodiphenyl ethane
- hexabromobenzene
- bis(2,4,6-tribromophenoxy)ethane

Subsequently EU-wide monitoring of these compounds was organised as of October 2006. Monitoring results will be made available to EFSA.

In order to assess the need for regulatory measures as regards BFR in food, EFSA is requested to assess the risks related to the presence of BFR in food.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for a scientific opinion on the risks to human health related to the presence of tetrabromobisphenol A (TBBPA) and other phenols in food.

In particular, the opinion should

- evaluate the toxicity of TBBPA for humans considering all relevant toxicological information available;

- carry out an exposure assessment on the basis of the occurrence data obtained in the monitoring exercise and other occurrence data that may be available;
- consider the exposure situation for specific groups of the population (e.g. infants and children, people following specific diets, etc.) and indicate the relative importance from other non-dietary sources;
- take into account, if available, biomonitoring data when assessing the exposure and compare the results with the calculated exposure;
- explore whether individual compounds can be used as markers for dietary exposure to BFRs;
- Identify potential data gaps for these specific groups of BFRs.

INTERPRETATION OF THE TERMS OF REFERENCE

In the terms of reference as provided by the European Commission (see above) EFSA was requested to address the risks to human health related to the presence of tetrabromobisphenol A (TBBPA) and other brominated phenols in food. Based on the information collected, the CONTAM Panel decided to focus the present opinion on TBBPA and its derivatives. Other brominated phenols such as 2,4,6-tribromophenol and tetrabromobisphenol S (TBBPS) and its derivatives will be dealt with by the CONTAM Panel in a further scientific opinion.

ASSESSMENT

1. Introduction

1.1. General information

Flame retardants include a broad and diverse group of compounds used to prevent fires or at least to slow down the development of a fire. There are three main categories of chemical flame retardants: halogenated hydrocarbons, organophosphorous compounds and inorganic products often based on metallic hydroxides (Vos et al., 2003). Within the halogenated hydrocarbons, the group of the brominated flame retardants (BFRs) consist of different chemicals with a variety of physicochemical properties and uses. The main BFRs are the polybrominated (i) neutral aromatic, (ii) neutral cycloaliphatic, (iii) phenolic, including neutral derivatives, (iv) aromatic carboxylic acid esters and (v) trisalkyl phosphate compounds. The major individual groups of BFRs within these five classes are, respectively polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDDs[6]), tetrabromobisphenol A (TBBPA), 2,4,6-tribromophenol-bis(2-ethylhexyl) tetrabromophthalate (bEH-TeBPht) and tris[3-bromo-2,2-bis(bromomethyl)propyl] phosphate (tBbBMPrP) (WHO, 1997; Örn and Bergman, 2004; Harju et al., 2009).

The present opinion will focus on 3,3',5,5'-tetrabromobisphenol A (TBBPA) and a number of its derivatives. This opinion does not consider TBBPA oligomers or polymers.

1.2. Previous risk assessments

Based on the European Union (EU) draft risk assessment (later published as ECB, 2006), the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) issued a statement on the toxicological data of TBBPA (COT, 2004). The COT concluded that the available data at the time of the report did not raise specific toxicological concerns. The highest dose tested in a 90-day study and in a two-generation reproductive toxicity study of 1,000 mg/kg body weight (b.w.) per day, at which no clear adverse effects were observed, was used as the basis for deriving a tolerable daily intake (TDI). An uncertainty factor of 100 for inter- and intra-species variation, and an additional factor of 10 for the absence of chronic toxicity studies were applied. The Committee recommended then a TDI of 1 mg/kg b.w. per day.

In 2006, the European Chemicals Bureau (ECB) published the risk assessment report on TBBPA (ECB, 2006). For adults, no adverse health effects of potential concern were identified. No comparison of the intake estimate (7.8×10^{-5} mg/kg b.w. per day) and data from the toxicological studies was done. For infants, a no-observed-adverse-effect level (NOAEL) of 40 mg/kg b.w. per day for nephrotoxicity in newborn rats (Fukuda et al., 2004) was used for the risk characterization. Due to the lack of an estimate of the exposure levels of infants, two surrogate scenarios were selected: one based on the highest environmental exposure of adults and one using the highest concentration of TBBPA in breast milk. These exposure estimates resulted in margins of safety (MOS) of 210 based on the "adult" scenario and 1.7×10^6 for breast-fed infants. The ECB report concluded that these MOS were sufficient to allow for inter and intra-species differences, and that no further information and/or testing were needed.

No risk assessments have hitherto been presented for any of the TBBPA derivatives.

[6] HBCDDs is used as the abbreviation for hexabromocyclododecanes (1,2,5,6,9,10-hexabromocyclododecane, CAS No 3194-55-6) instead of HBCD in this document, to avoid misunderstandings. HBCD is occasionally used as an abbreviation of hexabromocyclodecane (CAS No 25495-98-1).

1.3. Chemical characteristics

The basic structure of 3,3',5,5'-tetrabromobisphenol A (TBBPA) consists of two hydroxyphenyl rings linked by a carbon bridge with bromine substitution at the 3, 3',5 and 5'-position (see Figure 1**).** There are several TBBPA derivatives, of which a number is commercially available as flame retardants: tetrabromobisphenol A bis(2-hydroxyethyl) ether (TBBPA-bOHEE), tetrabromobisphenol A bisallyl ether (TBBPA-bAE), tetrabromobisphenol A bis(2,3-dibromopropyl ether) (TBBPA-bDiBPrE), tetrabromobisphenol A bis(glycidyl ether) (TBBPA-bGE). For other TBBPA derivatives there is some uncertainty about their commercial use as flame retardants: tetrabromobisphenol A bisacrylate (TBBPA-bAcr), 3,3',5,5'-tetrabromobisphenol A bis-acetate (TBBPA-bOAc) and tetrabromobisphenol A bis(2-hydroxyethyl)ether bisacrylate (TBBPA-bOHEE-bAcr). TBBPA derivatives that may potentially be used as BFRs are: tetrabromobisphenol A bismethyl ether (TBBPA-bME) and tetrabromobisphenol A bispropanoate (TBBPA-bOPr). The structures of all these derivatives are presented in Figure 1.

TBBPA is manufactured by bromination of bisphenol A leading to the formation of primarily the tetrabrominated form of bisphenol A. The two phenolic groups in TBBPA have been shown to have different pK_a values (Table 1). Traces of isomeric TBBPA and tribromobisphenol A may be present in commercial TBBPA (ECB, 2006). Each of the TBBPA derivatives (Figure 1) is produced as an individual chemical, and not as a mixture. The purity of the compounds, however, is related to the technical quality of the product, which means that there may be traces of by-products present in the commercial products.

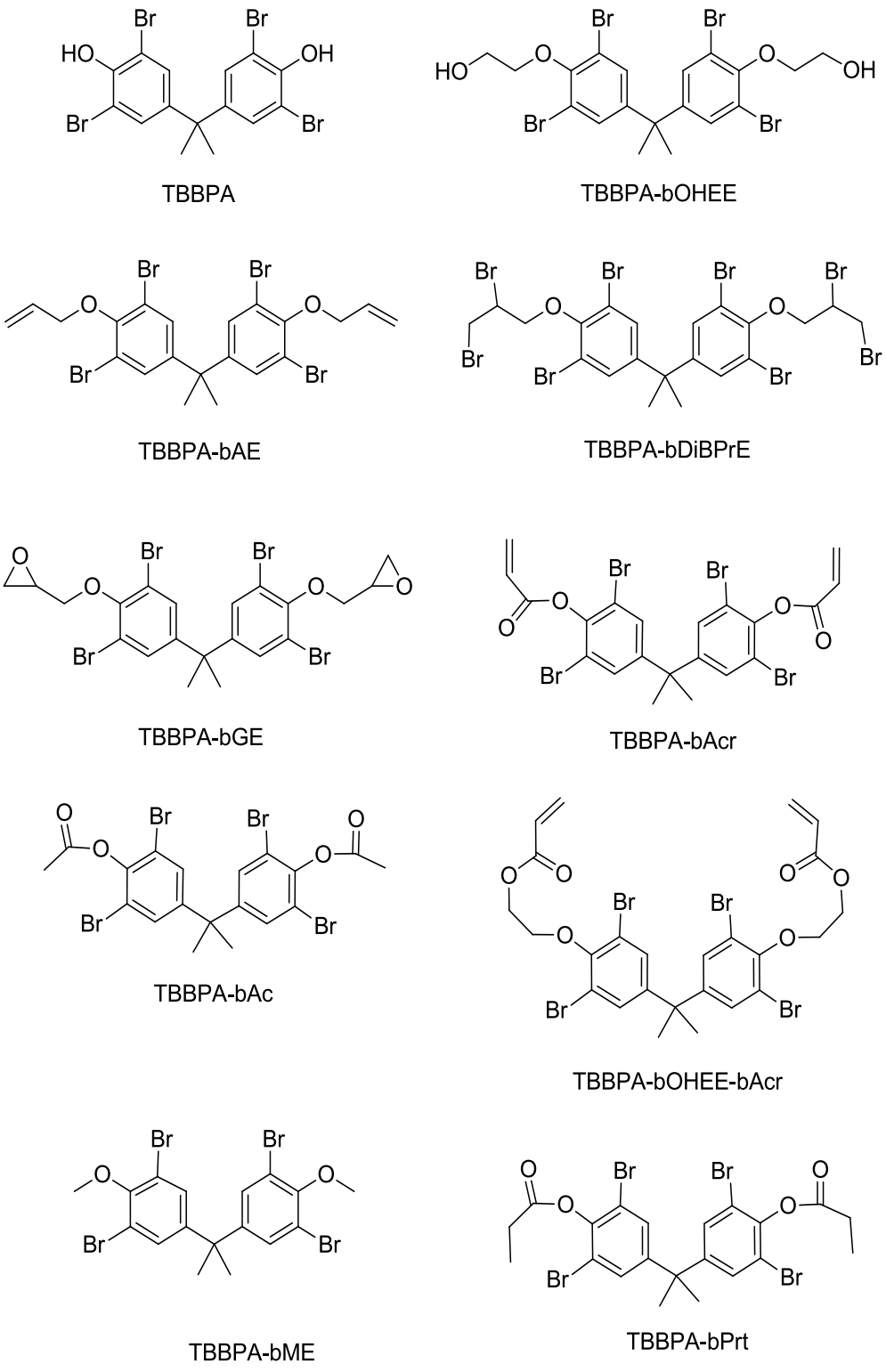

Figure 1: General structure of TBBPA and its major derivatives.

Major physicochemical characteristics of TBBPA and its derivatives are presented in Table 1. The detailed information on the physicochemical characteristics of TBBPA is given in the EU risk assessment document (ECB, 2006). Additional data presented here are either experimental data as reported in the open literature (references given in the table) or modelled data as presented in Chemical Abstracts Service (CAS) on line (Scifinder, 2011).

Table 1: Major physicochemical characteristics of tetrabromobisphenol A (TBBPA) and its derivatives.

Abbreviation	CAS number.	MW	Log K_{ow}	pK_a	Vapour pressure (Torr)
TBBPA	79-94-7	543.9	9.7[(a)]	7.5/8.5[(b)]	1.41×10^{-7}
TBBPA-bOHEE	4162-45-2	632.0	8.5	N[(c)]	2.17×10^{-14}
TBBPA-bAE	25327-89-3	642.0	11.4	N	1.37×10^{-10}
TBBPA-bDiBPrE	21850-44-2	943.6	13.0	N	2.14×10^{-14}
TBBPA-bGE	3072-84-2	656.0	8.9	N	1.23×10^{-12}
TBBPA-bAcr	55205-38-4	652.0	9.4	N	2.88×10^{-13}
TBBPA-bOAc	33798-02-6	627.9	9.4	N	2.46×10^{-11}
TBBPA-bOHEE-bAcr	66710-97-2	740.1	10.8	N	1.47×10^{-16}
TBBPA-bME	70156-79-5	593.9	6.0	N	2.57×10^{-13}
TBBPA-bOPr	37419-42-4	656.0	10.5	N	3.13×10^{-12}

The physiochemical constants are all calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2011 ACD/Labs) (Scifinder, 2011).
(a): Log K_{ow} of the protonized compound. Experimental Log K_{ow} show lower values, such as 3.2-6.4 at neutral pH (ECB, 2006).
(b): Since TBBPA has two phenol groups the compound has two pK_a values.
(c): N means neutral.

As determined under experimental conditions, TBBPA undergoes photolysis (Eriksson et al., 2004) and oxidative transformations (Moreira Bastos et al., 2008). A number of transformation products, including debromination products, dibromohydroquinone, dibromo-isopropylphenol and brominated alkylphenols have been detected. The anaerobic degradation of TBBPA was confirmed by Gerecke et al. (2006). TBBPA is not hydrolysed and does not undergo substitution reactions. It is easily polymerized or co-polymerized, due to the reactivity of the phenol groups.

2. Legislation

In order to protect public health, Article 2 of Council Regulation (EEC) No 315/93 of 8 February 1993[7] laying down Community procedures for contaminants in food stipulates that, where necessary, maximum tolerances for specific contaminants shall be established. Thus, a number of maximum tolerances are currently laid down in Commission Regulation (EC) No. 1881/2006 of 19 December 2006[8] setting maximum levels for certain contaminants, e.g. dioxins, dioxin-like polychlorinated biphenyls and several polycyclic aromatic hydrocarbons in foodstuffs. TBBPA and its derivatives are not regulated so far under this Regulation or under any other specific EU regulation for food.

[7] Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food. OJ L 37, 13.2.1996, p. 1.
[8] Commission Regulation (EC) No. 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. OJ L 364, 20.12.1996, p. 5-24.

Council Directive 2002/32/EC[9] regulates undesirable substances in animal feed. While maximum levels are set for a number of inorganic and organic contaminants in various feed materials, TBBPA and its derivatives are not regulated so far by the European Commission (EC) under this Directive.

TBBPA has been registered in REACH (Commission Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals).

3. Sampling and methods of analysis

3.1. Sampling

There are no specific guidelines for the sampling of foods to be analysed for TBBPA and its derivatives. Therefore, basic rules for sampling of organic contaminants or pesticides should be followed. Respective requirements are for example laid down in Commission Regulation (EC) No 1883/2006 of 19 December 2006[10] for sampling and analysis for the official control of levels of dioxins and dioxin-like PCBs in certain foodstuffs. This Regulation contains inter alia a number of provisions concerning methods of sampling depending on the size of the lot, packaging, transport, storage, sealing and labelling. The primary objective is to obtain a representative and homogeneous laboratory sample with no secondary contamination.

3.2. Methods of analysis

The analytical method starts with the extraction of the TBBPA from the sample. Several methods for extraction of biological samples have been proposed in the literature as reviewed by Covaci et al. (2009). For extraction of solid material, the Soxhlet procedure is used in some laboratories because it is simple and provides high extraction efficiency (Morris et al., 2004). Other techniques include pressurized liquid extraction (PLE) (Webster et al., 2009; Zhou et al., 2010), column extraction (Klif, 2010) and ultra turrax extraction with organic solvents. Most often solvent mixtures (e.g. hexane-acetone or hexane-dichloromethane) are used for extraction. For liquids (milk, blood), liquid-liquid extraction and solid-phase extraction (SPE) are employed (Cariou et al., 2005; Covaci et al., 2009). It should be kept in mind that TBBPA has pK_a values of 7.5 and 8.5, meaning that the pH should be carefully controlled in order not to have losses of TBBPA in the analytical procedure.

Cleanup of the extract is performed to isolate TBBPA from the co-extracted interfering compounds such as lipids and other matrix constituents. Several methods, or combinations thereof, have been employed including gel permeation chromatography (Morris et al., 2004; Webster et al., 2009), neutral or acidified silica (Harrad et al., 2009), Florisil (Klif, 2010) or sulphuric acid treatment (Fernandes et al., 2008). The next step is fractionation, which may be needed to isolate TBBPA from other pollutants (such as PBDEs and HBCDDs) and potentially interfering compounds. This is typically done by silica column fractionation (Covaci et al., 2009; Morris et al., 2004) or reversed-phase fractionation (Cariou et al., 2005).

TBBPA is analysed mostly by liquid chromatography-mass spectrometry (LC-MS) methods, although analysis by gas chromatography-MS (GC-MS) is reported as well. The analysis of TBBPA-bDiBPrE and TBBPA-bAE on the other hand, is primarily done by GC-MS methods. Splitless injection is the most commonly used injection technique for GC analysis (Covaci et al., 2009). Long sample residence times at high temperatures in the injector should be avoided to prevent degradation of the target compound. GC separations are done on capillary columns with an apolar or slightly polar

[9] Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p. 1-24.
[10] Commission Regulation (EC) No 1883/2006 of 19 December 2006 laying down methods of sampling and analysis for the official control of levels of dioxins and dioxin-like PCBs in certain foodstuffs. OJ L 364, 20.12.2006, p. 32-43.

stationary phase. The chromatography of TBBPA on a GC column can be improved by derivatisation of the hydroxyl groups (Covaci et al., 2009), although GC analysis can also be performed without (Korytár et al., 2005). The TBBPA derivatives do not require derivatisation (Ali et al., 2011; Shi et al., 2009). The column dimensions are typically 15-30 m length, 0.25 mm diameter and 0.1-0.25 µm film thickness (Gauthier et al., 2009; Shi et al., 2009; Cariou et al., 2005; Korytár et al., 2005). Korytár et al. (2005) applied comprehensive two dimensional GC (GC × GC) for the successful separation of TBBPA from a commonly observed interference such as the brominated diphenyl ether BDE-153.

TBBPA is amenable to LC without derivatisation (Morris et al., 2004; Harrad et al., 2009; Covaci et al., 2009). The analysis is often combined with HBCDDs. Zhou et al. (2010) presented an LC method for the analysis of TBBPA together with several other BFRs such as PBDEs, HBCDDs and others. Both LC and ultra performance LC (UPLC) have been applied, using reversed phase columns (mostly C18) for the analysis of TBBPA (see Covaci et al. (2009) for details).

