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Update of the risk assessment of brominated phenols and their derivatives in food

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Abstract

The European Commission asked EFSA to update its 2012 risk assessment on brominated phenols and their derivatives in food, focusing on five bromophenols and one derivative: 2,4,6-tribromophenol (**2,4,6-TBP**), 2,4-dibromophenol (**2,4-DBP**), 4-bromophenol (**4-BP**), 2,6-dibromophenol (**2,6-DBP**), tetrabrominated bisphenol S (**TBBPS**), tetrabromobisphenol S bismethyl ether (**TBBPS-BME**). Based on the overall evidence, the CONTAM Panel considered in vivo genotoxicity of **2,4,6-TBP** to be unlikely. Effects in liver and kidney were considered as the critical effects of 2,4,6-tribromophenol (**2,4,6-TBP**) in studies in rats. A $BMDL_{10}$ of 353 mg/kg body weight (bw) per day for kidney papillary necrosis in male rats was identified and was selected as the reference point for the risk characterisation. The derivation of a health-based guidance value was not considered appropriate due to major limitations in the toxicological database. Instead, the margin of exposure (MOE) approach was applied to assess possible health concerns. Around 78,200 analytical results for **2,4,6-TBP** in food were used to estimate dietary exposure for the European population. Considering the resulting MOE values, all far above an MOE of 6000 that does not raise a health concern, and accounting for the uncertainties affecting the exposure and hazard assessments, the CONTAM Panel concluded with at least 95% probability that the current dietary exposure to **2,4,6-TBP** does not raise a health concern. Due to lack of occurrence data, no risk assessment could be performed for breastfed or formula-fed infants. No risk characterisation could be performed for any of the other brominated phenols and derivatives included in the assessment, due to lack of data both on the toxicity and occurrence.

KEYWORDS

2,4,6-TBP, brominated phenols, food, human exposure, occurrence, risk assessment, toxicology

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SUMMARY

Brominated flame retardants (BFRs) are anthropogenic chemicals, which are used in a wide variety of consumer/commercial products to improve their resistance to fire. Concern has been raised because of the occurrence of several chemical compounds from the group of BFRs in the environment, food and in humans. This has led to bans on the production and use of certain formulations.

The European Commission asked the European Food Safety Authority (EFSA) to update its 2010–2012 risk assessments on the different families of BFRs, i.e. hexabromocyclododecanes (HBCDDs), polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, brominated phenols and their derivatives, and novel and emerging BFRs. The CONTAM Panel is updating the risk assessments of different classes of BFRs in a series of separate Opinions.

The similarities in chemical properties and effects seen in the previous EFSA assessments for the different BFR families warrant the consideration of a mixture approach. The Panel on Contaminants in the Food Chain (CONTAM Panel) will evaluate the appropriateness of applying a mixture approach in an additional Opinion once the risk assessment for each BFR family has been updated. It will be based on the EFSA Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals published in 2019 and 2021.

The first Opinions in the current series updated the risk assessments of HBCDDs in food, PBDEs in food and TBBPA and its derivatives in food. This fourth Opinion updates the risk assessment of brominated phenols and their derivatives in food previously performed by EFSA and published in 2012. The current assessment focusses on five brominated phenols, i.e. 2,4,6-tribromophenol (2,4,6-TBP), 2,4-dibromophenol (2,4-DBP), 4-bromophenol (4-BP), 2,6-dibromophenol (2,6-DBP), tetrabrominated bisphenol S (TBBPS) and one derivative, i.e. TBBPS bismethyl ether (TBBPA-bME), as requested in the terms of reference by the European Commission.

Brominated phenols have been used since the 1920s as flame retardants and for applications including the synthesis of other BFRs, pigments, herbicides, germicides and antifungal agents. They can be released into the environment through transformation of TBBPA, PBDEs and other BFRs. In the past, **2,4,6-TBP** was used as a wood preservative due to its fungicidal properties. Brominated phenols along with some other brominated aromatic compounds can be naturally produced by marine organisms. This, along with the fact that brominated phenols are used for applications other than flame retardants, make it difficult to assess the relative proportions that may be found in the environment as a result of their use as a BFR and from other sources. While action has been taken to restrict the production and use of some classes of BFRs, this is not the case specifically for brominated phenols.