In GC-low resolution MS (LRMS), electron chemical negative ionization (ECNI) can be used for ionization of TBBPA, monitoring the bromine isotopes (*m*/*z* 79 and 81). This ionization method provides very good sensitivity compared to electron impact (EI) ionization, although at the cost of selectivity. EI combined with high resolution MS (HRMS) is used in some studies (cited in Covaci et al., 2009) for the detection of TBBPA after derivatisation in the analytical run. Korytár et al. (2005) used electron capture detection (µ-ECD) for the detection of TBBPA and methyl TBBPA.

LC-MS detection is performed on various MS instruments, such as single quadrupole MS, triple-quadrupole (MS/MS), ion trap MS (ITMS) and time-of-flight MS (TOF-MS). Electrospray ionisation (ESI) is more commonly applied than atmospheric pressure chemical ionisation (APCI) or atmospheric pressure photo ionisation (APPI). For an overview of methods used see Covaci et al. (2009). In the ESI source, the formation of $[M-H]^-$ takes place. The MS spectrum exhibits bromine clusters because of the two bromine isotopes *m*/*z* 79 and *m*/*z* 81 present. Several ions (*m*/*z* 540.9, 541.7, 542.7), have been selected for detection (single MS) or for multiple reaction monitoring (MRM) experiments in triple quadrupole instruments. In the latter case, several product ions are available for monitoring (see Covaci et al. (2009) for details). In some studies (cited in Covaci et al., 2009), ultraviolet (UV) detection and diode array detection have been applied.

A major advantage of LC-ESI-MS(/MS) and GC-EI-HRMS over GC-ECNI-MS is the option of using ^{13}C labelled internal standards. These standards allow correction for losses during extraction and clean-up. Furthermore, isotope labelled standards effectively correct for matrix suppression or enhancement occurring in the ESI source.

Quality control and quality assurance

The analysis of TBBPA and derivatives is laborious and complex and involves several critical steps. Errors are easily made in extraction, cleanup, GC determination and quantification. A number of factors determine the final accuracy and precision (i.e. the quality) of the results reported. Exposure to high temperatures should be avoided, as discussed earlier. Exposure to UV radiation may lead to degradation (WHO/IPCS, 1995). Due to this fact, it is recommended that all analytical work is carried out in such a manner that UV light is excluded, e.g. treatments can be undertaken in brown glass or in glassware covered with aluminium foil.

Interlaboratory studies and certified reference materials

A number of interlaboratory studies have been organised for biota samples by QUASIMEME (QUality ASsurance of Information for Marine Environmental Monitoring in Europe). In many cases, TBBPA levels in the samples were too low to allow an assessment of the intercomparability (Crum, 2011, personal communication). Standard or Certified Reference Materials are important tools for

laboratory performance evaluation against external references. However, food type and dust-type reference materials are lacking.

4. Sources, use and environmental fate

TBBPA is the highest-volume brominated flame retardant in the world representing about 60 % of the total BFR market (Lowell, 2006). It is mainly used in several types of polymers and electronics (laminate for printed circuit boards).

4.1. Formation and production

TBBPA is produced by the bromination of bisphenol-A in the presence of a solvent. This reaction may be conducted in the presence of a hydrocarbon solvent only or with water, 50 % hydrobromic acid or aqueous alkyl mono ethers. When methanol is used as the solvent, methyl bromide is formed as a by-product. The production process is largely conducted in closed systems (WHO/IPCS, 1995).

TBBPA is produced in various countries, including the USA, Israel, China and Japan. It is no longer produced in the EU. The total amount of TBBPA produced was estimated to be >120,000 tonnes per year (Hakk, 2001) and 150,000 tonnes per year (Arias, 2001). The global demand for TBBPA is reported to have increased from 50,000 tonnes per year in 1992 to 145,000 tonnes per year in 1998, with an average growth of 19 % per year (BKH, 2000). Global demand for TBBPA was expected to grow by 8-9 % per year between 1998 and 2004. TBBPA has been, and is sold, under many different trade names. A set of these names is listed below in Table 2, as well as trade names of its derivatives (Scifinder, 2011).

Table 2: Trade names of TBBPA and its derivatives (Scifinder, 2011).

TBBPA	BA 59, BA 59BP, BA 59P, Bromdian, CP 2000, FG 2000, FR 1524, Fire Guard 2000, Firemaster BP 4A, Flame Cut 120G, Flame Cut 120R, GLCBA 59P, NSC 59775, PB 100, RB 100, Saytex CP 2000, Saytex RB 100, Saytex RB 100PC, T 0032, Tetrabromodian
TBBPA-bME	No trade names identified
TBBPA-bOHEE	AFR 1011, BA 50, BA 50P, FG 3600, Fire Guard 3600, BA-EO 20; T
TBBPA-bAE	BE 51, FG 3200, Fire Guard 3200, Flame Cut 122K, Pyroguard SR 319, SR 319, TBBPA-DE
TBBPA-bGE	Glycidyl tetrabromodian ether
TBBPA-bDiBPrE	Bromkal 66-8, D 5532, FG 3100, FR 720, Fire Guard 3100; Flame Cut 121K, Flame Cut 121R, GX 5532, HP 800A, PE 68, Pyroguard SR 720, SR 720, Saytex HP 800A, Saytex HP 800AG

4.2. Use

TBBPA is imported into the EU in various forms, either as a primary product or in finished or partially finished products such as plastics, printed circuit boards and other electronic equipment. These imports may be an important source of TBBPA in the EU, but limited information on the import of TBBPA is available. The annual import of TBBPA into the EU was estimated by ECB (2006) to be 40,000 tonnes: 13,800 tonnes as the substance as such, 6,000 tonnes in partly finished products (e.g. masterbatch and epoxy resins), and 20,200 tonnes in finished products.

Some 90 % of the total use of TBBPA is as a reactive intermediate in the manufacture of epoxy and polycarbonate resins. As a reactive intermediate, it will be covalently bound in the polymer. However, the polymer will also contain a portion of unreacted TBBPA as a result of excess TBBPA added during the production process. As this unreacted TBBPA is not bound to the polymer, it represents a fraction that can easily leach out from the polymer matrix into the environment and subsequently result in exposure of animals and humans.

TBBPA is also used as an additive flame retardant in the manufacture of acrylonitrile butadiene styrene (ABS) resins, high impact polystyrene (HIPS) and phenolic resins. TBBPA is considered as an alternative additive flame retardant to octabromodiphenyl ether in ABS. When used as an additive flame retardant, it is generally used with antimony oxide (Hakk, 2001). As an additive flame retardant, TBBPA may more or less readily leach out of the polymer matrix. Additive use accounts for approximately 10 % of the total use of TBBPA (ECB, 2006).

TBBPA is also used in the manufacture of derivatives such as TBBPA bismethyl ether (TBBPA-bME), TBBPA bis(2,3-dibromopropyl)ether (TBBPA-bDiBPrE), TBBPA bisallyl ether (TBBPA-bAE), TBBPA bis(2-hydroxyethyl) ether (TBBPA-bOHEE), TBBPA brominated epoxy oligomer, and TBBPA carbonate oligomers (WHO/IPCS, 1995). The main use of these derivatives is as flame retardants, usually in niche applications. The total amount of TBBPA derivatives used is less than the amount of TBBPA used (approximately 25 % on a weight basis) (WHO/IPCS, 1995). The derivatives may be used as either reactive or additive intermediates in polymer manufacture.

ECB (2006) contains a comprehensive description of these derivatives: *"TBBPA bis(2,3-dibromopropyl ether) (CAS Number 21850-44-2) is used as an additive flame retardant in polyolefins and copolymers such as high density polyethylene, low density polyethylene, polypropylene and polybutylenes (OECD, 1994; WHO, 1995; Ash and Ash, 1997). TBBPA bis(2,3-dibromopropyl ether) is the most popular flame retardant for applications such as water discharge pipes and also for lamp sockets (Bar Yaakov et al., 2000) and TBBPA bis(allyl ether) (CAS Number 25327-89-3) is used as a reactive flame retardant in polystyrene foams (OECD, 1994; WHO, 1995; Ash and Ash, 1997). TBBPA bis(2-hydroxyethyl ether) (CAS Number 4162-45-2) is used as an additive flame retardant in a number of different polymers (OECD, 1994; WHO, 1995; Ash and Ash, 1997). Epoxy oligomers of TBBPA are also known as TBBPA diglycidyl ethers (CAS Number 68928-70-1). They are e.g. used in polystyrene and ABS housings for business machinery and electrical/electronics parts. The concentrations of the flame retardant in ABS is around 20 %. TBBPA carbonate oligomers can be considered similar to the reactive use of TBBPA in polycarbonates described above. These oligomers are used as an additive flame retardant in ABS and engineering thermoplastics (OECD, 1994; WHO, 1995). Both phenoxy-terminated TBBPA carbonate oligomers (CAS Number 94334-64-2) and tribromophenoxy-terminated TBBPA carbonate oligomers (CAS Number 71342-77-3) are produced"* (WHO/IPCS, 1995).

Finally, OECD (1994) reported that a type of polyester fibre can be made from bis(hydroxyethyl) TBBPA ethylene glycol by reacting with terephthalic acid and that flame retardant polyester-cotton can be made from TBBPA by reacting with terephthaloyl chloride in methylene chloride. Ash and Ash (1997, as cited by ECB, 2006) indicated that TBBPA bisacrylate (CAS Number 55205-38-4) can be used in automotive coatings and wire and cable coatings. A TBBPA bis(2-ethylether acrylate) derivative (CAS Number 6710-97-2) has also been reported (ECB, 2006).

4.3. TBBPA and its derivatives in the environment

4.3.1. Release into the environment

TBBPA is found in the environment in biological matrices such as fish and birds. It can enter the environment as a result of releases at production sites but probably more importantly via leakage from products where it has been introduced as an additive flame retardant.

4.3.2. Transformation in the environment

TBBPA is used in large amounts in products that have been, and will continue to be, disposed of in landfills, from which TBBPA may leach. Experimental microbial degradation studies have shown that in sediments under anaerobic reducing conditions TBBPA can be completely dehalogenated to bisphenol A (BPA) (Ronen and Abeliovich, 2000; Voordeckers et al., 2002; Gerecke et al., 2006). Ronen and Abeliovich (2000) also showed that BPA can be further degraded under aerobic conditions, indicating that a sequential anaerobic-aerobic process may possibly be used to completely degrade TBBPA present in contaminated soil.

It has also been suggested that TBBPA may be subjected to microbial methylation, since TBBPA-bismethyl ether (TBBPA-bME) has been found in environmental samples such as mussels (*Mytilus edulis*) and river sediments (Watanabe et al., 1983a, 1983b).

4.3.3. Occurrence in the environment

Despite its extensive use, TBBPA data for abiotic and biotic matrices are scarce compared to data available for other BFRs, such as PBDEs and HBCDDs.

4.3.3.1. Air and dust

Air

Xie et al. (2007) analysed TBBPA in outdoor air samples from a rural site in northern Germany, over the Wadden Sea and offshore in the Northeast Atlantic Ocean. Comparable concentrations of TBBPA were found both at the northern German site (ranging from <0.04 to 0.85 pg/m^3) and over the Wadden Sea (ranging from 0.31 to 0.69 pg/m^3) whereas the concentrations over the Northeast Atlantic Ocean ranged from <0.04 to 0.17 pg/m^3, with the highest concentration present in a sample collected at the West Norwegian coast, indicating an input source from land to ocean.

Elevated indoor air concentrations, up to several orders of magnitude above those found in outdoor air, have been reported for specific occupational environments, such as electronics dismantling plants. In Sweden, a mean TBBPA concentration of 29.7 ng/m^3 was detected in air samples at a plant for the recycling of electronics (Bergman et al., 1999). In another Swedish study, Sjödin et al. (2001) reported a mean TBBPA concentration of 0.036 ng/m^3 in six office microenvironments containing computers, 0.093 ng/m^3 in two teaching halls and 0.035 ng/m^3 in two computer repair facilities. In the same study they found that TBBPA was present primarily in the particulate phase rather than in the vapour phase. Abdallah et al. (2008) reported concentrations of TBBPA (average, min and max) in UK homes of 16, 9 and 22 pg/m^3, in offices of 16, 4 and 33 pg/m^3, in public microenvironments of 26, 17 and 32 pg/m^3, and outdoors of 0.8, 0.7 and 0.9 pg/m^3.

Indoor dust

In a study of dust in offices from the European Parliament building, concentrations in 9 out of 16 samples were reported to be between 5 and 47 ng/g (Leonards et al., 2001). Takigami et al. (2007)

reported TBBPA concentrations of 490 and 520 ng/g in two samples of domestic dust from Hokkaido, Japan. TBBPA was present in four out of ten pooled samples of UK domestic dust in concentrations ranging from 190 to 340 ng/g (Santillo et al., 2008). Abdallah et al. (2008) reported TBBPA concentrations (average, min, max) in homes to be 87, < the limit of detection (LOD) and 382 ng/g dust, in offices 49, < LOD and 140 ng/g dust, in cars 6, <LOD and 25, and in public microenvironments 220, 52 and 350 ng per g dust. In a study by Harrad et al. (2010), the mean and 95th percentile concentrations of TBBPA in dust from classrooms in primary schools and daycare centres were reported to be 200 and 460 ng/g dust, with a maximum concentration of 1,400 ng/g dust. A Belgian study (D'Hollander et al., 2010) reported median and 95th percentile concentrations to be 11.7 and 141 ng/g in house dust and 70.4 ng/g and 212 ng/g in office dust, respectively.

In a study by Harrad and Abdallah (2011), the concentration of TBBPA in dust from the four seats in five different cars ranged from <0.2 to 16 ng/g dust, with a median of 2 ng/g dust. TBBPA concentrations in the dust from the front seats were usually higher than those in dust from seats in the rear.

Ali et al. (2011) investigated the occurrence of TBBPA-bDiBPrE in dust from 36 UK classrooms, 39 Belgian homes and six Belgian offices. The mean (95th percentile) concentrations were 729 (2,891), 144 (402) and 608 (1,852) ng/g dust, respectively.

4.3.3.2. Soil and uptake by plants

There are very few reports on concentrations of TBBPA in soil. Jin et al. (2006) reported 0.12 ng TBBPA/g soil in a sample taken outside a TBBPA production plant in China. Given its reported propensity for partitioning to the atmospheric particulate phase (Sjödin et al., 2001) and its octanol-water partition coefficient, soil would be expected to constitute a major sink. However, this will be influenced by the rate of degradation in soil coupled to subsequent atmospheric transport and deposition. The concentration of TBBPA in other Chinese soil samples was 25.2±2.7 ng/g (n=4) (Peng et al., 2007).

In a study by Sun et al. (2008) uptake of TBBPA from water by hornwort (coontail) (*Ceratophyllum demersum*) was demonstrated to occur in a dose dependent manner. Uptake occurred mainly during the first four days and exposure to 0.2 mg/L resulted in a TBBPA level of about 0.35 mg/g dry weight, whereas a concentration of 1 mg/L resulted in about 1.2 mg/g dry weight after 14 days.

4.3.4. Occurrence and bioaccumulation in wildlife

There are a number of studies of TBBPA in wildlife. Concentrations of TBBPA in herring (*Clupea harengus)* from the Baltic proper and Kattegat are reported to be in the range of 0.5-5 ng/g fresh weight, Northern pike (*Esox lucius*) from Swedish inland waters 2-4 ng/g fresh weight and moose (*Alces alces*) 1-3 ng/g fresh weight (Remberger et al., 2002). Johnson-Restrepo (2008) reported concentrations in bottlenose dolphin (*Tursiops truncatus)* blubber and bull shark (*Carcharhinus leucas*) muscle tissue in the range of 0.06-8.48 and 0.035-36 ng/g lipid, respectively.

Morris et al. (2004) analysed cod (*Gadus morhua*) and cormorant (*Phalacrocorax carbo)* liver as well as common tern (*Sterna hirundo*) and harbour porpoise blubber (*Phocoena phocoena*) from the North Sea and reported concentrations of up to 1.8, 2.5, <2.9 and 418 ng/g lipid, respectively.

Fish bioconcentration factors (BCF) for TBBPA has been determined experimentally in a number of studies. BCF were all < 5,000 and ranged from 20 in edible tissue in Blue gill sunfish *(Lepomis macrochirus)* (Nye, 1978) to 1,200 in Fathead minnows *(Pimephalus promelas)* (Fackler, 1989).

4.4. Combustion

The combustion of domestic products containing common BFRs such as TBBPA may lead to formation and release of polybrominated dibenzo-*p*-dioxins and furans (PBDD/Fs). Large amounts of brominated and mixed chloro-bromodioxins and furans can be formed in accidental fires where BFRs are present (Söderström and Marklund, 1999; Lundstedt, 2009).

A comprehensive study of degradation products formed during thermal decomposition (combustion and pyrolysis) of TBBPA has been carried out. High yields of some brominated light hydrocarbons were observed, as well as phenolic derivatives (Ortuño et al., 2011). The authors found more than one hundred semi-volatile compounds. The main ones, were phenol, benzoic acid, 2-bromo-4-methyl-phenol, 1-bromo-2,4,5-trimethyl-benzene, 2-bromo-4-isopropenylphenol, 2,6-dibromo-4-methyl-phenol and 2,6-dibromo-4-isopropenylphenol, as well as derivatives from TBBPA (bromobisphenol A, dibromobisphenol A, tribromobisphenol A, 2-bromo-4-(1-(3,5-dibromophenyl)-1-methylethyl)-phenol and 2,6-dibromo-4-(1-(3,5-dibromophenyl)-1-methylethyl)-phenol. The authors also reported at least six tetra- to hexa-BDD/Fs.

5. Occurrence of TBBPA and its derivatives in food

5.1. Current occurrence of TBBPA and its derivatives in food: call for data

In 2005, the CONTAM Panel (EFSA, 2006) concluded that it was desirable to monitor TBBPA as an important BFR. From October 2006, EU-wide monitoring of BFRs was organised and the results of this exercise were made available to EFSA. In addition, a call for data on BFRs[11] from the Dietary and Chemical Monitoring Unit (DCM) (former Data Collection and Exposure Unit, DATEX) was issued by EFSA in December 2009, with different deadlines according to the chemicals to be collected. The closing date for data submissions on "TBBPA and other brominated phenols" was December 2010.

EFSA evaluated the results reported from the analysis of 652 food samples, which were provided by four European countries and covered the period from 2003 to 2010.

The data submission to EFSA followed the requirements of the Standard Sample Description model. On the EFSA webpage of the call for data detailed instructions on how to submit data[12] and the Guidance on Standard Sample Description for Food and Feed[13] specifying the data elements, the sample data structure of the analytical results for chemical contaminants and residues in food and feed were provided.

SAS Enterprise software was used to extract information from the occurrence data submitted. As a standard routine the DCM unit sends a Data Standardisation report to data providers listing each data management action taken in Advanced Data Standardisation procedure, asking data providers to check and eventually confirm that the extracted information was correct and provide clarifications in case of unclear or missing detailed information.

5.1.1. Summary of data collected

In total, 652 results on TBBPA were reported, with no data on TBBPA derivatives. Around 37 % of the data were provided by Norway, followed by the UK (32 %), and Ireland and Spain (15 %, respectively).

[11] http://www.efsa.europa.eu/en/data/call/datex091215.htm
[12] http://www.efsa.europa.eu/en/datexcallsfordata/datexsubmitdata.htm
[13] http://www.efsa.europa.eu/en/scdocs/scdoc/1457.htm

As illustrated in Figure 2, 7 % of the results were reported for 2003, 2% for 2005, 21% for both years 2006 and 2008, while 34 %, 15% and 1 % of the food were sampled in 2007, 2009 and 2010, respectively. The year 2010 was not a complete year of sampling, as the closing date of the call for data for "TBBPA and other brominated phenols" was December 2010.

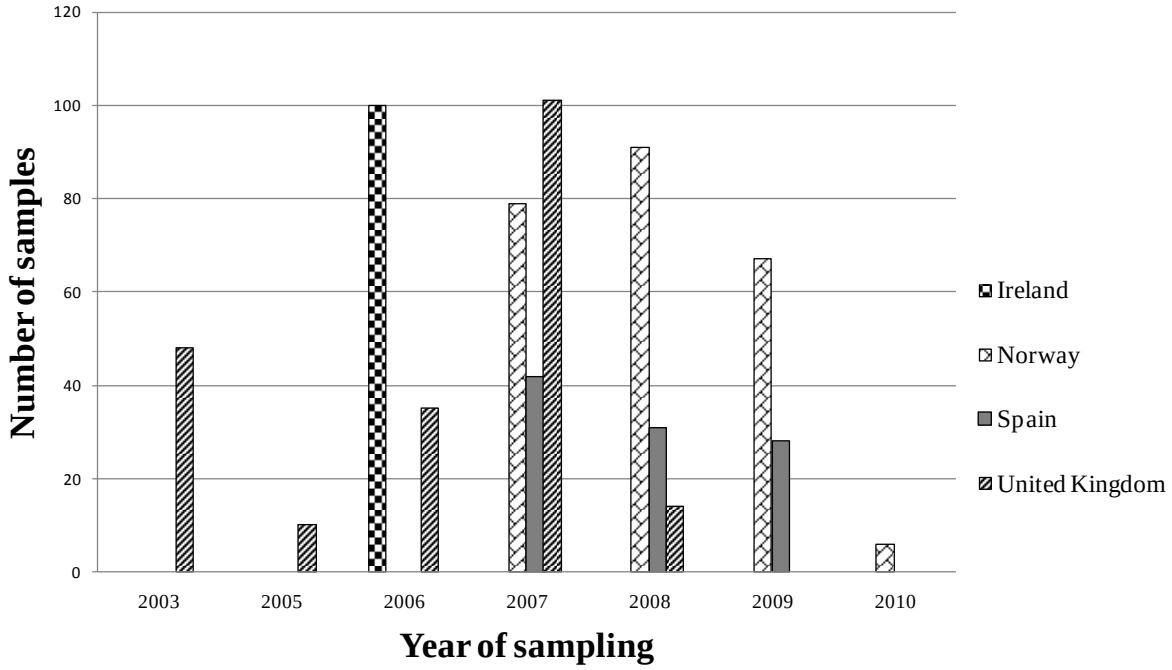

Figure 2: Distribution of food samples across four European countries and over the years of sampling.

During the data cleaning steps, analytical results identified with incomplete or incorrect description of any of the required variables (e.g. parameter type, food classification, results value or results LOD-LOQ of the Standard Sample Description template (EFSA, 2010)), were returned to the respective data provider for further check, before excluding or modifying the records in the database.

Finally, a total of 652 analytical results from food samples were included in the TBBPA dataset.

5.1.2. Occurrence data on TBBPA from food samples: data analysis

Data providers were asked to codify all food descriptors according to the food classification system of the EFSA Concise European Food Consumption Database (EFSA concise food categories).[14]

In order to improve the estimation of the dietary exposure assessment, the "Comprehensive European Food Consumption Database" was established in 2010 with a refined food classification, named FoodEx. FoodEx is a food classification system developed by EFSA's DCM Unit in 2009 with the objective to simplify the link between occurrence and food consumption data when assessing the dietary exposure to hazardous substances. FoodEx contains 20 main food groups (first level),[15] which

[14] http://www.efsa.europa.eu/en/datex/datexfooddb.htm

[15] Grains and grain-based products, Vegetables and vegetable products (including fungi), Starchy roots and tubers, Legumes, nuts and oilseeds, Fruit and fruit products, Meat and meat products (including edible offal), Fish and other seafood (including amphibians, reptiles, snails and insects), Milk and dairy products, Eggs and egg products, Sugar and confectionary, Animal and vegetable fats and oils, Fruit and vegetable juices, Non-alcoholic beverages (excepting milk based beverages), Alcoholic beverages, Drinking water (water without any additives except carbon dioxide; includes water

are further divided into subgroups having 160 items at the second level, 1,261 items at the third level and about 1,800 end-points (food names or generic food names) at the fourth level. It is based on a hierarchical coding for easy cross-checking and it is structured as a child-parent relation (EFSA, 2011a).

From the 20 aggregated food groups available at the first level of FoodEx (FoodEx level 1), the dominant food category was "Fish and other seafood (including amphibians, reptiles, snails and insects)" (n=465). This category was followed by "Meat and meat products (including edible offal)" (n=49), "Milk and dairy products" (n=40), "Animal and vegetable fats and oils" (n=41) and "Eggs and egg products" (n=27). Considering more disaggregated food groups (FoodEx levels 2 and 3), some 60 % of the results were obtained from the analysis of "Fish meat", followed by "Water molluscs" (9 %), "Animal fat" (6 %), "Liquid milk" (5 %), "Edible offal, farmed animals" (5 %), "Eggs" (4 %) and "Crustacean" (3 %). The food groups "Dietary supplements", "Cheese", "Livestock meat", "Poultry" and "Sausages" represented between 1 and 3 %. Some other food groups represented only less than 1 % of the samples each.

The submitted analytical results have all been reported in ng/g wet weight (w.w.), and only data from the UK and Ireland reported information on percentage of fat of the original samples.

The analytical methods reported to perform the analyses of TBBPA in food samples were all LC-MS/MS. For the reporting countries, the LOQs of the methods are 0.05 ng/g w.w. (UK), 0.17 ng/g w.w (IE), 1.0 ng/g w.w. (NO) and 0.9 ng/g w.w. (ES) on average.

Table 3 shows the maximum LOQs reported by food group (FoodEx level 1).

ice for consumption), Herbs, spices and condiments, Food for infants and small children, Products for special nutritional use, Composite food (including frozen products), Snacks, desserts, classification not possible.

Table 3: Maximum LOQ values across different food groups in FoodEx level1.

Food group	N	Maximum reported LOQ (ng/g w.w.)
Fish and other seafood (including amphibians, reptiles, snails and insects)	465	1.00
Meat and meat products (including edible offal)	49	0.14
Milk and dairy products	40	0.65
Animal and vegetable fats and oils	41	4.99 [(a)]
Eggs and egg products	27	0.08
Products for special nutritional use	10	0.34
Vegetables and vegetable products (including fungi)	9	0.02
Grains and grain-based products	3	0.01
Snacks, desserts, and other foods	3	0.10
Starchy roots and tubers	3	0.01
Fruit and fruit products	2	0.02

(a): For three samples (ghee, 4.99 ng/g w.w., pork lard, 2.3 ng/g w.w. and carcass fat, 1.4 ng/g w.w.) LOQs higher than 1 ng/g w.w. were reported.

All the analytical results on TBBPA in food samples from the food groups covered were reported as less than LOQ. Because of this, in accordance with the guidelines of the WHO-Global Environment Monitoring System-Food Contamination Monitoring and Assessment Programme (GEMS/Food), no statistical descriptors for the purpose of exposure assessment could be estimated from this data set (GEMS/Food-EURO, 1995).

5.2. Previously reported literature data on occurrence of TBBPA and its derivatives

5.2.1. Occurrence in Food

5.2.1.1. Fish

Occurrence data on TBBPA and its derivatives in fish, shellfish and crustaceans are scarce. In Table 4, a selection of data is presented. TBBPA has been determined in aquatic biota from The Netherlands, Scotland, the UK, Norway, Belgium, Greenland and China. The levels in fish, when expressed on a wet weight basis, are all below the LOQ, which was generally reported to be <1 ng/g w.w. When slightly higher LOQs were reported (van Leeuwen, 2009), this was the result of analytical determinations on a fat basis, the results of which were converted by means of the fat content of the respective fish species into a concentration expressed on a wet weight basis. There is one high level of 245 ng/g fat in whiting from the North Sea (Morris et al., 2004). However, if this level is converted into a wet weight basis (assuming a fat content of 1 %), it would become 2.5 ng/g w.w., being close to the other reported levels in Table 4.

TBBPA bismethyl ether (TBBPA-bME) was determined in a Dutch study. Levels of this derivative were mostly <LOQ (0.1 ng/g w.w.). In some cases, TBBPA-bME was detected at levels of 0.01-0.6 ng/g w.w. in eel, pike-perch and mussels. TBBPA bis(2,3-dibromopropyl) ether (TBBPA-bDiBPrE) was also determined in capelin from Svalbard, but was always <LOQ (<0.023 ng/g w.w.) (Klif, 2010).

No data on other TBBPA derivatives in fish, shellfish and crustaceans could be identified.

5.2.1.2. Food samples other than fish

Driffield et al. (2008) analyzed TBBPA and other BFRs in the UK 2004 total diet study. Samples were collected throughout the UK at different locations to reflect the UK population. The food was prepared for consumption and combined to give 19 food groups representing the UK diet for 2004. The samples analyzed include bread, miscellaneous cereals, carcass meat, offal, meat products, poultry, oils and fats, eggs, sugars and preserves, green vegetables, potatoes, other vegetables, canned vegetables, fresh fruit, fruit products, milk, dairy products and nuts. TBBPA was not detected in any sample above the LOD, which ranged from 0.02 to 0.2 ng/g w.w. for the different food groups.

Shi et al. (2009) investigated the dietary exposure of Chinese adults and nursing infants to TBBPA and HBCDDs. TBBPA was determined in 48 Chinese total diet study samples. Levels of TBBPA ranged from < LOD to 2.024 ng/g fat. The food samples were collected in 2007 in 12 Chinese provinces. TBBPA was detected above the LOD in about 70 % of all samples. The highest contamination level was found in the aquatic food group followed by the meat products group. The lowest concentrations occurred in the egg and egg products group. Mean concentrations for TBBPA (given in ng/g fat) were found for meat at 0.263 (range: < LOD-1.386), for eggs 0.194 (range: < LOD-0.892) and for milk 0.211 (range: < LOD-0.848). The LODs of TBBPA in meat were 0.07 ng/g w.w., in milk 0.06 ng/g w.w. and in eggs 0.05 ng/g w.w. The concentrations below LOD were treated as ½ LOD for determining the arithmetic mean.

Päpke et al. (2010) analyzed a small number of food samples for TBBPA and other BFRs. Mean values for 15 milk samples were reported at < 0.005 ng/g w.w. (range: < 0.005-0.006 ng/g w.w.).

5.2.1.3. Effects of processing

There are no data available on effects of processing on the levels of TBBPA and its derivatives in food.

5.2.2. Occurrence in human milk

Data on TBBPA in human milk are scarce and limited to three studies from Europe and one study from China. The results of these studies are summarized in Table 5. All concentrations are given as ng/g fat. The TBBPA concentrations range from <0.04 to 37.34 ng/g fat with average levels between 0.06 and 4.11 ng/g fat. The data from the French study (Cariou et al., 2008) show the widest range and the highest median and average concentrations. The CONTAM Panel noted that, in contrast to the other studies, the analytical method applied in the French investigation included a hydrolysis step in the sample preparation in order to cleave potential glucuronide or sulphate conjugates. This may explain the higher values reported.

In the Chinese study (Shi et al., 2009), 1,237 individual human milk samples from 12 provinces were collected in 2007 and pooled into either one rural or one urban sample from each province making up a total of 24 pools. A general difference in the TBBPA concentrations between samples from rural and urban areas was not found as high and low concentrations were determined in both sample types.

Table 4: A selection of occurrence data available in the open literature on TBBPA in fish, shellfish and crustacean.

Country	Location	Year	N	Species	TBBPA	Fat (%)	Unit	Reference
NL	North Sea	2003	2p[(a)]	Cod	<0.4		ng/g w.w.	Van Leeuwen, 2009
n.s.	North Europe	2007-2009	2	Cod	<0.005		ng/g w.w.	Päpke et al., 2010
NL	North Sea	1999	2	Cod (liver)	<0.3-1.8		ng/g fat	Morris et al., 2004
NL	Rivers	2003	14p	Eel	<5.3		ng/g w.w.	Van Leeuwen, 2009
NL	Rivers	1999-2001	11p	Eel	<0.1-1.3		ng/g fat	Morris et al., 2004
NL	North Sea	2003	2p	Flounder	<0.6 - 0.2		ng/g w.w.	Van Leeuwen, 2009
BE	Scheldt basin	1999-2001	19p	Eel	<0.1-13		ng/g fat	Morris et al., 2004
Not specified	North Europe	2007-2009	2	Haddock	<0.005		ng/g w.w.	Päpke et al., 2010
NL	North Sea	2003	2p	Haddock	<0.4		ng/g w.w.	Van Leeuwen, 2009
NL	Atlantic	1999	1	Hake (liver)	<0.2		ng/g fat	Morris et al., 2004
Greenland	-	2007-2009	1	Halibut	<0.005		ng/g w.w.	Päpke et al., 2010
NL	North Sea	2003	4p	Herring	<4.9		ng/g w.w.	Van Leeuwen, 2009
NL	North Sea	2003	3p	Mackerel	<4.8		ng/g w.w.	Van Leeuwen, 2009
NL	North Sea	2003	2p	Mussels	<0.6		ng/g w.w.	Van Leeuwen, 2009
Not specified	North Europe	2007-2009	3	Mussel	<0.26		ng/g w.w.	Päpke et al., 2010
No	Lakes	n.s.	3	Perch	1.2-7.7	2.4-3.6	ng/g fat	Schlabach et al., 2004
No	Lakes	n.s.	3	Pike	1.0-13.7	1.3-2.9	ng/g fat	Schlabach et al., 2004
NL	Rivers	2003	2p	Pike perch	<0.6		ng/g w.w.	Van Leeuwen, 2009
NL	North Sea	2003	2p	Plaice	<0.5		ng/g w.w.	Van Leeuwen, 2009
Not specified	North Europe	2007-2009	1	Redfish	<0.005		ng/g w.w.	Päpke et al., 2010
NL	North Sea	2003	2p	Shrimps	<2.5		ng/g w.w.	Van Leeuwen, 2009
NO	Lake Mjøsa	n.s.	1	Smelt	2.3	2.0	ng/g fat	Schlabach et al., 2004

Table 4: Continued.

Country	Location	Year	N	Species	TBBPA	Fat (%)	Unit	Reference
NL	North Sea	2003	2p	Sole	<0.6		ng/g w.w.	Van Leeuwen, 2009
NO	Lakes	n.s.	4	Trout	2.7-10.4	0.8-9.8	ng/g fat	Schlabach et al., 2004
NO	Lake Mjøsa	n.s.	1	Vendace	5.8	2.9	ng/g fat	Schlabach et al., 2004
NL	North Sea	1999	3	Whiting	<97-245		ng/g fat	Morris et al., 2004
UK	Freshwater lakes	2008	31	Various	<0.25 - 1.7		ng/g fat	Harrad et al., 2009
UK	n.s.	2004	n.s.	Fish (n.s.)[(b)]	<0.081		ng/g w.w.	Driffield et al., 2008
Scotland	Rockall Trough	2006	47	Deep sea fish	<0.3		ng/g w.w	Webster et al., 2009
Scotland	Coast	2006	35	Various shellfish	<0.01		ng/g w.w	Fernandes et al., 2008
China	Various	2007	13	Aquatic food (n.s.)[(b)]	<0.1 - 2.0		ng/g fat	Shi et al., 2009

n.s. not specified.
(a): p indicates that every sample was a pool of several individual samples.
(b): Total diet study sample.

Table 5: TBBPA in human milk samples from different countries as reported in the literature (concentrations expressed in ng/g fat).

Year	Country	n	Range	Median	Average	95th percentile	Maximum	Reference
n.r.	UK	34(a)	<0.04 - 0.65	<0.04	0.06	0.24	0.65	Abdallah and Harrad, 2011
2001	Norway	1(b)	-	-	0.067(b)	-	-	Thomsen et al., 2002
2004-2006	France	77(c)	0.06 - 37.34	0.477	4.11	n.r.	37.34	Cariou et al., 2008
2007	China	24(d)	<LOD - 5.1	n.r.	0.933	n.r.	5.1	Shi et al., 2009

n.r. not reported.
(a): 36 % of samples positive.
(b): pool of 9 samples.
(c): 34 samples positive, samples collected manually on 3rd and 4th day postpartum.
(d): 1,237 human milk samples were collected from 12 Chinese provinces and pooled either into one rural and one urban sample from each province.