The present assessment takes into account the occurrence data in food and biological samples submitted to EFSA after the publication of its previous Opinion on brominated phenols and their derivatives, as well as the newly available scientific information of relevance to hazard identification and characterisation.

The draft Scientific Opinion underwent a public consultation from 13 June 2024 to 1 August 2024. The comments received were taken into account when finalising the Scientific Opinion and are presented and addressed in Annex E.

Methods of analysis for brominated phenols and derivatives generally use a similar approach to those used for PBDEs and HBCDDs. While liquid chromatography (LC) with ultraviolet (UV) detection has been used in the past, more advanced methods use either gas chromatography (GC) or LC with MS detection.

No risk characterisation could be performed for any of the compounds included in the TORs other than **2,4,6-TBP**, due to insufficient or lack of data both on the toxicity and occurrence.

Hazard identification and characterisation

In rodents, **2,4,6-TBP** has an oral bioavailability of 30% and is distributed in different organs without accumulation. It is mainly excreted in urine. There is evidence of maternal transfer during gestation and lactation. **2,4,6-TBP** is metabolised into sulfate and glucuronic acid conjugates, with an elimination half-life of less than 5 h. There appears to be no major difference between rats and mice regarding disposition after a single oral dose exposure.

In humans, there are no data regarding the absorption and elimination of **2,4-DBP** or **2,4,6-TBP**. Several studies have measured concentrations of **2,4,6-TBP** in human samples, including human milk and serum. **2,4-DBP** and **2,4,6-TBP** are metabolised either into sulfate or glucuronic acid conjugates.

The main targets in repeated-dose subacute toxicity studies in rats exposed by gavage to **2,4,6-TBP** are the liver and kidney. There were increases in organ weights and also histopathological changes at 1000 mg/kg bw per day. There were also statistically significant, dose-related increases in serum creatinine in males at 300 and 1000 mg/kg bw per day.

No reproductive effects were observed at 300 mg/kg bw per day in a subacute toxicity study in rats. However, in a developmental toxicity study where rats were exposed by gavage from GD6–15, an increase in post-implantation loss and a slight decrease in the number of viable fetuses were observed at 1000 mg **2,4,6-TBP**/kg bw per day. The NOAEL for developmental toxicity was 300 mg/kg bw per day.

2,4,6-TBP did not induce mutations in bacteria but induced chromosomal aberrations in mammalian cells in vitro. In in vitro Comet assays, **2,4,6-TBP** induced DNA single strand breaks (SSB) and double strand breaks (DSB) as well as oxidised DNA bases in human peripheral blood mononuclear cells. It did not induce micronuclei in bone marrow of mice in vivo after ip injection up to the maximum tolerated dose of 300 mg/kg bw per day. Although no toxicity in the bone marrow was demonstrated, systemic exposure is expected after ip injection and clinical signs of toxicity were reported. Based on the overall evidence, the CONTAM Panel considered in vivo genotoxicity of **2,4,6-TBP** to be unlikely.

The volume of the available epidemiological evidence on brominated phenols and their derivatives is very limited and is mostly related to the association between **2,4,6-TBP** levels and thyroid hormones. A few signals coming from statistically significant associations were reported but the confidence in a true underlying effect is low due to methodological issues.

Regarding the mode of action, **2,4,6-TBP** and **TBBPS** can induce oxidative stress and apoptosis. There is evidence that **2,4,6-TBP** and **TBBPS** can have effects on thyroid hormone signalling, possibly mediated by inhibition of sulfotransferase and deiodinase-2, and binding to thyroid hormone receptor β (TRβ). The available data suggest that **2,4,6-TBP** might have antiandrogenic effects and exhibit effects on neurodevelopment and immune function.

The evidence from the available human data did not provide a sufficient basis for the risk assessment. Thus, the CONTAM Panel considered the data from studies in experimental animals to identify reference points for the human risk characterisation.