6. Food consumption

6.1. EFSA's Comprehensive European Food Consumption Database

In 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) was built from existing national information on food consumption at a detailed level. Competent authorities in the European countries provided EFSA with data from the most recent national dietary survey in their country at the level of consumption by the individual consumer. This included food consumption data concerning infants (2 surveys from 2 countries), toddlers (8 surveys from 8 countries), children (17 surveys from 14 countries), adolescents (14 surveys from 12 countries), adults (21 surveys from 20 countries), elderly (9 surveys from 9 countries) and very elderly (8 surveys from 8 countries) for a total of 32 different dietary surveys carried out in 22 different European countries (EFSA, 2011b). Surveys on children were mainly obtained through the Article 36 project "Individual food consumption data and exposure assessment studies for children" (acronym EXPOCHI) (Huybrechts et al., 2011).

Overall, the food consumption data gathered at EFSA in the Comprehensive Database are the most complete and detailed such data currently available in the EU. However, consumption data were collected with different methodologies and thus they are not suitable for direct country-to-country comparison.

The occurrence data submitted to EFSA were all reported as < LOQ. Therefore a meaningful exposure assessment for the general population is not possible. The CONTAM Panel decided, however, to provide a hypothetical, worst case exposure assessment of TBBPA for two specific population groups with potential high exposure: i) adults with a high fish consumption, and ii) high cow's milk consumers (i.e. toddlers).

6.1.1. High and frequent fish consumers

In order to make a rough estimation of the dietary exposure to TBBPA for high fish consumers, a daily consumption of 2.6 g/kg b.w. of fish meat was used. This value was identified as the highest 95th percentile for consumers only, retrieved from the Comprehensive Database (see food consumption statistics according to the FoodEx food classification system for the total population and for consumers of respective food categories only[16]).

6.1.2. High consumers of cow's milk (i.e. toddlers)

In order to make a rough estimation of the dietary exposure to TBBPA for high consumers of liquid cow's milk (i.e. toddlers), a daily consumption of 85.7 g/kg b.w. of liquid milk was used. This value was identified as the highest 95th percentile for consumers only, retrieved from the Comprehensive Database (see food consumption statistics according to the FoodEx food classification system for the total population and for consumers of respective food categories only[16]).

6.2. Food consumption data for specific age

6.2.1. Breast-fed infants

Estimating the potential dietary exposure to TBBPA and its derivatives for infants from human milk and infant formula requires information about the quantity of liquid consumed per day and the

[16] http://www.efsa.europa.eu/en/datex/datexfooddb.htm

duration over which such consumption occurs. According to the Institute of Medicine of the U.S. National Academies of Sciences (IOM), average human milk consumption is about 750-800 g per day (range, 450-1,200 g per day) for the first 4-5 months of life. Infant birth weight and nursing frequency have been shown to influence consumption (IOM, 1991). The WHO related human milk consumption to body weight rather than age with an estimated 125 mL/kg or 763 mL for a 3 month old child weighing 6.1 kg (Onyango et al., 2002). According to the German DONALD study, mean consumption of infant formula for a three month old child weighing on average 6.1 kg, was 780 mL per day with a 95th percentile consumption of 1,060 mL/day (Kersting et al., 1998). A common mean of 800 mL per day is used in this opinion for consumption of human milk when calculating exposure, with a high of 1,200 mL per day.

7. Human dietary exposure assessment

The analytical results on TBBPA reported to EFSA through the DCM call for data were provided by four European countries (Ireland, Norway, Spain and the UK). The majority of the results collected related to food samples from the food group "Fish and other seafood" (72 %), while the remaining food groups each represented less than 10 % of the total samples. All results were reported as <LOQ. Therefore, the CONTAM Panel concluded that the available occurrence data are not appropriate to carry out a meaningful dietary exposure assessment for the general population or specific population groups including vegetarians. The CONTAM Panel decided, however, to provide a hypothetical, worst case exposure assessment of TBBPA for specific groups of the population with potential high exposure such as adults with a high fish consumption, and high consumers of cow's milk (i.e. toddlers).

Considering the limitations in the submitted data set and the lack of occurrence data from other European countries, the CONTAM Panel assumed that the occurrence levels of TBBPA in "Fish and other seafood" in other European countries would also not exceed the levels of the highest LOQ reported in the data set (≤ 1 ng/g w.w., see 5.1.2). This assumption is supported by the occurrence data in fish as reported in open literature. When reported on a wet weight basis, these values were also below the LOQ, with LOQ values generally below 1 ng/g w.w. (see Section 5.2.1.1).

Following this consideration, the CONTAM Panel decided to use a value of 1 ng/g w.w. as a worst case, "upper bound" scenario for the levels of TBBPA in "Fish and other seafood" all reported to be below the LOQ. Combining this value with a daily consumption of 2.6 g/kg b.w. of fish meat for high fish consumers (see Section 6.1.1), a hypothetical worst case (i.e. "upper bound") chronic dietary exposure to TBBPA of 2.6 ng/kg b.w. per day for this specific population group, considered to be the population with the highest dietary exposure to TBBPA, was estimated.

The CONTAM Panel also considered it relevant to estimate the hypothetical worst case chronic dietary intake of TBBPA for high consumers of liquid cow's milk, i.e. toddlers with the highest consumption/body weight ratio. The value of 0.65 ng/g w.w. was used as a worst case, "upper bound" scenario for the levels of TBBPA in "Liquid milk" all reported to be below the LOQ (see Section 5.1.2.). Combining this value with a daily consumption of 85.7 g/kg b.w. per day of liquid milk (see Section 6.1.2.) a hypothetical worst case (i.e. "upper bound") chronic dietary exposure to TBBPA of 55.7 ng/kg b.w. per day for this specific population group was estimated.

The CONTAM Panel noted that these estimations should be considered with caution, as they are derived from limited occurrence data across four European countries and are based on upper bound levels of TBBPA in only two food groups. Therefore, it does not cover the whole diet, but only reflects the hypothetical worst case exposure to TBBPA for two specific groups of the population, adults with high fish consumption and toddlers with high consumption of cow's milk.

7.1. Dietary exposure to specific sub-groups of the population

7.1.1. Breast-fed infants

For the exposure assessment of breast-fed infants an age of three months was selected, equivalent to a weight of about 6.1 kg, with an estimated average daily consumption of about 800 mL and a high consumption of 1 200 mL of human milk, each with a mean fat content of 3.5 %.

The exposure scenario based on average human milk consumption and the reported range for TBBPA in human milk (see Table 5) results in daily exposures of <0.18-171 ng/kg b.w. For infants with high human milk consumption the respective daily exposures range from <0.28 to 257 ng/kg b.w.

The exposure scenario based on average human milk consumption and average contamination levels across the three European studies results in daily TBBPA exposures of 0.28-18.9 ng/kg b.w. For infants with high human milk consumption, the respective daily exposures range from 0.41 to 28.3 ng/kg b.w.

Average and high consumption of human milk results, for the median TBBPA concentration of 0.48 ng/g fat found in the French study where a hydrolysis step was applied, in daily exposures of 2.2 and 3.3 ng/kg b.w., respectively.

7.2. Previously reported data on dietary intake of TBBPA and its derivatives

Few studies have been found in the literature reporting the dietary intake of TBBPA (Table 6). No studies have been found on any of the TBBPA derivatives considered in this opinion. Comparison between studies should be made carefully due to the use of different methodologies (sampling methods and food consumption data) and food groups covered.

The UK COT issued an assessment on organic chlorinated and brominated contaminants in shellfish, farmed and wild fish where composite samples of 47 species of farmed and wild fish and shellfish consumed in the UK were analysed for, among others, TBBPA (COT, 2006a). The total dietary exposure was estimated by using the consumption data from the 2000/01 National Diet and Nutrition Survey. The estimated intake of TBBPA from the non-fish part of the diet was taken from the 2004 total diet study (TDS) where TBBPA was found < LOD (generally 0.36 µg/kg w.w.) in all the food groups and the intake was estimated at 1.5 ng/kg b.w. per day (COT, 2006b). For the fish part of the diet, a consumption of 140 g of mackerel, identified as the species containing the highest TBBPA concentrations (0.21 µg/kg fresh weight) was considered, and resulted in a total daily intake (non fish part plus fish part of the diet) of 1.6 ng/kg b.w. per day considering a body weight of 60 kg, less than in the hypothetical scenario above. For children (different age groups covering from 4 to 18 years old), the estimated upper bound (UB) average dietary intake ranged from 3.7 to 1.3 ng/kg b.w. per day, and for toddlers (different age groups covering from 1.5 to 4.5 years old) it ranged from 7.0 to 4.6 ng/kg b.w. per day. These estimates were reported to be considerably below the TDI of 1 mg/kg b.w. per day recommended by the COT in 2004 (COT, 2004, see Section 1.2.).

In The Netherlands, the dietary exposure to TBBPA was estimated through the analysis of food samples (n=91) including dairy products, meat, animal fat, eggs and vegetable oils (Winter-Sorkina et al., 2003). The consumption data were from the third Dutch National Food Consumption survey. The mean medium bound (MB) dietary exposure was estimated at 0.04 ng/kg b.w. per day (0.04 ng/kg b.w. per day for LB). The authors noted that the limited number of samples analysed (n=91) and the high percentage of non-detects might have introduced uncertainties in the exposure estimates.

In China, Shi et al. (2009) reported the results of a TDS carried out in 2007 comprising 662 food items collected from local markets, groceries and rural households, and aggregated into 13 food groups. From these, four food groups of animal origin ((i) egg and eggs products, (ii) aquatic food,

(iii) milk and milk products and (iv) meat and meat products) were analysed for TBBPA. In about 70 % of the samples TBBPA was detected. The highest levels were found in the aquatic food group, followed by the meat and meat products group, while the lowest concentrations were found in egg and egg products. The total estimated daily intake of TBBPA was 0.232 ng/kg b.w. per day (lower bound (LB)), 0.256 ng/kg b.w. per day (medium bound (MB)) or 0.280 ng/kg b.w. per day (upper bound (UB)). The food group Meat and meat products contributed 52 % to the estimated daily intake followed by aquatic food (30 %). Milk and milk products and eggs and egg products contributed 10 % and 8 %, respectively.

Table 6: Dietary TBBPA intake for different countries as reported in the literature.

Country, year	Estimation	TBBPA (ng/kg b.w. per day)	Reference
China, 2007	LB MB UB	0.232 0.256 0.280	Shi et al., 2009(a)
The Netherlands	MB LB	0.04 0.04	Winter-Sorkina et al., 2003
UK, 2003-04	UB	1.6(b)	COT, 2006

b.w.: body weight; LB: lower bound: MB: medium bound; UB: upper bound.
(a): original concentrations given in pg/kg b.w. per day.
(b): Adults.

7.3. Non-dietary exposure

TBBPA has generally been found in outdoor air samples at concentrations ranging from <0.04 to 0.85 pg/m^3. TBBPA was, when the distribution was investigated, present primarily in the particulate phase rather than in the vapour phase. This is also the case in indoor settings. Mean TBBPA concentration in homes offices and public microenvironments ranged from 16 to 93 pg/m^3. Considering children (20 kg) and a daily ventilation volume of 5 m^3, the daily exposure via inhalation could reach 0.023 ng/kg b.w.

As shown in Section 4.3.3.1, mean concentrations of TBBPA in indoor dust from homes, offices, cars and public microenvironments were reported to range from 6-220 ng per g dust. Using a typical (50 mg dust per day) and a high end exposure scenario (200 mg dust per day) and assuming a body weight of 20 kg, oral exposure through dust can be estimated to be 0.015-0.55 and 0.06-2.2 ng/kg b.w. per day, respectively. Harrad et al. (2010) reported a 95th percentile concentration of TBBPA in classrooms of schools and day care centres of 460 ng/g dust. Based on a typical or high end scenario, this would result in an exposure of 1.2 or 4.6 ng/kg b.w. per day, respectively.

Abdallah et al. (2008) calculated an average daily exposure of toddlers (6-24 months) of 100 pg via inhalation of TBBPA in air. The corresponding daily exposure via average dust intake was 4.4 ng and 18.0 ng for high dust intake. At a body weight of 15 kg, the mean daily exposure to TBBPA via dust could reach 0.29 ng/kg b.w. and the high exposure 1.20 ng/kg b.w.

In conclusion, daily non-dietary intake of TBBPA via dust based on typical and high end scenarios were 1.2 or 4.6 ng/kg b.w., respectively. It should however be noted that there is no information on the bioavailability of TBBPA in dust.

8. Hazard identification

8.1. Toxicokinetics

Studies on the toxicokinetics of TBBPA are scarce. WHO and ECB reported that after a single oral dose (approximately 7 mg/kg b.w.) of [^{14}C]-TBBPA in corn oil the highest tissue concentrations were found in the liver and in the gonads, and tissue half-lives were reported to vary from 20 h in the blood to 71 h in adipose tissue. By 72 hours post-dosing, approximately 95 % of the radioactivity was eliminated in the faeces and <1.1 % in the urine (Brady, 1979, as cited in WHO/IPCS, 1995; Velsicol Chemical Corporation, 1978, as cited in ECB, 2006). This could be due to poor absorption from the gastrointestinal tract or the result of extensive excretion of TBBPA in the bile.

More recently Hakk et al. (2000) investigated the fate of [^{14}C]-TBBPA administered by gavage to conventional and bile-duct cannulated rats as a single dose (2 mg/kg b.w.). They found that more than 70 % of the dose was eliminated through the bile, suggesting that gastrointestinal absorption should be higher than 70 % of the dose. Three days after dosing, radioactivity retained in tissues of conventional rats represented 2 % of the dose, the highest levels being found in intestine and lung. The percentage of administered radioactivity excreted in the faeces and urine was 91.7 and 0.3 %, respectively. Three metabolites were identified from bile, namely a monoglucuronide and a diglucuronide conjugate of TBBPA as well as a glucuronic acid/sulphate ester diconjugate of TBBPA.

Szymańska et al. (2001) investigated the disposition of [^{14}C]-TBBPA after a single dose (250 or 1,000 mg/kg b.w.) administered intraperitoneally to rats. After 1, 4, 12, 24, 48 or 72 h, the highest concentration was found in adipose tissue. The half-life in plasma, based on radioactivity measurement was found to be 230 h. Almost 10 % of the radioactivity eliminated in faeces corresponded to tribromobisphenol A, suggesting that debromination of TBBPA can occur in mammals.

Analyses carried out in several tissues, including adipose tissue, sampled from rats receiving for 90 days daily dietary doses of 0, 0.3, 30 or 100 mg/kg TBBPA did not reveal any difference in bromine concentration between the control and the treatment groups, suggesting no bioaccumulation (The Dow Chemical Company, 1975, as cited by ECB, 2006).

Meerts et al. (1999) investigated the distribution and the excretion of TBBPA in pregnant rats orally dosed with 5 mg/kg b.w. [^{14}C]-TBBPA, daily on days 10-16 of gestation (GD10-GD16). Approximately 80 % of the radioactivity was excreted in feces by 48 h after the final dose, the percentage eliminated in urine being < 0.2 %. Measurement of the radioactivity in different tissues following termination at GD20, showed that 0.34 % of the administered dose was present in fetuses.

Riu (2006) investigated the metabolic fate of [^{14}C]-TBBPA in pregnant rats dosed daily by gavage (190 µg/kg per day) from GD16 to GD19. Animals were killed at GD20. Total radioactivity measured in animals accounted for less than 0.5 % of the administered dose, the highest levels being found in intestine and liver, and the amount found in fetuses representing less than 0.01 % of the dose, suggesting minor trans-placental transfer. The major part of the radioactivity present in the intestine was found to be due to sulphate and glucuronide conjugates of TBBPA, but these metabolites were not formally identified by LC-MS.

The detection of TBBPA in cord serum collected from French volunteer women during caesarian deliveries (Cariou et al., 2008) confirms that trans-placental transfer of TBBPA occurs in humans.

Schauer et al. (2006) studied the toxicokinetics of TBBPA in rats and humans. Rats received by gavage a single oral dose of TBBPA (300 mg/kg b.w.). TBBPA plasma concentration peaked at 103 µmol/L 3 hours after administration, and thereafter declined with a half-life of 13 hours. TBBPA

glucuronide and TBBPA sulphate where also found in plasma at maximal concentrations of 25 and 694 µmol/L, 3 and 6 hours after administration, respectively. In addition to these metabolites, TBBPA-diglucuronide, TBBPA glucuronide/sulphate, tribromobisphenol A, and tribromobisphenol A-glucuronide were detected at low concentrations in plasma, urine or faeces. In humans (3 men and 2 women) receiving a single oral dose of 0.1 mg TBBPA/kg b.w., parent TBBPA was not detected in plasma (LOD not reported) whereas TBBPA-glucuronide was detected in all human subjects (in both plasma and urine) and TBBPA sulphate was only present in blood from two male subjects. Only a minor part (<0.1 %) of the administered dose was recovered as TBBPA-glucuronide in urine collected up to 178 hours post dosing. The half-life of TBBPA-glucuronide in plasma appeared to be between 48 and 72 hours.

Hagmar et al. (2000) calculated the half-life of TBBPA in blood serum from 4 employees working in an electronics equipment dismantling plant in Sweden. Samples were collected just before the summer vacation and at various times during the vacation. The concentration of TBBPA in serum was found to decrease during the vacation period and a half-life of 2.2 days was estimated.

Based on half-lives determined in rats, Geyer et al. (2004) estimated the terminal elimination half-lives in adult humans. The values reported by these authors for blood and adipose tissue in males, corresponding to the parent compound plus metabolites, were 6.6 and 23.6 days, respectively, whereas in females, the values in plasma and adipose tissue were 76.7 and 21.0 days, respectively. These values seem to be an overestimate compared to those directly calculated from human data.

The *in vitro* metabolism of [^{14}C]-TBBPA was studied in rat and human using subcellular liver fractions (Zalko et al., 2006). TBBPA was metabolised into the corresponding glucuronide (liver S9 fractions) and several metabolites produced by cytochrome P450 dependent pathways (liver microsomes and liver S9 fractions). No major qualitative differences were observed between rat and human, regardless of the selected concentration, within the 20-200 µM range. TBBPA undergoes an oxidative cleavage near the central carbon of the molecule, leading to the production of hydroxylated dibromophenol, hydroxylated dibromoisopropylphenol and glutathione conjugated dibromoisopropylphenol. The main metabolites of TBBPA are two molecules of lower polarity than the parent compound, characterised as a hexa-brominated compound with three aromatic rings and a hepta-brominated dimer-like compound, respectively. Both structures, as well as the lower molecular weight metabolites resulting from the breakdown of the molecule, suggest the occurrence of chemically reactive intermediates formed following a first step oxidation of TBBPA. For both phase I and phase II pathways, metabolites are formed at a higher rate in rat compared to humans and in both cases, a gender difference was observed, males being more efficient than females.

A few studies demonstrate the presence of TBBPA in human milk, with average levels between 0.06 and 4.11 ng/g fat (see Section 5.2.2, Table 5), suggesting that milk represents a substantial route of excretion for TBBPA in humans. The significantly higher values obtained in France by Cariou et al. (2008) in human milk extracts submitted to an enzymatic hydrolysis (β-glucuronidase + sulfatase) prior to GC-HRMS analysis, suggest that milk samples may contain free and conjugated TBBPA.

Overall these data indicate that TBBPA is well absorbed following oral exposure in mammals (>70 % of the administered dose in rat) and then rapidly distributed in different tissues. Experiments performed in pregnant rats as well as analyses carried out on human cord serum demonstrate the occurrence of transplacental transfer. There is no significant tissue retention or bioaccumulation, most of the TBBPA and/or metabolites being eliminated in the faeces, mainly through biliary excretion. There is also evidence that TBBPA and/or its metabolites can be excreted in the milk. The metabolites identified from serum or bile extracts, indicate that TBBPA is conjugated, mainly to glucuronic acid, prior to excretion. Some minor other metabolites have been identified, including TBBPA sulphate, TBBPA diglucuronide, TBBPA glucuronide sulphate, and free and conjugated tribromobisphenol A. The reported half-life of TBBPA-glucuronides in plasma is 2-3 days.

8.1.1. TBBPA derivatives

Only one study was identified concerning the toxicokinetics of TBBPA derivatives. Knudsen et al. (2007) investigated the absorption, distribution, metabolism and excretion of TBBPA bis(2,3-dibromopropyl ether) (TBBPA-bDiBPrE) in male Fischer-344 rats. Animals were dosed with ^{14}C-TBBPA-bDiBPrE (20 mg/kg b.w.) by gavage or intravenous administration. Based on the ratio AUC_{oral}/AUC_{iv}, the systemic bioavailability following a single oral administration was calculated to be 2.2 % of the dose. C_{max} did not occur until 7.5 h after gavage and only unchanged TBBPA-bDiBPrE was found in the blood following oral or *i.v.* administration. Once absorbed, the TBBPA-bDiBPrE half-life of elimination from blood was 13.9 h. At 24 h following a single oral administration, total radioactivity recovered from tissues and gastrointestinal tract contents was below 18 % of the dose, the major part being found in gastrointestinal tract contents. Liver, and to a lesser extent, gastrointestinal and adipose tissues were the major sites of deposition of radioactivity. No radioactivity accumulation was found after repeated oral administration of ^{14}C-TBBPA-bDiBPrE (5 or 10 daily administrations of 20 mg/kg b.w.). Following a single oral administration, faecal elimination was extensive (approximately 95 % of dose by 96 h) and was mainly due to a low gastrointestinal absorption of ^{14}C-TBBPA-bDiBPrE, as demonstrated by a limited biliary excretion (1 % of the dose after 24 h, a period in which more than 70 % of the dose was recovered in the faeces). Excretion in urine was less than 1 % of the dose. Radio-HPLC analyses of radioactive compounds extracted from bile and faecal samples suggest the presence of unidentified metabolites, mainly consisting of glucuronides.

8.2. Biomarkers of exposure

The studies in the literature reporting levels of TBBPA in human samples other than human milk are very limited. No studies have been found reporting levels of TBBPA derivatives.

In France, Cariou et al. (2008) analysed the concentration of TBBPA in maternal and cord serum, and adipose tissue sampled from volunteers during caesarean deliveries, and human milk. TBBPA was not detected in any of the adipose tissue samples analysed (n=44). In maternal serum, TBBPA was quantified in 29 out of the 91 samples analysed with a median (min-max) concentration of 16.14 (0.23-93.22) ng/g fat, while in cord serum it was quantified in 27 out of the 90 samples analysed with a median concentration of 54.76 (2.09-649.45) ng/g fat. When the concentrations were expressed on a fresh weight basis the levels found appeared similar for maternal and cord serum (154 pg/g w.w. and 199 pg/g w.w., respectively). No significant correlation could be established by the authors between the concentrations of TBBPA in maternal and cord serum. No relation was found between the age of the volunteer women and the concentration in maternal serum.

Dirtu et al. (2010) investigated the levels of TBBPA in serum samples from Belgium (n=20) and Romania (n=53) collected during 2000 and 2006-2007, respectively. In both sets of samples the median concentrations were < LOQ (method LOQ=2 pg/mL). The reported minimum and maximum concentrations were <LOQ-2.5 and <LOQ-13 pg/mL, respectively. In another study, the same author reported median TBBPA concentrations in 7 individual serum samples and 14 pooled samples, all from Belgium, of 0.08±0.02 ng/mL and 0.096±0.03 ng/mL, respectively (Dirtu et al., 2008).

Jakobsson et al. (2002) studied the levels of TBBPA in serum samples collected in 1999 from computer technicians working full time with client software and hardware support. TBBPA was detected in 8 out of the 10 samples analysed, but quantified in just four of them. The median concentration was reported < LOQ (1 pmol/g fat) and range of <1-3.4 pmol/g fat. Hagmar et al. (2000) reported concentration of TBBPA in serum samples from workers (n=4) at an electronic dismantling plant in 1997-1998 ranging from <2-7.4 pmol/g fat.

In Norway, Thomsen et al. (2007) analysed TBBPA in archived pooled serum samples from Norway sampled from different county hospitals yearly since 1975. TBBPA was found in all serum pools from

1982 to 2003, as well as methylated TBBPA. The concentration for the sum of both TBBPA and methylated TBBPA ranged from <LOQ (0.1 ng/g fat) to 2.0 ng/g fat.

The CONTAM Panel noted that, in contrast to the other studies, the analytical method applied in the study by Cariou et al. (2008) included an enzymatic hydrolysis step in the sample preparation in order to cleave potential glucuronide or sulphate conjugates. This may have led to the higher values reported compared to those studies where no hydrolysis is carried out. This hampers a direct comparison of the outcome of the studies.

8.3. Toxicity

8.3.1. Acute toxicity

The acute toxicity of TBBPA is reported as very low in rodents with an oral LD_{50} >50,000 mg/kg in rat and >10,000 mg/kg in mice (ECB, 2006). There is no information available on acute toxicity in other mammals or humans after oral exposure.

8.3.2. Sub-chronic and chronic toxicity

In a 90-day toxicity study Sprague Dawley rats were administered orally TBBPA at doses 0, 0.3, 3, 30 or 100 mg/kg b.w. per day (The Dow Chemical Company, 1975, as cited by ECB, 2006). The dose groups consisted of 7 male and 7 female animals. In the control and 3 mg/kg b.w. dose group an additional 12 animals were included to be used for a recovery experiment. After 90 days, 7 animals/sex/group were autopsied and underwent gross pathological examination. From 5 animals/sex/group liver, kidney, skeletal muscle, fat and serum were collected. There were no treatment related mortalities, and no effects on appearance, behaviour, bodyweight and food consumption. No treatment related morphological changes were observed. In female rats of the high dose group a statistically significant reduction in packed cell volume and a slight (not statistically significant) reduction in red blood cell counts were observed. Both effects were in the normal range and therefore considered by ECB to be "of no toxicological relevance". Also in females at the high dose a statistically significant increase in serum glutamate-pyruvate transaminase activity was found. In the absence of morphological changes in the liver this effect was considered by ECB to have no physiological or toxicological significance. Therefore ECB concluded that no adverse effects were seen up to a dose of 100 mg TBBPA/kg b.w.

In another 90-day toxicity study (MPI Research, 2002a, as cited by ECB, 2006) rats received daily gavage doses of 0, 100, 300 or 1,000 mg TBBPA/kg b.w. in corn oil. The 100 and 300 mg/kg b.w. group consisted of 10 animals per sex. In the control and highest dose group an additional 5 animals per sex were included for a six week post-treatment observation. A detailed functional observational battery (FOB) included in this study did not reveal any behavioural effect (see Section 8.3.2.3). During the study 5 animals died (2 in the control and 3 in the high dose) one female animal in the high dose group was euthanised in extremis. None of the deaths were treatment related but due to dosing injuries. No effects on macroscopic and microscopic morphological endpoints were observed. No effects on organ weights were observed with the exception of a decrease in spleen weight in males of the 300 and 1,000 mg/kg b.w. dose group. Haematological evaluation showed a statistically significant decrease in platelet counts in males of the highest dose group. Clinical examination revealed a decrease in bilirubin in males and females at 1,000 mg/kg b.w. and females at 300 mg/kg b.w. In addition a decrease in alkaline phosphatase activity was found in high dose females. In addition, a statistically significant decrease in T4 was found in males and females, however, according to ECB (2006) there was no clear dose response (see also Section 8.3.2.1). The ECB considered that the highest dose (1,000 mg/kg b.w.) could be considered as a NOAEL.

8.3.2.1. Endocrine related effects

In a sub-chronic toxicity study rats were exposed for 13 weeks to TBBPA (100, 300 and 1,000 mg/kg b.w. per day) by gavage. Thyroid hormone levels were evaluated at day 33 (~5 weeks), day 90 (13 weeks) and at the end of the recovery period (MPI Research, 2002a, as cited in ECB, 2006). The levels of thyroid stimulating hormone (TSH) and triiodothyronine (T3) were similar between control and treated animals. A significant, but not dose dependent, decrease in serum thyroxine (T4) levels was observed in males at all dose levels on day 33 and on day 90. In females a significant decrease in serum T4 levels was reported only on day 33. After 30 days recovery the T4 levels were similar between control and treated animals. No other treatment related pathological changes were observed.

In a two generation reproductive toxicity study (MPI research 2002b, 2003, as cited in ECB, 2006) Sprague Dawley rats were exposed to 10, 100 or 1,000 mg TBBPA/kg b.w. per day by gavage in the F0 generation during 10 weeks pre-mating and a 2 weeks mating period. Females were treated also during gestation and lactation. The same treatment regime as in F0 animals was also applied in F1 animals (see also Section 8.3.2.2). Serum T3, T4 and TSH concentrations were determined in F0 and F1 animals several days prior to termination. In the F0 generation the levels of serum T4 were statistically significantly lower in males exposed to 100 and 1,000 mg TBBPA/kg b.w. per day and in females at 1,000 mg/kg b.w. per day. In the F1 generation statistically significantly lower serum T4 concentrations were observed in both sexes exposed to 100 and 1,000 mg/kg b.w. per day. T3 serum levels were significantly lower only in F0 males of the 1,000 mg/kg b.w. per day group. No changes in serum TSH levels, compared to control animals, were observed in any of the treated groups. Extensive histopathological examination performed in this study did not show any changes in any of the organs. The thyroid gland, however, was not included in the examination.

Van der Ven et al. (2008) performed a sub-acute toxicity study and one-generation reproductive toxicity study of TBBPA (from Bromine Science and Environmental Forum, 98 % purity with tribromobisphenol A and o,p'-TBBPA as identified impurities). In the 28-day toxicity study, Wistar rats were dosed with 0, 30, 100 or 300 mg TBBPA/kg b.w. per day via the diet. In the one-generation reproduction assay the rats were dosed with 0, 3, 10, 30, 100, 300, 1,000 or 3,000 mg TBBPA/kg b.w. per day via the diet starting 70 and 14 days prior to the mating for males and females, respectively, and in dams was continued during pregnancy and lactation. Major effects were observed in the thyroid hormone system. The only effects observed in the sub-acute toxicity study were decreased circulating T4 and increased T3 levels in males ($BMDL_{10}$ 48 and 124 mg/kg b.w. per day), and non-significant trends for these parameters in females. In F1 offspring in the one-generation reproduction study decreased circulating T4 was observed in male and female ($BMDL_{10}$ 31 and 16 mg/kg b.w. per day, respectively) and plasma T3 was increased in F1 females ($BMDL_{10}$ 2.3 mg/kg b.w. per day). In F1 males, exposure to TBBPA caused increased weight of testes ($BMDL_5$ of 0.5 mg/kg b.w. per day) and increased weight of the pituitary ($BMDL_{10}$ of 0.6 mg/kg b.w. per day). The CONTAM Panel noted however the unclear dose response for the effects on testes and pituitary.

Saegusa et al. (2009) evaluated effects of TBBPA (98 % purity) in pregnant Sprague-Dawley rats that were administered the chemical at levels of 100, 1,000 or 10,000 ppm in a soy-free diet from gestation day 10 until the day 20 after delivery. Dietary dose levels corresponded to about 9.5-23, 87-202 or 820-2,130 mg/kg b.w., respectively, for maternal exposure. At day 20 after delivery a slight increase in the incidence of diffuse thyroid follicular cell hypertrophy was observed in dams from the mid dose onwards. Male offspring exposed to TBBPA showed a slight non dose-related decrease in serum T3 concentration at PND20, while no changes in serum T4 and TSH concentrations were detected. On PNW11, there were no changes in any of the thyroid hormone related parameters in any of the dose groups.

Meerts et al. (1999) previously reported that oral exposure of rats to 5 mg/kg b.w. TBBPA (^{14}C-ring labelled TBBPA) from day 10 to day 16 of gestation increased fetal plasma TSH concentration, but circulating concentrations of T3 and T4 were unaltered in dams or fetuses.

In conclusion, the studies indicate that TBBPA can affect thyroid hormone homeostasis. Most of the studies indicated a decrease in serum T4. The effects on other parameters such as the levels of T3 and TSH as well as effects on the target organs are not consistent throughout different studies.

8.3.2.2. Reproductive effects and teratogenicity

The effect of TBBPA on reproductive performance has been evaluated in a 2-generation study (MPI research 2002b, 2003, as cited in EBC, 2006). The dosing regimen of this study is described in Section 8.3.2.1. Detailed clinical and macro and microscopic organ examinations were performed in F0, F1 and F2 animals. In F2 animals also neuropathological and neurobehaviour parameters were assessed (see Section 8.3.2.3.). No treatment related clinical or pathological effects were observed in F0 and F1 animals except for a transient decrease in body weight gain during the pre-mating period at 1,000 mg/kg b.w per day in F1 males.

Tada et al. (2006) found no effect of dietary exposure (0 % control, 0.01 % low, 0.1 % middle and 1 % high dose) of ICR mice to TBBPA (99.1 % purity) from GD0 to PND27 on the measured reproductive endpoints (average litter size, average litter weight, total number of offspring, and average male or female offspring weights) and no effect on reproductive organ weights and histopathological changes.

No studies on potential teratogenicity were found in the open literature, but in the International Programme on Chemical Safety (IPCS) report (WHO/IPCS, 1995) and the literature review prepared for NIEHS (2002) several studies have been reported.

TBBPA as Firemaster® BP4-A dosed to rats by gavage at doses of 0.03, 0.1, 0.3, 1, 3 or 10 g/kg b.w. per day on GD6-GD15 was not teratogenic (IRDC, 1978; Velsicol Chemical Corporation, 1978a,b, as cited in NIEHS, 2002). Also in rats treated with 0, 0.28, 0.83 or 2.5 g TBBPA/kg b.w. from GD0 - GD19 the treatments did not impair the birth rate, no toxic effects were observed on the embryo or fetus, and there were no skeletal or visceral abnormalities (Noda, 1985, as cited in WHO/IPCS, 1995).

Taken together, the available studies in the literature indicate that there are no reproductive nor teratogenic effects of TBBPA.

8.3.2.3. Nervous system

The information on TBBPA neurotoxicity is very limited. There are a few *in vivo* studies, summarized in Table 7, that have provided contradictory results especially with regard to the developmental neurotoxic potential of TBBPA.

Eriksson et al. (2001) did not observe any behavioural alteration in adult mice exposed to a single dose of TBBPA (0.75 or 11.5 mg/kg b.w. by gavage) at PND10.

In a sub-chronic toxicity study (MPI Research, 2002a, as cited by ECB, 2006), Sprague-Dawley rats were administered doses of 0, 100, 300 or 1,000 mg/kg per day TBBPA daily by gavage in corn oil for 13 weeks (for study description see Section 8.3.2.1). Detailed physical and neurobehavioral evaluations were made weekly. A detailed FOB was conducted pre-test and at week 12, motor activity was also assessed at week 12. No neurobehavioural effects were observed.

A two-generation study using Crl:CD(SD) IGS BR rats did not identify any effects following exposure to doses up to 1,000 mg/kg on either locomotor activity or spatial learning and acoustic startle habituation in F2 pups (Schroeder, 2002, as cited by Williams and deSesso, 2010). Similarly, in a two-generation study (MPI Research 2002b, 2003, as cited by ECB, 2006), Wistar rats were administered TBBPA by gavage at 10, 100 or 1,000 mg/kg b.w. per day from pre-mating until the end of the lactation. The behavioural testing included locomotor activity (horizontal and vertical), and learning and memory tests in the Morris water maze and passive avoidance test. There were no differences in the F2 pups between exposed and control animals.