The CONTAM Panel concluded that liver and kidney toxicity observed in a subacute oral toxicity study in rats were the critical effects for the hazard characterisation. Benchmark dose (BMD) modelling was performed according to the 2022 EFSA Guidance on the use of the BMD approach in risk assessment, applying endpoint-specific benchmark responses. A $BMDL_{10}$ of 353 mg/kg bw per day for kidney papillary necrosis was identified as the most appropriate reference point for **2,4,6-TBP** risk characterisation.

There were insufficient or no data on the toxicity of any of the other compounds included in the TORs to derive reference points. There were insufficient data to assess if **2,4,6-TBP** and other compounds included in the TORs have a common mode of action or otherwise contribute to common adverse outcomes. It was therefore not possible to assign the brominated phenols in the TOR to assessment groups for the purposes of combined risk assessment.

Occurrence and dietary exposure assessment for the European population

Following data cleaning, 78,169 analytical results were made available for inclusion in the assessment of dietary exposure to **2,4,6-TBP**. The limited number of analytical results available for **2,4-DBP** ($n = 51$), **2,6-DBP** ($n = 41$) and **4-BP** ($n = 51$) were not used to perform a dietary exposure assessment as the CONTAM Panel deemed it not possible to identify a reference point or perform a risk assessment for them due to lack of toxicological studies. No data were available for other brominated phenols and derivatives considered (i.e. **TBBPS** and **TBBPS-bME**).

For **2,4,6-TBP**, analytical results were 100% left-censored for all food categories with very few exceptions. Quantified results were found in 'Fish and seafood' ($n = 8$, 90% left censorship), 'Fruit and fruit products' ($n = 5$, 99.98% left censorship) and 'Spices' ($n = 1$, 99.8% left censorship).

For drinking water and some subcategories of fish and seafood, occurrence data extracted from the literature were used. For the assessment of dietary exposure to **2,4,6-TBP**, the CONTAM Panel decided to include food categories that had 100% left-censored results at the Level 1 of the FoodEx2 classification if in the literature there was evidence of a possible contamination from **2,4,6-TBP** within these categories. Dietary exposure to **2,4,6-TBP** was calculated using the LB and UB concentration estimates.

Due to the very high number of left-censored results and the LOQ reported in the analysis of **2,4,6-TBP** in most of the food categories, the difference between LB and UB estimates was up to three orders of magnitude. The LB mean dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 0.078 to 3.1 ng/kg bw per day. LB P95 dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 0.34 to 16 ng/kg bw per day. The UB mean dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 140 to 1600 ng/kg bw per day. UB P95 dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 270 to 2400 ng/kg bw per day.

The CONTAM Panel noted that while the LB estimates are expected to be an underestimation of the true exposure, the UB estimates are likely to be a large overestimation. The UB dietary exposure estimates represent worst-case scenarios, not representative of the true exposure to **2,4,6-TBP**.

The identification of main contributors to the dietary exposure to **2,4,6 TBP** is subject to uncertainty as only two food categories had quantified values (fish and seafood, and fruit and fruit products), and for drinking water, the highest concentration value of **2,4,6-TBP** found in literature was used.

No exposure assessment could be performed for breastfed or formula-fed infants due to lack of occurrence data.

The available data suggest that for most of the population, diet represents the largest source of exposure to **2,4,6-TBP**.

No suitable data were identified in the scientific literature with respect to the effects of cooking and processing on levels of brominated phenols and the derivative considered.

Risk characterisation

Due to limited information on hazard for **2,4,6-TBP**, the derivation of a health-based guidance value (HBGV) was not considered appropriate. Instead, the margin of exposure (MOE) approach was applied to assess possible health concerns.

The CONTAM Panel considered that MOEs ≥ 6000 do not raise a health concern. This MOE would cover variability with respect to kinetic and dynamic differences between animal species and humans and within the human population (factor of 100), account for the shorter duration of the critical study compared to a lifetime exposure (factor of 6), and account for major deficiencies in the database (factor of 10).

Comparison of the exposure estimates to the reference point identified for **2,4,6-TBP** resulted in MOEs of about 22,000,000 at the maximum P95 LB exposure, and of about 145,000 at the maximum P95 UB exposure.

The CONTAM Panel noted that these MOEs are far above 6000, and therefore, current dietary exposure to **2,4,6-TBP** does not raise a health concern.

No conclusion could be made for breastfed or formula-fed infants due to insufficient occurrence data.