In a one-generation reproductive toxicity study by Lilienthal et al. (2008), Wistar rats were exposed to TBBPA added to the standard laboratory diet in doses equivalent to 0, 3, 10, 30, 100, 300, 1,000 or 3,000 mg/kg b.w. The exposure started 10 weeks prior to mating for female rats and 2 weeks before for males. From PND21 the offspring received the same dose of TBBPA as the mother throughout life. The brainstem auditory evoked potentials (BAEP) evaluated in F2 animals at 50-110 days of age showed predominant cochlear effects in females, while in males neural effects were more apparent. A $BMDL_5$ of about 8 mg/kg b.w. for prolongation of wave IV latencies has been reported for male and female rats. $BMDL_5$ values for hearing thresholds in female rats ranged from about 1 to 40 mg/kg b.w. The CONTAM Panel noted that the ratios between these BMDLs and their corresponding BMD value were rather large, indicating a high uncertainty in these outcomes. The cue conditioned fear and sweet preference test did not show any significant alteration.

A study performed in 3 week old mice treated with a single oral dose (gavage) of 0.1, 5 or 250 mg TBBPA/kg b.w. showed behavioural alterations in the open field, contextual fear conditioning and Y maze tests 3 hours after dosing. Effects were observed at the two lower doses and not at the highest dose (Nakajima et al., 2009). Considering the limited information given about the experimental protocol and the lack of a clear dose response, the CONTAM Panel did not find these results adequate for risk characterization purposes.

Histological analyses performed on brain sections from rats exposed to different levels of TBBPA from GD10 to PND20 showed no morphometric alterations (Saegusa et al., 2009). Also Viberg and Eriksson (2011) did not detect any significant changes in the level of proteins involved in brain development, such as CaMKII, GAP-43, synaptophysin and tau, effects that were observed after exposure to other BFRs such as BDE-99.

8.3.2.4. Immunotoxicity

Host immunity to respiratory syncytial virus (RSV) was investigated after exposure of five weeks old mice to 1 % TBBPA (purity not stated) in the diet (approximately 1,700 mg/kg b.w. per day) for 28 days followed by RSV infection (Watanabe et al., 2010). TBBPA significantly increased the viral titer on day 5 post infection, in contrast to treatment with HBCDDs or DecaBDE. Other than slight histological changes observed in lung tissues, no toxicological signs were seen in TBBPA-treated mock-infected animals. TBBPA treatment also altered production of various cytokines in the RSV-infected animals. In RSV-infected mice TBBPA exposure increased the fraction of immature B-lymphocytes in the bronchoalveolar lavage fluid, but not in the spleen.

The effects of TBBPA (mixed into the feed, eight dose groups 0-3,000 mg/kg b.w. per day, 98 % purity, tribromobisphenol A and *o,p'*-TBBPA identified as impurities) on immune parameters were investigated in a one-generation reproduction assay in Wistar rats which was enhanced for endocrine parameters, and in a 28-days repeat dose study (four dose groups 0-300 mg/kg b.w. per day) (van der Ven et al., 2008). There was no effect on immunisation response against sheep red blood cells (SRBC) in male F1 animals, and the natural killer (NK) cell activity test in spleen cells showed no change. There was an increase of total spleen cell count and an increase of blood monocytes, but these observation showed high statistical uncertainty (high BMD to BMDL ratio). No other effects on blood

or on bone marrow cell populations were seen. There were no important TBBPA related effects in the immune and haematological parameters in the 28-days repeat dose study.

A 13 weeks study in rats dosed with TBBPA at 0, 100, 300 or 1,000 mg/kg b.w. per day by gavage showed no effects of toxicological significance on spleen weight. Microscopic examination revealed no treatment related findings (MPI Research, 2002a, as cited in ECB, 2006).

In summary, available studies indicate that TBBPA can affect the host immunity in mice after administration of 1,700 mg/kg b.w. per day for 28 days, whereas doses up to 3,000 mg/kg b.w. per day did not affect the immunisation response to SRBC in rats.

8.3.2.5. Nephrotoxicity

Polycystic lesions of the kidney were reported in newborn rats and not in young (5-week-old) rats exposed repeatedly to 200 or 600 mg TBBPA/kg; the nephrotoxicity of TBBPA might be specific for newborn rats although the toxic dose level was relatively high (Fukuda et al., 2004). Male Sprague-Dawley rats at 8 week of age were treated orally with TBBPA at 200, 500 or 1,000 mg/kg in two experiments, a single-dose study and 14-day-repeated dose study. Acute one-day high-dose administration elevated transiently renal lipid peroxidation and superoxide dismutase activity. A repeated dose study in rats administered TBBPA at 200, 500 or 1,000 mg/kg in corn oil showed that TBBPA was not toxic to the kidney (Kang et al., 2009).

Table 7: Effects of TBBPA on the nervous system.

TBBPA	Exposure model	Age	Exposure level	LOAEL	Purity	Outcome	Reference
From Aldrich	NMRI mice	PND10	Single exposure 0.75 (1.4 µmol) or 11.5 mg/kg (21.1 µmol) b.w. oral (gavage)		98 %	• No significant changes in locomotion, rearing, total activity, habituation capability, swim maze performance in 2 and 4 month old mice.	Eriksson et al., 2001
	Crl:CD(SD) rats	10 weeks premating in P generation until weaning of F2 litters	0, 10, 100 or 1,000 mg/kg b.w. oral (gavage)	N/A		• No effect on behaviour, auditory startle habituation, or learning	Schroeder, 2002 (as cited by Williams and deSesso, 2010)
	Sprague-Dawley rats		0, 10, 100 or 1,000 mg/kg b.w. (gavage) for 13 weeks			• No effects on behaviour or neuropathology	MPI Research, 2002a (as cited by ECB, 2006)
	Wistar rats	10 weeks premating until weaning	0, 10, 100 or 1,000 mg/kg b.w. oral (gavage)			• No effects on locomotor behaviour, learning and memory.	MPI Research 2002b, 2003 (as cited by ECB, 2006)
From Dr. Rothen-bacher	Wistar rats	Maternal exposure 10 weeks prior mating; paternal 2 weeks. Offspring from PND21	0, 3, 10, 30, 100, 300, 1,000 or 3000 mg/kg b.w. added to the standard laboratory diet.	BMDL 8 mg/kg	98 % (main contaminants tribromobis-phenolA and o,p'-TBBPA)	• No effects on cue conditioned fear and sweet preference. • BAEPs evaluated at 50-110 days of age show cochlear effects in females, and neural effects in males.	Lilienthal et al., 2008

Table 7: Continued.

TBBPA	Exposure model	Age	Exposure level	LOAEL	Purity	Outcome	Reference
From Tokyo Chemical Industry	Mice	3 weeks	0.1, 5 or 250 mg/kg b.w.	0.1 mg/kg	99 %	• All measurements were performed 3 hours after the exposure. • Alterations in horizontal movement activity in the open field at 5 mg/kg. • Alterations freezing behaviour in contextual fear conditioning at 0.1 and 5 mg/kg. • Alterations in spontaneous alternation behaviour in the Y-maze test at 0.1 and 5 mg/kg. • No effects at 250 mg/kg.	Nakajima et al., 2009
From Tokyo Kasei Kogyo Co.	SD rats	GD10 to PND20	100, 1,000 or 10,000 ppm		>98 %	• No alterations in brain morphometry in the adult offspring	Saegusa et al., 2009
From Stockholm University	NMRI mice	PND10	11.5 mg/kg (21 µmol) b.w. oral (gavage)		>98 %	• No alterations in the levels of CaMKII, GAP-43, Synaptophysin and Tau proteins in hippocampus and cortex (24 h after exposure).	Viberg and Eriksson, 2011

8.3.2.6. Hepatotoxicity

Szymańska et al. (2000) administered TBBPA intragastrically daily for 7 days (375, 750 and 1,125 mg/kg b.w. per day) or 7-28 days at three dose levels (10, 50, or 250 mg/kg b.w. per day), to male and female outbred IMP:Wist rats. In the 7-days-study, the level of glutathione (GSH) was lowered at the two higher doses (female rats only) and malondialdehyde (MDA) was elevated by the highest dose (male rats only). The 5-aminolevulinate dehydratase (ALA-D) activity was slightly enhanced in females at the highest dose. In the 28-day study no significant changes in the aforementioned parameters were obtained.

In a study carried out by MPI Research (2002a, as cited in ECB, 2006), rats were administered daily gavage doses of 0, 100, 300 or 1,000 mg/kg b.w. per day TBBPA in corn oil for 13 weeks. In clinical chemistry analysis at study termination, total bilirubin values in the 1,000 mg/kg b.w. males and females and the 300 mg/kg b.w. females were statistically significantly higher (2-3 fold) than in the controls. Serum alkaline phosphatase (ALP) levels in the 1,000 mg/kg b.w. females were also statistically significantly higher (1.7 fold) than in the controls. However, bilirubin and ALP levels in the control and treated groups were comparable at the end of the recovery period. In view of the absence of differences between the test and control groups in other clinical chemistry markers of liver toxicity (e.g. aspartate aminotransferase (AST), alanine aminotransferase (ALT) and the absence of evidence of liver damage on histopathological examination, it is concluded in ECB (2006) that the clinical chemistry parameters did not represent a toxic response of the liver.

Germer et al. (2006) treated juvenile/young male and female Wistar rats orally with various doses of TBBPA via the feed. The estimated doses were approximately 0, 30, 100 and 300 mg/kg b.w. per day. After 28 days of treatment the animals were terminated and hepatic mRNA and microsomes were isolated. The parameters measured, i.e. hepatic CYP2B1 mRNA, CYP2B1/2B2 protein and 7-pentoxyresorufin O-dependentylase (PROD) activity, CYP3A1/3A3 mRNA, CYP3A1 protein, and luciferin benzylether debenzylase (LBD) activity, CYP1A2 mRNA, CYP1A1/1A2 protein, and microsomal 7-ethoxyresorufin O-deethylase (EROD) activity were unchanged.

Tada et al. (2006) administered TBBPA (99.1 % pure) in the diet to pregnant ICR mice at doses of 0 % (control), 0.01 %, 0.1 % or 1.0 % from GD0 to weaning at PND27. Liver weights of treated dams and offspring were higher than those of the control mice. Histological findings in treated dams or offspring showed (an increase of) focal necrosis of hepatocytes and inflammatory cell infiltration in the liver.

In a subsequent study, Tada et al. (2007) examined the effects of TBBPA on the liver after administration to male mice for 14 consecutive days. Groups of seven (control group) or eight (treated group) Crlj:CD1 (ICR) male mice were given 0 (control), 350, 700 or 1,400 mg/kg b.w. per day TBBPA (99.1 % pure) in olive oil. Absolute and relative liver weights were dose-dependently increased, and were statistically significantly increased in the high-dose (1,400 mg/kg b.w. per day) group. It is noteworthy that some control animals already showed enlargement of the hepatocytes, inflammatory cell infiltrations and focal necropsis of hepatocytes. The histological findings were more marked in liver of treated groups (from 350 mg/kg b.w. per day on) than in control group.

In summary, TBBPA exhibits some signs of hepatotoxicity in rats and mice, particularly in juvenile mice, at high doses (i.e. in the g per kg b.w. dose range). At lower doses (below 350 mg/kg b.w.) no signs of hepatic changes including effects on hepatic drug metabolism were found.

8.3.2.7. Genotoxicity

No studies were found in the open literature, but in the ECB risk assessment report (ECB, 2006), in the literature review for NIEHS (2002) and in the IPCS report (WHO/IPCS, 1995) a number of *in vitro* genotoxicity tests are reported.

In the Salmonella/microsomal reverse mutation assay with strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 and in yeast test system with *Saccharomyces cerevisiae* strains D3 or D4 in the presence and in the absence of metabolic activation and at concentrations of TBBPA up to 10 mg/plate the results were consistently negative (Mortelmans et al., 1986; Ethyl Corp., 1981; Litton Bionetics, Inc., 1976, 1977a,b; Velsicol Chemical Corporation, 1978, as cited in ECB, 2006; SRI Int.,1978, as cited by NIEHS, 2002).

TBBPA (6.25, 25 and 75 µg/mL) in the presence and absence of metabolic activation also did not induce chromosomal aberrations in human peripheral lymphocytes (BioReliance, 2001, as cited in ECB, 2006).

TBBPA tested at concentrations from 5 to 70 µg/mL in an unconventional *in vitro* Sp5/V79 and SPD recombination assay also gave a negative response (Hellayday et al., 1999, as cited in ECB, 2006). The compound in a concentration range from 5.3 -500 µg/mL also did not induce sister chromatid exchanges in Chinese hamster ovary (CHO) cells in the presence and absence of metabolic activation (Cavagnaro and Cortina, 1984a, as cited by WHO/IPCS, 1995) and was negative *in vitro* in a rat hepatocyte unscheduled DNA synthesis assay (10-1,000 µg/mL) (Cavagnaro and Sernau, 1984b, as cited by WHO/IPCS, 1995).

In conclusion, the *in vitro* data indicate that TBBPA is not genotoxic. *In vivo* genotoxicity data are not available.

8.3.2.8. Carcinogenicity

No carcinogenicity data on TBBPA or its derivatives could be identified.

Imai et al. (2009) investigated the effects of early life exposure of rats to TBBPA on the carcinogenicity of 7,12-dimethylbenz(a)anthracene (DMBA) and N-bis(2-hydroxypropyl)nitrosamine (DHPN) administered later in life. Groups of 6 female Fischer F344 rats were administered TBBPA at concentrations of 0, 0.01 %, 0.1 % or 1 % in soybean-free modified NIH-07 diet for 3 weeks after parturition, to expose pups during lactation. Four days after birth, litters were reduced to 4 males and 4 females, by random selection. Offspring were exposed for a further 2 weeks after weaning to the same dietary levels of TBBPA, after which they were switched to the soybean-free diet alone, for a further 4 weeks. All male and female offspring were administered drinking water containing 0.08 % and 0.2 % DHPN, respectively, from weeks 7 to 10. In addition, at week 7, females were administered a single intragastric dose of 50 mg/kg b.w. DMBA in 5 ml/kg b.w. sesame oil. Animals were monitored for the appearance of tumours from week 17 until termination at 37 weeks of age for males and 47 weeks of age for females.

Treatment had no significant effect on survival, body weight, body weight gain, food or water intake in any of the groups.

The incidence of thyroid follicular adenomas was statistically significantly increased ($p < 0.05$) in females receiving 1 % TBBPA (13/22 (59 %) in controls; 9/13 (69 %) in 0.01 % TBBPA group; 11/17 (65 %) in 0.1% group; 12/13 (92 %) in 1 % group).

The incidences of transitional cell papillomas in the urinary bladder were statistically significantly increased (P<0.05) in females receiving 0.01 %, 0.1 % and 1 % TBBPA (0/23 (0 %) in controls; 3/13 (23 %) in 0.01 % TBBPA group; 4/17 (24 %) 0.1 % group; 4/13 (31 %) in 1 % group).

It was noted that there was no increase in the incidence of malignant tumours in either tissue over the course of the study. There was no dose-response relationship for the incidences of transitional cell papillomas of the urinary bladder.

There are no long term toxicity or carcinogenicity studies of TBBPA in animals. The CONTAM Panel noted however that TBBPA was not genotoxic *in vitro*. In addition, in studies of up to 90 days repeated administration of TBBPA there were no indications of a carcinogenic potential (e.g. proliferative changes, cytotoxicity, or immunosuppression, except possibly at high doses). It is therefore concluded that there are no indications that TBBPA might be carcinogenic.

8.3.3. Biochemical effects and molecular mechanisms

Experimental animal models have shown that TBBPA might affect thyroid hormone homeostasis and the immune system, and that it might exert weak estrogenic activity. In this Section, mechanistic *in vitro* studies are summarized and linked to experimental *in vivo* data.

8.3.3.1. Endocrine related modes of action of TBBPA

CYP induction has been reported to affect metabolism of steroids and other hormones. However, TBBPA did not induce CYP1, CYP2B1 or CYP3A mRNA, protein and respective monooxygenase activities in rats after 28-day exposure to TBBPA – at doses up to 300 mg/kg b.w. per day (Germer et al., 2006). Modulation of heme metabolism in rats has been reported at high doses (Szymańska et al., 2000) (see also Section 8.3.2.6). Effects of TBBPA did not involve a significant activation of AhR as shown in the DR-CALUX assay (Hamers et al., 2006), although a weak induction of AhR-dependent gene expression was reported previously by another group in the same assay (Behnisch et al., 2003). However, Behnisch et al (2003) also reported no induction of AhR-dependent 7-ethoxyresorufin-*O*-deethylase activity.

Aromatase activity, a key step of synthesis of estrogens, was not modulated by TBBPA up to 7.5 μM concentration in H295R adrenocortical carcinoma cells (Cantón et al., 2005). TBBPA (0.5 μM) slightly induced CYP21 expression (the gene required for the synthesis of both aldosterone and corticosteroids) but not other steroidogenic enzymes (Song et al., 2008). Thus TBBPA does not significantly affect steroidogenesis.

Weak estrogenic potency was found, determined as the ability of TBBPA to bind to the estrogen receptor, to induce estrogen receptor (ER)-dependent cell proliferation and ER-dependent expression of pS2 and progesterone receptor proteins (Samuelsen et al., 2001). The maximal effects were observed at a relatively high (30 μM) concentration of TBBPA (Olsen et al., 2003). Hamers et al. (2006) reported no positive or suppressive modulations of estrogen receptor-dependent gene expression in ER-CALUX assay up to a concentration of 10 μM. Similarly, Riu et al. (2011) found no significant ER-mediated reporter gene expression in human HGELN-ERα and HGELN-ERβ cell lines (HeLa cells stably transfected with an ERE-driven luciferase plasmid). MCF-7 cell proliferation (dependent on estrogenic signalling) was not affected by TBBPA (Dorosh et al., 2010). A weak ER-mediated activity (EC_{50} = 19 μM) was found in ERE-luciferase reporter assay with MCF-7 cells, on the other hand, also a partial antiestrogenic activity (suppression of E2-dependent gene expression) has been reported (Kitamura et al., 2005a). These data suggest that modulation of estradiol receptor signalling is not a significant mode of action of TBBPA.