No conclusion could be made for the compounds other than **2,4,6-TBP** included in the TORs due to lack of toxicological and occurrence data.

Uncertainty analysis

An uncertainty analysis was performed. The CONTAM Panel concluded with at least 95% probability that **2,4,6-TBP** is not genotoxic in vivo. Considering the large margin between the exposure estimates and the reference point, and taking account of all associated uncertainties, the CONTAM Panel concluded with at least 95% probability that current dietary exposure to **2,4,6-TBP** would not raise a health concern.

No risk characterisation or uncertainty analysis could be performed for any of the other compounds included in the TORs, due to lack of data both on the toxicity and occurrence.

Recommendations

The CONTAM Panel made the following recommendations to reduce the uncertainty in the risk assessment of **2,4,6-TBP** in food: to monitor occurrence in human milk and food for infants, with appropriate analytical methods, to enable an exposure assessment for infants. Despite the very large MOEs identified in the current Opinion, a refined risk assessment would benefit from the following data: toxicokinetic data in humans, longitudinal epidemiological studies of sufficient power and appropriate exposure and co-exposure assessment, as well as subchronic toxicity studies, reproductive/developmental studies, neurodevelopmental and immunotoxicity studies.

The CONTAM Panel made the following recommendations for obtaining additional data in order to perform a risk assessment of the other brominated phenols included in the TORs: Occurrence data in food, including human milk and food for infants, with appropriate analytical methods; toxicokinetic data in rodents and humans; genotoxicity and toxicological studies.

1 | INTRODUCTION

1.1 | Background and terms of reference as provided by the requestor

Background

Brominated flame retardants (BFRs) are anthropogenic chemicals, which are added to a wide variety of consumer/commercial products in order to improve their fire resistance. The major classes of BFRs are brominated bisphenols, diphenyl ethers, cyclododecanes, phenols, biphenyl derivatives and the emerging and novel BFRs.

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 humans. This has led to bans on the production and use of certain formulations of polybrominated diphenyl ethers (PBDEs).

Between September 2010 and September 2012, the Scientific Panel on Contaminants in the Food of EFSA adopted six Scientific Opinions on different classes of brominated flame retardants.[1] Because in its Opinion EFSA highlighted several data gaps, hampering the consumer risk assessment for these substances, by means of Commission Recommendation 2014/118/EU on the monitoring of traces of brominated flame retardants in food, Member States were recommended to collect in 2014 and 2015 occurrence data for specific substances in specific foodstuffs.

The newly available occurrence data would enable an updated consumer exposure assessment. Furthermore, since the publication of the EFSA Scientific Opinions between 2010 and 2012, new scientific information has become available, therefore it would be necessary to verify whether an update of these Scientific Opinions would be appropriate, including an update of the consumer risk assessment.

Terms of reference

In accordance with Art. 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for an updated exposure assessment for the brominated flame retardants, covered by Recommendation 2014/118/EU, taking into account the occurrence data in food, submitted after the publication of the 2010–2012 EFSA Scientific Opinions, and an updated consumer risk assessment, taking into account newly available scientific information.

1.2 | Interpretation of the terms of reference

Following the request from the European Commission, the CONTAM Panel will update its 2010–2012 risk assessments on the different classes of BFRs: hexabromocyclododecanes (HBCDDs), polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, brominated phenols and their derivatives and novel and emerging BFRs (EFSA CONTAM Panel, 2011a, 2011b, 2011c, 2012a, 2012b).

The first three Opinions in the series updated the risk assessments of HBCDDs in food (EFSA CONTAM Panel, 2021), PBDEs in food (EFSA CONTAM Panel, 2024a) and TBBPA and its derivatives in food (EFSA CONTAM Panel, 2024b). This fourth Opinion is an update of the risk assessment of brominated phenols and their derivatives in food previously performed by EFSA (EFSA CONTAM Panel, 2012a). In Commission Recommendation 2014/118/EU, the following brominated phenols were listed and will be considered in the current update:

- 2,4,6-tribromophenol (**2,4,6-TBP**, CAS No 118-79-6),
- 2,4-dibromophenol (**2,4-DBP**, CAS No 615-58-7),
- 4-bromophenol (**4-BP**, CAS No 106-41-2),
- 2,6-dibromophenol (**2,6-DBP**, CAS No 608-33-3),
- tetrabrominated bisphenol S (**TBBPS**, CAS No 39635-79-5),
- tetrabromobisphenol S bismethyl ether (**TBBPS-BME**, CAS No 70156-79-5).

The similarities in chemical properties and effects seen in the previous EFSA assessments for the different BFR classes warrant the consideration of a mixture approach. The CONTAM Panel will evaluate the appropriateness of applying a mixture approach for the different classes of BFRs in an additional Opinion once the risk assessment for each BFR class has been updated. It will be based on the EFSA Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019) and on the EFSA Guidance Document on Scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2021).

[1]EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Polybrominated Biphenyls (PBBs) in Food. *EFSA Journal* 2010; 8(10): 1789 (151 pp.). Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. *EFSA Journal* 2011; 9(5):2156 (274 pp.). Scientific Opinion on Hexabromocyclododecanes (HBCDDs) in Food. *EFSA Journal* 2011; 9(7):2296 (118 pp.). Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. *EFSA Journal* 2011; 9(12):2477 (61 pp.). Scientific Opinion on Brominated Flame Retardants (BFRs) in Food: Brominated Phenols and their Derivatives. *EFSA Journal* 2012; 10(4):2634 (42 pp.). Scientific Opinion on Emerging and Novel Brominated Flame Retardants (BFRs) in Food. *EFSA Journal* 2012; 10(10):2908 (125 pp.).

1.3 | Supporting information for the assessment

1.3.1 | Physicochemical properties

Several brominated phenols are used as BFRs. These include TBBPA and its derivatives, which were subject to a separate EFSA Opinion (EFSA CONTAM Panel, 2011c, 2024b), and several other compounds that were previously considered by EFSA (EFSA CONTAM Panel, 2012a). This update focuses on the six compounds listed above whose physicochemical properties are given in Table 1 below, and whose structures are shown in Figure 1.

Trade names and synonyms identified for **2,4,6-TBP** are 1,3,5-tribromo-2-hydroxybenzene, Bromkal Pur 3, Bromol, Flammex 3BP, NSC 2136, PH 73, PH-73FF and FR-613, TBP.

TBBPS is commercially available from ca. 60 suppliers globally. It is known under trade names as EB 400S, FG 400S, Flame Cut 160R, NFPP and Tetrabromobisphenol S.

TBBPS-BME is not a pre-registered chemical within REACH and no trade names have been identified. There does not appear to be any bulk production of this BFR. It is available as an authentic reference standard for chemical analysis.

2,4-DBP, **2,6-DBP** and **4-BP** are other di- and mono-brominated phenols with lower molecular mass and greater vapour pressure than those compounds with a greater number of halogens.

TABLE 1 Physicochemical characteristics of brominated phenols and their derivatives considered in this Opinion (from Bergman et al., 2012).

Compounds	Abbreviation	CAS	Molecular weight (g/mol)	Log K_{ow}	pK_a	Vapour pressure (Torr)
2,4,6-tribromophenol	**2,4,6-TBP**	118-79-6	330.8	4.40	6.34	1.12×10^{-5}[a] (2.00×10^{-1}) 4.7×10^{-4}[h] 5.2×10^{-5}[i]
2,4-dibromophenol	**2,4-DBP**	615-58-7	251.9	3.47	7.86	2.7×10^{-2}[a]
4-bromophenol	**4-BP**	106-41-2	173.0	2.59[b]	9.17[c]	1.17×10^{-2}[g]
2,6-dibromophenol	**2,6-DBP**	608-33-3	251.9	3.36[d]	6.67[e]	9.5×10^{-3}[f]
Tetrabromobisphenol S	**TBBPS**	39635-79-5	565.8	5.81	3.53	3.02×10^{-12}
Tetrabromobisphenol S bismethyl ether	**TBBPS-BME**	70156-79-5	593.9	6.05	–	2.57×10^{-13}

Abbreviations: CAS, Chemical Abstract Service; log K_{ow}, n-octanol–water partition coefficient; pK_a: logarithm of the acid dissociation constant.
[a]EFSA CONTAM Panel (2011c).
[b]Hansch et al. (1995).
[c]Kortum et al. (1961).
[d]Sotomatsu et al. (1993).
[e]Serjeant and Dempsey (1979).
[f]Calculated value using ACD labs software.
[g]Parsons et al. (1961).
[h]ECHA (2016).
[i]ICSC web report (2004).