In a uterotrophic assay in ovariectomized B6C3F1 mice *i.p.* administration of 20-500 mg TBBPA/kg per day for three consecutive days caused a modest increase in relative uterine weights with a maximum response at 300 mg/kg b.w. Compared to 17-β estradiol, TBBPA showed weak estrogenic activity (Kitamura et al., 2005a). Hamers et al. (2006) found inhibition of estradiol sulfotransferase activity by TBBPA with an IC_{50} of 1.6 nM. Therefore, the *in vivo* estrogenic activity of TBBPA might be explained by inhibition of 17β-estradiol sulfotransferase by TBBPA rather than a direct effect on estrogen receptor-mediated gene expression.

No anti-androgenic activity of TBBPA was found in a mouse fibroblast NIH3T3 cell line, transiently transfected with human AR and an androgen receptor response element in front of a reporter (luciferase), after co-treatment with 5α-dihydrotestosterone and TBBPA (Kitamura et al., 2005a). Similarly, Hamers et al. (2006) reported no agonistic nor antagonistic activities of TBBPA against androgen receptor- or progesterone receptor-mediated gene expression. TBBPA bis(2,3-dibromopropyl ether) (TBBPA-bDiBrPE) also showed no activities towards the ER, AhR or AR in CALUX assays and its potency to inhibit 17β-estradiol sulfotransferase activity (IC_{50}=0.3 μM) was lower than that of TBBPA (Hamers et al., 2006).

Contradictory results were reported on TBBPA-induced changes in concentrations of thyroid hormones in experimental animals (see 8.3.2.3). *In vitro* studies suggested the possible critical modes of action of TBBPA on thyroid hormone system. High affinity binding of TBBPA to transthyretin was reported by two groups (Meerts et al., 2000; Hamers et al. 2006). A low (31 nM) IC_{50} value of the capacity of TBBPA to compete with T4 for binding to human transthyretin was estimated (Hamers et al., 2006) suggesting that this step of thyroid hormone signalling might be one of the critical effects of TBBPA. The TBBPA derivative, TBBPA-DiBPrE, caused only weak competitive binding to the human transthyretin with EC_{50} = 5.2 μM.

Further studies were focused on direct modulation of thyroid hormone receptor (TR) activity. TBBPA significantly inhibited the binding of T3 to the TR from a concentration of 100 nM with IC_{50}=3.5 μM (Kitamura et al., 2005b). However, TBBPA showed no induction of TRα- or TRβ-dependent gene expression in a TRE-responsive reporter assay in CHO cells but a significant antagonistic effect against T3 activity was reported. Significant anti-thyroid hormone effects were observed from a concentration of 3.1 and 25 μM TBBPA using TRα1- and TRβ1-transfected Chinese hamster cells, respectively (Kitamura et al., 2005b). The TRβ1 antagonistic activity of TBBPA was confirmed in the TRβ1-mediated reporter gene assay based on transiently transfected human HepG2 cells (Sun et al., 2009). TBBPA (from a concentration of 5 μM) also suppressed the T3-induced luciferase activity in a stable TR-specific reporter gene assay in the GH3.TRE-Luc cell line; the rat pituitary tumor cell line GH3 constitutively expresses both TR isoforms (Freitas et al., 2011).

Inhibition of deiodinase activity (found *in vitro* from a concentration of 1 μM using human liver microsomes) might contribute to overall antagonistic activity of TBBPA against thyroid hormone signalling (Butt et al., 2011).

Anti-thyroid activity was evident *in vivo* from the suppressive effect on amphibian metamorphosis stimulated by thyroid hormone. TBBPA in the concentration range of 0.01 to 1 μM showed suppressive action on T3-dependent enhancement of *Rana rugosa* tadpole tail shortening in the tadpole metamorphosis bioassay (Kitamura et al., 2005b).

TBBPA was reported to bind to the PPARγ nuclear receptor, resulting in the activation of this receptor involved in the regulation of fatty acids storage and glucose metabolism (Riu et al., 2011). TBBPA (10 μM) was also found to promote the expression of PPARγ target genes and to induce adipogenesis in the mouse 3T3L1 preadipocyte cell line. The effect was inhibited by a specific PPARγ inhibitor indicating that the adipogenic action of TBBPA is mediated via the PPARγ nuclear receptor (Riu et al., 2011).

Activation of the melatonin 4 receptor (Mc4r) in the hypothalamus by thyrotropin-releasing hormone (Trh) and T3, reduces food intake and increases energy usage (Decherf et al., 2010a). TBBPA decreased expression of luciferase reporter activity, linked to Mc4r and Trh promoters injected into the hypothalamus of newborn mice. Effective doses were a single *s.c.* injection of 2.1 g/kg b.w. or 150 mg/kg b.w. for 7 days. This decrease in Mc4r and Trh expression by TBBPA might lead to disruption of food intake control and obesogenic processes (Decherf et al., 2010b).

Taken together, *in vitro* mechanistic studies indicate significant effects of TBBPA on the thyroid hormone system (binding to transport protein transthyretin, antagonistic action towards TRα- and TRβ-dependent gene expression). These antagonistic effects might be critical for the toxicity of TBBPA, but need to be further investigated *in vivo*. Further, inhibition of estradiol sulfotransferase activity (and not a direct modulation of ER-mediated gene expression) might be the key event responsible for the weak estrogenic activity of TBBPA. Additionally, activation of PPARγ-dependent gene expression by TBBPA observed *in vitro* might disrupt the adipogenesis regulation and might increase the risk of metabolic diseases. TBBPA-induced suppression of key regulators of food intake (Mc4r and Trh) may be another possible mechanism to affect metabolic processes. Available *in vivo* studies (see Section 8.3.2) however, have not provided evidence for such type of effects.

8.3.3.2. Modes of action which may underlie neurotoxic and neurodevelopmental processes

As experimental *in vivo* studies indicate a possibility of neurodevelopmental behavioural effects of TBBPA, several *in vitro* studies have focused on searching for a mechanism of action of TBBPA. *In vitro* mechanistic studies showed in synaptosomes inhibition of uptake of neurotransmitters dopamine, glutamate and gamma-amino-n-butyric acid (GABA); the IC_{50} values for TBBPA were 9, 6 and 16 μM, respectively (Mariussen and Fonnum, 2003). At low micromolar concentrations, TBBPA increased reactive oxygen species (ROS) formation, extracellular glutamate and intracellular calcium in cerebellar granule cells leading to apoptosis-like nuclear shrinkage, chromatin condensation, DNA fragmentation and cell death (Reistad et al., 2007). These effects, associated with activation of MAP kinases ERK1/2, may underlie a mode of action of TBBPA.

8.3.3.3. Effects of TBBPA associated with immunotoxicity

Lysis of infected cells by NK cells is a frontline defence against virus infection. Treatment of isolated human natural killer cells (NK cells) with TBBPA (2.5 μM and 5μM) for 24 h caused a dose-dependent reduction in their lytic function (>95 % reduction at 5μM), decreased binding to target cells and decrease in ATP level in the cells (only at 5 μM). The reduced lytic function was also seen after 1 h exposure to 5 μM followed by 24h incubation in fresh media (Kibakaya et al., 2009). The observations might result from a TBBPA induced decrease in cell-surface proteins involved in NK-cell-dependent target cell lysis (Hurd and Whalen, 2011).

TBBPA (at concentrations of 1-10 μM) may modulate inflammatory responses. TBBPA induced cyclooxygenase-2 (via activation of proinflammatory transcription factors NF-κB and AP-1) and prostaglandin E2 production in murine RAW 264.7 macrophages. In addition, TBBPA increased the secretion and mRNA levels of proinflammatory cytokines such as tumor necrosis factor-α, interleukin-6 and interleukin-1β. Activation of phosphatidylinositol 3 kinase and MAP kinases by TBBPA was involved in induction of these processes (Han et al., 2009).

Although no significant modulations of immune responses were found in a 28-day repeated dose study in rats, TBBPA affected host immunity in mice at high doses (see Section 8.3.2.4). Based on *in vitro* data, induction of inflammation might be another mode of action of TBBPA.

Overall, TBPPA has been shown to affect a number of cellular signalling systems *in vitro*, generally at concentrations around 2.5 μM or greater. The significance of these effects, if any, to consumers

exposed to low levels of TBBPA in the diet has yet to be determined, and will require estimation of target tissue concentrations to enable extrapolation to the *in vivo* situation.

8.4. Observations in humans

No studies on health effects in humans due to exposure to TBBPA and/or its derivatives have been identified in the open literature.

8.5. Consideration of critical effects and possibilities for derivation of a health based guidance value

The limited toxicokinetics data suggest that, following oral administration of TBBPA to rats about 70 % is absorbed, distributed in different tissues and rapidly excreted via the bile in faeces. Metabolites identified in the bile were mainly glucuronide or sulphate conjugates of TBPPA. Tribromo-BPA has been identified in faeces, suggesting that debromination of TBBPA can occur in mammals. The plasma half-life in rats was estimated to be about half a day. In humans, the half-life of TBBPA-glucuronide in plasma appeared to be between 48 and 72 h.

Toxicological studies with TBBPA have been carried out using different experimental designs with single or repeated dosing during gestation, postnatally or in adulthood. The main target for TBBPA toxicity was thyroid hormone homeostasis.

Two 90-day toxicity studies in which rats were administered TBBPA orally at doses of 0, 0.3, 3, 30 or 100 mg/kg b.w. per day and 0, 100, 300 or 1,000 mg/kg b.w. per day were evaluated by ECB (2006). The CONTAM Panel did not have access to the original reports of these studies and based its assessment on the EU risk assessment report (ECB, 2006). In the first 90-day study no treatment related effects were observed with the exception of a reduction in packed cell volume in the highest dose group (100 mg/kg b.w.) which was according to ECB "*within the normal range and therefore not considered to be of toxicological relevance*". The CONTAM Panel agreed with this conclusion by ECB (2006). In the second 90-day toxicity study no effects on haematological, clinical chemical parameters, organ weights or macroscopic and microscopic morphological endpoints have been observed with the exception of a decrease in bilirubin in males at 1,000 mg/kg b.w. and in females at 300 and 1,000 mg/kg b.w., and a decrease in spleen weight in males at 300 and 1,000 mg/kg b.w. In addition, a decrease in alkaline phosphatase was found in high dose females. A decrease in T4 was found in males at all dose levels, however without a clear dose response. In this study a detailed functional observational battery was conducted to investigate possible effects on neurobehaviour but no such effects of TBBPA were found. The ECB considered that in this study "no clear toxicologically significant effects" were found and that the highest dose (1,000 mg/kg b.w.) could be considered as a NOAEL. The CONTAM Panel had no access to the raw data of the study and could not judge this conclusion.

In a more recent 28-day study with oral doses of TBBPA of 0, 30, 100 or 300 mg/kg b.w., van der Ven et al. (2008) reported a decrease in T4 levels in male rats with a $BMDL_{10}$ of 48 mg/kg b.w. In a one-generation reproduction study in rats dosed with 0, 3, 10, 30, 100, 300, 1,000 or 3,000 mg TBBPA/kg b.w. per day, a $BMDL_{10}$ for a decrease in T4 of about 16 and 30 mg/kg b.w. for female and male rats, respectively was reported (van der Ven et al., 2008). The same authors reported an increased absolute weight of testes and pituitary in male rats as the most sensitive effects. They calculated a $BMDL_5$ of 0.5 mg/kg b.w. per day for effects on testes weight and a $BMDL_{10}$ of 0.6 mg/kg b.w. per day for effects on pituitary weight. In contrast, in a 2-generation reproduction study in rats, with doses up to 1,000 mg/kg b.w., TBBPA had no effects on testes or pituitary weights (MPI research 2002b, 2003, as cited in ECB, 2006).

The CONTAM Panel noted that the dose response curve for changes in testes weight in the 28-day study was somewhat atypical, in that (relatively modest) changes were observed only over the first two dose groups, thereafter the curve flattened and even showed signs of reversing at high doses. In addition, the Panel noted that the ratio between the BMDU and BMDL was approximately 14, indicating a large uncertainty in the outcome of the BMD modelling. Due to this uncertainty, the Panel concluded not to use this BMDL as the reference point.

Also the changes in pituitary weight showed a similar trend to those for the testes, with no real change evident in the 3rd dose group (30 mg/kg b.w.), and a flat dose response curve over two orders of magnitude of dosing. The ratio between the BMDU and the BMDL was approximately 17, indicating a large uncertainty in the outcome of the BMD modelling. There were no histological or histochemical changes (no increase in TSH staining in thyrotroph cells, or in FSH, LH or prolactin staining in gonadotroph cells) in the pituitary. Due to this uncertainty, the CONTAM Panel concluded not to use this BMDL as the reference point.

Since both effects could have been initiated by a decrease in T4 levels, it was noteworthy that effects on thyroid hormone levels were not evident until much higher doses than those at which changes in testes or pituitary weight were observed. For the one-generation study, van der Ven et al. (2008) reported a $BMDL_{10}$ for a decrease in T4 of about 16 and 30 mg/kg b.w. for female and male rats, respectively. In the same study also increased T3 levels were observed in female rats with a $BMDL_{10}$ of 2.3 mg/kg b.w. The reported ratio between the BMD and the BMDL for this endpoint was 5.7 indicating a much larger ratio between BMDU (not reported by the authors) and the BMDL, and thus a large uncertainty in the outcome of the BMD modelling. Therefore, the CONTAM Panel concluded not to use this BMDL as the reference point.

There are a few studies on the possible effects of TBBPA on neurodevelopmental behaviour. In most of these studies covering single post natal dosing (0.75 or 11.5 mg/kg b.w.) or repeated oral administration (90 day, or two-generation studies) with dosing in the range of 10 to 1,000 mg/kg b.w. no effects on neurobehaviour were found. In contrast, in a study with single administration (0.1, 5, 250 mg/kg b.w.), effects were observed 3 hours after dosing (Nakajima et al., 2009). Considering the limited information given about the experimental procedures and the unusual dose response (effects at the two lower doses but not at the highest one), the CONTAM Panel concluded that these results could not be used for risk characterization of TBBPA.

In a one-generation study by Lilienthal et al. (2008), BMDLs for a 5 % increase in hearing thresholds effect were reported in the range of about 1-40 mg/kg b.w. in female rats. The CONTAM Panel noted, however, that the reported ratio between the BMD and BMDL was about 5 or larger indicating a much larger ratio between the BMDU (not reported by the authors) and the BMDL, and thus a large uncertainty in the outcome of the BMD modelling. In addition, the Panel noted that the increased thresholds in the brainstem auditory evoked potentials (BAEPs) are difficult to interpret and have to be confirmed by other independent investigations. Therefore, the Panel concluded that these BAEP results do not form a sound basis on which to base the risk assessment of TBBPA.

The limited information on the effects of TBBPA on the immune system indicate that TBBPA can affect the host immunity in mice after administration of 1,700 mg/kg b.w. per day (the only dose tested) for 28 days (Watanabe et al., 2010), whereas doses up to 3,000 mg/kg b.w. for 28 days did not affect the immunisation response to sheep red blood cells (SRBC) in rats (van der Ven et al., 2008).

The limited studies available do not indicate reproductive or teratogenic effects of TBBPA.

The available *in vitro* studies indicate that TBBPA is not genotoxic. No data from *in vivo* studies are available.

No long term carcinogenicity studies on TBBPA or its derivatives were identified. However, based on the weight of evidence (absence of genotoxicity *in vitro*, no indications for proliferative changes or cytotoxicity in studies with up to 90 days repeated administration, no immunosuppression, except possibly at high doses) the CONTAM Panel concluded that there are no indications that TBBPA might be carcinogenic.

No studies on health effects in humans due to exposure to TBBPA and/or its derivatives have been identified in the open literature.

The CONTAM Panel concluded that the critical effect of TBBPA was on circulating thyroid hormone (T4) in female and male rats. Lowest reliable $BMDL_{10}$ values of 16 and 30 mg/kg b.w. per day, respectively, were identified from a 28-day study (van der Ven et al., 2008). The Panel decided to use the $BMDL_{10}$ of 16 mg/kg b.w. as the critical reference point.

As indicated in Section 8.1, there is no large discrepancy between the elimination kinetics of TBBPA in humans compared to rodents. As a consequence, exposure to similar external doses of TBBPA most probably will result in similar concentrations in the human body as in the rodent. Therefore, the use of external dose levels of TBBPA associated with toxic effects in animals can be used for the risk assessment in humans.

The $BMDL_{10}$ of 16 mg/kg b.w. for changes in circulating thyroid hormone levels could in principle be used as the basis to derive a human health based guidance value, e.g. a tolerable daily intake.

The CONTAM Panel concluded, however, that due to the limitations and uncertainties in the current database, the establishment of a health based guidance value for TBBPA was not appropriate. Therefore, the Panel used a margin of exposure[17] (MOE) approach for the risk characterisation of TBBPA.

9. Risk characterisation

For TBBPA derivatives there were no occurrence data and no information on their toxicity, therefore the risk characterisation focuses only on TBBPA.

Due to the lack of occurrence data above LOQ for TBBPA in food, the CONTAM Panel was not able to estimate a meaningful dietary exposure for the general population, meaning that a conventional risk characterisation was not possible. In order to provide some indication of whether there could be a possible health concern with respect to dietary exposure to TBBPA, the Panel made a hypothetical worst case exposure estimate for the specific group of adult high fish consumers and for high cow's milk consumers (i.e. toddlers) by substituting the concentration levels of TBBPA in fish and milk, all reported as not quantified, by the LOQ of 1 and 0.65 ng/g wet weight, respectively for fish and milk. The resulting "upper bound" exposure estimates were 2.6 ng/kg b.w. per day for adult high fish consumers, and 55.7 ng/kg b.w. per day for high cow's milk consumers (i.e. toddlers, see Section 7). Compared with a $BMDL_{10}$ of 16 mg/kg b.w. identified as reference point for the risk characterisation (see Section 8.5), the resulting margins of exposure (MOE) are 6×10^6 and 3×10^5.

Usually an MOE of 100 is sufficient to cover uncertainties and variability with respect to kinetic and dynamic differences between animal species and humans (factor $4 \times 2.5 = 10$) and within the human population (factor $3.2 \times 3.2 = 10$), and to conclude that there is no health concern. In the case of TBBPA, the CONTAM Panel noted that an additional factor would be needed to cover deficiencies in the database. The MOE reported for the hypothetical exposure scenario for high fish consumers (6×10^6) and for high cow's milk consumers (i.e. toddlers, 3×10^5) are, however, so large that the

[17] The margin of exposure (MOE) is the ratio between a defined point on the dose-response curve for the adverse effect and the human intake.

CONTAM Panel concluded that it is unlikely that current dietary exposure to TBBPA raises a health concern for these specific population groups.

The limited data for other food groups, all reported as less than LOQ, did not facilitate a hypothetical exposure assessment. However, since the highest reported LOQs for all these other food groups, with the exception of three samples of "Animal and vegetables fats and oils", are below those reported for milk and fish, and given the large MOEs for high fish consumers and high cow's milk consumers (i.e. toddlers), the CONTAM Panel concluded that it is unlikely that current dietary exposure of the general population to TBBPA raises a health concern.

The CONTAM Panel noted that data on levels of TBBPA in human milk are limited. In addition, the reported values differ widely. In one study (see Section 5.2.2.) higher levels were found, probably due to a hydrolysis step included in the analytical procedure, resulting in hydrolysis of glucuronide and sulphate TBBPA conjugates that might be present in human milk. The CONTAM Panel considered that hydrolysis of TBBPA conjugates might also occur in the gastrointestinal tract and therefore used the result of this study to estimate the exposure to TBBPA of breast-fed infants. The reported TBBPA levels range from 0.06 to 37.3 ng/g fat, with a median of 0.48 ng/g fat. With average human milk consumption (800 mL per day), this leads to a daily exposure of 0.28 to 171 ng/kg b.w. This results in MOEs ranging from about 6×10^7 to 9×10^4. For infants with a high human milk consumption (1,200 mL per day), the exposure is 0.41 to 257 ng/kg b.w., resulting in MOEs ranging from about 4×10^7 to 6×10^4. Average and high consumption of human milk with the median TBBPA concentration level of 0.48 ng/g fat will result in MOEs of about 7×10^6 and 5×10^6, respectively. Based on these large MOEs, the CONTAM Panel concluded that current exposure via human milk does not raise a health concern.

Dust in homes, classrooms and cars, can be an additional source of exposure to TBBPA, particularly for children. Based on an average 'typical' and 'high end' scenario, exposure of young children to TBBPA through ingestion of dust has been estimated to range from 0.015 to 2.2 ng/kg b.w. per day (see Section 7.3). Considering the 95th percentile TBBPA concentration of 460 ng/g dust, the exposure based on a typical or high end exposure scenario would be 1.2 or 4.6 ng/kg b.w. per day, respectively. The CONTAM Panel concluded that the 'typical' exposure scenario provided the most realistic estimate of exposure to TBBPA from dust. Comparing the TBBPA intake resulting from the typical dust ingestion scenario (1.2 ng/kg b.w.) with the $BMDL_{10}$ of 16 mg/kg b.w., results in an MOE of about 1.3×10^7. This large MOE indicates that also children's exposure to TBBPA from dust does not raise a health concern.

Based on the large MOEs derived for both dietary exposure and exposure through dust, the CONTAM Panel concluded that it is unlikely that combined exposure through food and dust would result in a health concern.

10. Uncertainty

The evaluation of the inherent uncertainties in the assessment of exposure to TBBPA and its derivatives has been performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2007). In addition, the report on "Characterizing and Communicating Uncertainty in Exposure Assessment" (WHO/IPCS, 2008) has been considered. According to the guidance provided by the EFSA opinion (EFSA, 2007) the following sources of uncertainties have been considered: assessment objectives, exposure scenario, exposure model, and model input (parameters).

10.1. Assessment objectives

The objectives of the assessment were clearly specified in the terms of reference. The CONTAM Panel assessed the new occurrence data that were submitted to EFSA. The uncertainty in the assessment objectives is considered to be negligible.

10.2. Exposure scenarios/Exposure model

In response to EFSA's request to submit data on brominated flame retardants, four European countries submitted 652 results on TBBPA in food analysed between 2003 and 2010. No data on TBBPA derivatives were received. Thus, the CONTAM Panel was not able to estimate the human exposure to TBBPA derivatives. The majority of the results on TBBPA (71 %) were obtained from the analysis of samples from the food group of "Fish and other seafood (including amphibians, reptiles, snails and insects)". In greater detail, considering more disaggregated food groups (FoodEx levels 2 and 3), some 60 % of the results were obtained from the analysis of "Fish meat", followed by "Water molluscs" (9 %), "Animal fat" (6 %), "Liquid milk" (5 %) and "Edible offal, farmed animals" (5 %), "Eggs" (4 %) and "Crustacean" (3 %). All results were reported as <LOQ. The limited number of food commodities analysed and the extrapolation of occurrence data from four countries to the whole of Europe introduces a high degree of uncertainty into the exposure assessment. Also the lack of information on the form in which TBBPA might be present in food, either free or in the form of glucuronide or sulphate conjugates, adds to the uncertainty of the reported occurrence data. On the other hand, the use of the LOQs for the analytical results in fish and milk, all reported as below the LOQ, for the calculation of the upper-bound exposure estimate, is a conservative approach in the risk assessment.

10.3. Model input (parameters)

There are no performance criteria for the analysis of TBBPA and its derivatives and laboratories can use any method of analysis, provided it can be demonstrated in a traceable manner that it fulfils the requirements according to ISO 17025. This may have added to the uncertainty in the analytical results. The scarce number of certified reference materials is a limitation when the method performance for the analytical methods for analysis of TBBPA in food is assessed, and adds thereby to the overall uncertainty in the analytical results.

10.4. Other uncertainties

The CONTAM Panel identified a number of limitations and uncertainties in the toxicological database which made the derivation of a health based guidance value inappropriate. Therefore, a margin of exposure approach was used for the risk characterization. Reported ratios between BMD and BMDL or BMDU and BMDL values for several toxicological endpoints were rather high, indicating considerable uncertainties in the outcome of the BMD modelling. Therefore, these endpoints could not be used as reference points.

10.5. Summary of uncertainties

In Table 8, a summary of the uncertainty evaluation is presented, highlighting the main sources of uncertainty and indicating an estimate of whether the respective source of uncertainty might have led to an over- or underestimation of the dietary exposure or the resulting risk.

Table 8: Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of the dietary exposure to TBBPA.

Sources of uncertainty	Direction
Measurement uncertainty of analytical results	+/- (a)
Limited information on the forms of TBBPA present in food	-
Extrapolation of occurrence data from only four countries to whole Europe	+/-
Limited occurrence data, mainly available for fish and other seafood, and all <LOQ	-
Influence of upper-bounds for non-detects on dietary exposure estimate	+
Lack of information on the impact of food processing	+/-
Limited toxicological data on TBBPA	+/-

(a): + = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure/risk.

The CONTAM Panel concluded that despite these uncertainties in the risk assessment, the magnitude of the MOE was such that these uncertainties would not impact on the conclusion regarding the level of concern from exposure to TBBPA.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

General

- Tetrabromobisphenol A (TBBPA) and its derivatives are a widely used group of flame retardants.
- TBBPA is primarily used as a reactive flame retardant, covalently bound to epoxy and polycarbonate resins. It is also used as an additive in acrylonitrile-butadiene-styrene (ABS), high impact polystyrene (HIPS) and phenolic resins.
- TBBPA is one defined chemical, synthesized through bromination of bisphenol A, containing traces of other brominated bisphenol A congeners.
- TBBPA is present in the environment both in its neutral and ionized forms.
- TBBPA has low persistency due to its vulnerability to undergo abiotic chemical reactions.
- TBBPA derivatives may be used either as reactive or additive intermediates in polymer manufacture.
- Although several TBBPA derivatives have trade names, indicating their commercial uses, it is unclear to what extent they are used as flame retardants.
- The existing information on chemical properties of TBBPA derivatives is limited.
- TBBPA derivatives are neutral compounds and more hydrophobic than TBBPA.

Occurrence

- Following an EFSA call for data, analytical results from 652 food samples were submitted by four European countries, covering the period from 2003 to 2010.
- The majority of the results submitted (60 %) were related to samples from the food group "Fish meat", followed by "Water molluscs" (9 %), "Animal fat" (6 %), "Liquid milk" (5 %), "Edible offal, farmed animals" (5 %), "Eggs" (4 %) and "Crustacean" (3 %). "Dietary supplements", "Cheese", "Livestock meat", "Poultry" and "Sausages" represent between 1 % and 3 %, while the remaining food categories are represented by less than 1% samples each.
- Values were all reported as below the limit of quantification (LOQ). With very few exceptions, the LOQ was generally ≤ 1 ng/g wet weight (w.w.).
- The submitted data only include analytical results on TBBPA, and no data on TBPPA derivatives. Samples were reported as being analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
- Concentrations of TBBPA in fish, expressed on a wet weight basis, reported in open literature were also <LOQ, with LOQs generally below 1 ng/g w.w.
- Data on concentrations of TBBPA in human milk in Europe are limited to three studies. In one study, higher levels were found which might be the result of a hydrolysis step included in the sample preparation to cleave potential glucuronide or sulphate metabolites. The TBBPA concentrations in this study ranged from 0.06 to 37.3 ng/g fat, with a median of 0.48 ng/g fat.

Human exposure

- The CONTAM Panel concluded that the submitted occurrence data were not suitable to carry out a meaningful dietary exposure assessment for the general population or specific population groups, such as infants, children or vegetarians.
- A hypothetical worst case dietary exposure estimate for TBBPA was considered for the specific group of adult high fish consumers by substituting the concentration levels of TBBPA in fish, all reported <LOQ, by the highest reported LOQ of 1 ng/g wet weight and assuming a high daily fish consumption of 2.6 g/kg body weight (b.w.). The resulting "upper bound" exposure estimate was 2.6 ng/kg b.w. per day.
- A hypothetical worst case dietary exposure estimate for TBBPA was also considered for high consumers of liquid cow's milk (i.e. toddlers), by substituting the concentration levels of TBBPA in milk, all reported <LOQ, by the highest reported LOQ of 0.65 ng/g wet weight and assuming a high daily milk consumption of 85.7 g/kg b.w. The resulting "upper bound" exposure estimate was 55.7 ng/kg b.w. per day.
- The exposure scenario based on average human milk consumption and the reported range for TBPPA in human milk (0.06 to 37.3 ng/g fat) results in daily exposures of 0.28 to 171 ng/kg b.w. For infants with high human milk consumption the respective daily exposures ranged from 0.41 to 257 ng/kg b.w.

Hazard identification and characterisation

- TBBPA is extensively absorbed through the gastrointestinal tract in rodents.

- No significant retention or bioaccumulation was observed in tissues, including adipose tissue. Most of the TBBPA and/or corresponding metabolites are eliminated in the faeces, mainly through biliary excretion.

- The main metabolic pathway is conjugation to glucuronic acid.

- Elimination half-lives of TBBPA in experimental animals (about half a day) and humans (about 2-3 days) do not differ considerably.

- The acute toxicity of TBBPA is low in rodents.

- Toxicity studies indicate that the thyroid hormone system is a target of TBBPA. The $BMDL_{10}$ value, the lower confidence limit for the benchmark dose of a 10 % relative decrease in circulating T4 levels in rats, was 16 mg/kg b.w.

- In contrast to other brominated flame retardants, such as polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDDs), liver is not a target for TBBPA. It exhibits some hepatotoxicity in rodents only at very high doses, i.e. in the g/kg b.w. dose range. At lower doses no signs of hepatic changes including effects on hepatic drug metabolism were found.

- From the limited available studies, exposure to TBBPA during development does not appear to induce relevant neurobehavioural changes.

- The limited studies available do not indicate reproductive or teratogenic effects of TBBPA.

- The in vitro data indicate that TBBPA is not genotoxic.

- TBPPA has not been tested for carcinogenicity. However, based on the weight of evidence (absence of genotoxicity *in vitro*, no indications for proliferative changes in studies with up to 90 days repeated administration, no immunosuppression) there are no indications that TBBPA might be carcinogenic.

- The CONTAM Panel decided that the lower confidence limit for a benchmark response of 10 % ($BMDL_{10}$) of 16 mg/kg b.w. could be used as the critical reference point, but due to the limitations and uncertainties in the database it concluded that establishing a health based guidance value for TBBPA was not appropriate. Therefore, a margin of exposure (MOE) approach was used for the risk characterization.

- No toxicological information on TBBPA derivatives was identified.

Risk characterisation

- The MOEs (6×10^6 and 3×10^5) between the $BMDL_{10}$ of 16 mg/kg b.w. and the worst case dietary exposure for high adult fish consumers and for high cow's milk consumers (i.e. toddlers) are much larger than the default value of 100, indicating that current dietary exposure to TBBPA for these population groups in the EU does not raise a health concern.

- Giving the high MOEs for these specific population groups, and the observation that the highest LOQs reported for other food groups are generally below those of fish and milk, it is unlikely that current dietary exposure of the general population to TBBPA raises a health concern.

- Exposure of breast-fed infants to TBBPA via human milk also shows very high MOEs (range 6×10^4 to 6×10^7), and therefore does not raise a health concern.

- Also combined exposure to TBBPA from food and dust, particularly for children, is unlikely to raise a health concern.

RECOMMENDATIONS

- Monitoring of TBBPA in food should be extended to other European countries.

- Information on production rates and use, chemical characteristics, occurrence in food and toxicity of TBBPA derivatives is needed.

- There is a need for certified reference materials and defined performance criteria for the analysis of TBBPA and its derivatives in various foodstuffs, as appropriate.

- Levels of TBBPA and its derivatives in human milk should be investigated. In addition, the presence and bioavailability of glucuronide and sulphate conjugates should be assessed.

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ABBREVIATIONS

ABS	Acrylonitrile butadiene styrene
AhR	Aryl hydrocarbon receptor
ALA-D	5-aminolevulinate dehydratase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APCI	Atmospheric pressure chemical ionisation
APPI	Atmospheric pressure photo ionisation
AR	Androgen receptor
AST	Aspartate aminotransferase
BAEP	Brainstem auditory evoked potentials
BCF	Bioconcentration factor
BFR	Brominated flame retardant
BMD	Benchmark dose
BMDL	Benchmark dose lower limit of the 90 % confidence interval
BMDU	Benchmark dose upper limit of the 90 % confidence interval
BMR	Benchmark response
BPA	Bisphenol A
b.w.	Body weight
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
Comprehensive Database	Comprehensive Food Consumption Database
CONTAM Panel	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
DCM	Dietary and chemical Monitoring Unit (former Data Collection and Exposure Unit, DATEX)
DHPN	N-bis(2-hydroxypropyl)nitrosamine
DMBA	7,12-dimethylbenz(a)anthracene
EC	European Commission
ECB	European Chemicals Bureau
ECNI	Electron chemical negative ionization
EFSA	European Food Safety Authority
EI	Electron impact
ER	Estrogen receptor
EROD	7-ethoxyresorufin O-deethylase
ESI	Electrospray (ESI)
EU	European Union
FOB	Functional observational battery
GABA	Gamma-amino-n-butyric acid
GC	Gas chromatography
GD	Gestational day
GEMS/Food	WHO-Global Environment Monitoring System-Food Contamination Monitoring and Assessment Programme
GSH	Glutathione
NIEHS	National Institute of Environmental Health Sciences
HBCDDs	Hexabromocyclododecanes
HIPS	High impact polystyrene
HPLC	High performance liquid chromatography
HRMS	High resolution MS
IOM	Institute of Medicine of the U.S. National Academies of Sciences
IPCS	International Programme on Chemical Safety

ITMS	Ion trap MS
LB	Lower bound
LBD	Luciferin benzylether debenzylase
LC	Liquid chromatography
LOAEL	Lowest-observed-adverse-effect level
LOD	Limit of detection
LOQ	Limit of quantification
LRMS	Low resolution MS
MB	Medium bound
Mc4r	Melantoin 4 receptor
MDA	Malondialdehyde
MOE	Margin of exposure
MOS	Margins of Safety
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MS/MS	Tandem MS
NK	Natural killer
NOAEL	No-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PBBs	Polybrominated biphenyls
PBDD/Fs	Polybrominated dibenzo-*p*-dioxins and furans
PBDEs	Polybrominated diphenyl ethers
PLE	Pressurized liquid extraction
PND	Postnatal day
PNW	Postnatal week
PROD	7-pentoxyresorufin O-dependentylase
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
SPE	Solid-phase extraction
SRBC	Sheep red blood cells
T3	Triiodothyronine
T4	Thyroxine
TBBPA	Tetrabromobisphenol A
TBBPA-bAcr	Tetrabromobisphenol A bisacrylate
TBBPA-bAE	Tetrabromobisphenol A bisallyl ether
TBBPA-bDiBPrE	Tetrabromobisphenol A bis(2,3-dibromopropyl ether
TBBPA-bGE	Tetrabromobisphenol A bis(glycidyl ether)
TBBPA-bME	Tetrabromobisphenol A bismethyl ether
TBBPA-bOAc	3,3',5,5'-tetrabromobisphenol A bis-acetate
TBBPA-bOHEE	Tetrabromobisphenol A bis(2-hydroxyethyl) ether
TBBPA-bOHEE-bAcr	Tetrabromobisphenol A bis(2-hydroxyethyl)ether bisacrylate
TBBPA-bOPr	Tetrabromobisphenol A bispropanoate
TBBPS	Tetrabromobisphenol S
TDI	Tolerable Daily Intake
TOF-MS	Time-of-flight MS
Trh	Thyrotropin-releasing hormone
TR	Thyroid hormone receptor
TSH	Thyroid stimulating hormone
UB	Upper bound
UPLC	Ultra performance LC
UV	Ultraviolet
w.w.	Wet weight

WHO/ICPS	World Health Organization/International Programme on Chemical Safety