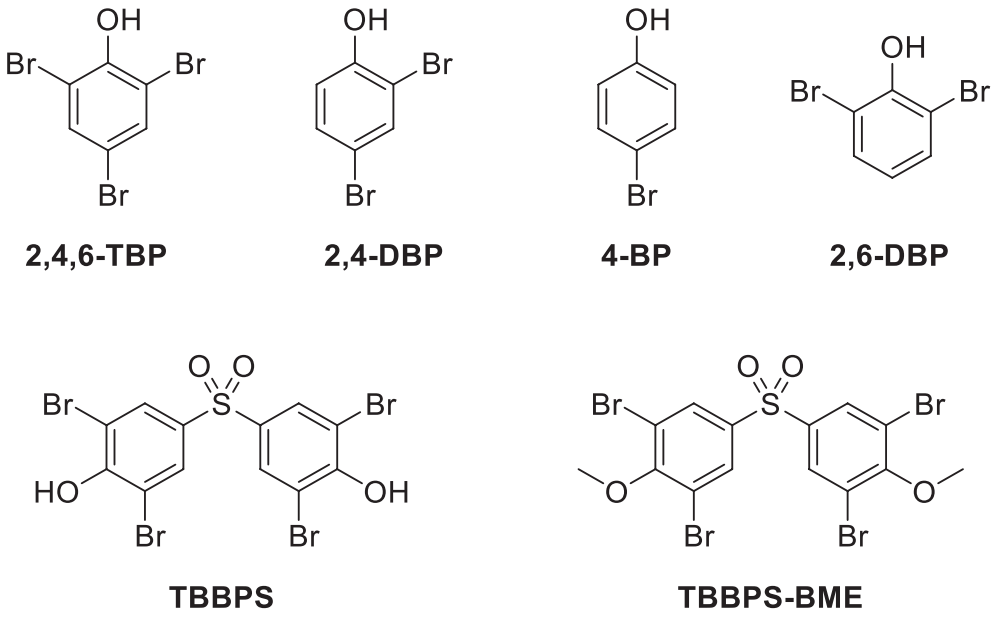

FIGURE 1 Chemical structures of brominated phenols and their derivatives considered in this Opinion: 2,4,6-tribromophenol (**2,4,6-TBP**), 2,4-dibromophenol (**2,4-DBP**), 4-bromophenol (**4-BP**), 2,6-dibromophenol (**2,6-DBP**), tetrabromobisphenol S (**TBBPS**), tetrabromobisphenol S bismethyl ether (**TBBPS-BME**).

1.3.2 | Production and industrial use

Brominated phenols are used as flame retardants and in the synthesis of other BFRs, pigments, resorcinol, herbicides, germicides and antifungal agents, and are produced during combustion of leaded petrol. They are released through transformation of TBBPA, PBDEs and other BFRs through UV photolysis, thermal treatment and biological processes (Michałowicz et al., 2022).

4-BP was synthesised as the first brominated phenol in the 1920s. Several brominated phenols have been synthesised since, including 2-bromophenol (2-BP), 3-bromophenol (3-BP), **4-BP**, **2,4-DBP**, 2,5-dibromophenol (2,5-DBP), **2,6-DBP**, 3,5-dibromophenol (3,5-DBP), **2,4,6-TBP**, 2,3,4,6-tetrabromophenol (2,3,4,6-TeBP) and pentabromophenol (PBP). Most of them are not important in terms of environmental presence whereas others such as 3,5-DBP and 2,3,4,6-TeBP appear to exist only in the laboratory. **2,4-DBP**, **2,4,6-TBP** and PBP are the most commonly used brominated phenols in the industry (Michałowicz et al., 2022).

It is probably the use of **2,4,6-TBP** as a wood preservative due to its fungicidal properties that has given rise to much of the attention to the possibility of finding brominated phenols in foods. However, it is no longer registered as a permitted biocide for use in the EU (ECHA, 2016).

Brominated phenols, along with some other brominated aromatic compounds can be naturally produced by marine organisms. This, along with the fact that brominated phenols are used for applications other than as flame retardants make it difficult to assess the relative proportions that may be found in the environment as a result of their source and use as a BFR.

The previous Opinion (EFSA CONTAM Panel, 2012a) reported that **2,4,6-TBP** is, or has been, produced in China, in Japan (3600 tonnes in 2003), and in the US (4500–23,000 tonnes in 2006) and that it is considered a high production volume chemical (HPVC) in the EU, i.e. a substance produced or imported in quantities in excess of 1000 tonnes per year. ECHA (2016) reported that aggregated tonnage for **2,4,6-TBP** was between 1000 and 10,000 tonnes per year, but after the lead producer was removed from the register, the remaining production was only between 1 and 10 tonnes per year, and by the end of 2015, there were no registered producers.

While action has been taken to restrict the production and use of some classes of BFRs, this is not the case specifically for brominated phenols. There are, however, proposals under discussion within the EU to restrict all BFRs with persistent, bio-accumulative and toxic (PBT) or very persistent and very bio-accumulative (vPvB) properties or those identified as substances of very high concern (SVHCs), in order to avoid regrettable substitution.[2]

Concerns have been raised about the presence of brominated phenols in drinking water, meaning that this can be a source of human exposure (Michałowicz et al., 2022). It is reported that they can be formed as a result of reactions between dissolved organic matter or xenobiotics (e.g. phenolic ions) and bromide ions in the presence of disinfectants containing, e.g. chlorine, or ozone. Disinfection of aquaculture seawater can also result in the formation of **2,4,6-TBP** (Wang et al., 2018). Low concentrations of both **2,4-DBP** and **2,4,6-TBP** have been found in chlorinated drinking waters originating from surface freshwater or sewages containing significant levels of bromide ions (Sharma et al., 2014; Watanabe et al., 1984). Brominated phenols formation in water may also arise from the oxidation of phenol with manganese dioxides when bromide is also present in the water (Lin et al., 2016).

1.3.3 | Environmental levels and fate

The sections below are not a comprehensive review of the literature but rather give an overview of some aspects related to the environmental fate and levels of brominated phenols and their derivatives covered in the TORs.

1.3.3.1 | *Biodegradation/transformation*

Sources of brominated phenols in the environment as a result of natural formation

In the previous Opinion EFSA CONTAM Panel (2012a), it was reported that emerging BFRs, e.g. 1,4-bis(pentabromophenoxy) tetrabromobenzene and 2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine and others, might degrade into more bioavailable compounds including brominated phenols such as **2,4,6-TBP** and PBP. Brominated phenols found in the environment could therefore in part be present as a result of degradation processes.

It was also noted that several brominated aromatic compounds, e.g. 2-BP, **4-BP**, **2,4-DBP**, **2,6-DBP** and **2,4,6-TBP**, are found naturally in a number of different marine organisms as a result of biogenic formation, e.g. algae and polychaetans (Bidleman et al., 2019; Chung, Ma, Ang, et al., 2003; Chung, Ma, & Kim, 2003; Dahlgren et al., 2015; Fielman et al., 2001; Flodin & Whitfield, 2000; Gribble, 2015; Jin et al., 2024). Brominated phenols have also been found in other marine organisms, such as sponges, hemichordates and ascidians, and thus, brominated phenols of natural origin can reach crustaceans and fish via ecological food chains, and natural formation is considered to be the primary source of brominated phenols in most food of marine origin (EFSA CONTAM Panel, 2012a) (see Section 1.3.3.2).

The function of naturally produced brominated phenols is not certain, but some may play a role in chemical defence against consumers and biofouling (Kicklighter et al., 2004). Some brominated compounds are also found in terrestrial

[2]https://echa.europa.eu/it/-/echa-identifies-certain-brominated-flame-retardants-as-candidates-for-restriction.

ecosystems in bacteria, fungi, plants, insects and in higher animals, but no information on the formation of phenols is available from terrestrial or limnic ecosystems (EFSA CONTAM Panel, 2012a; Gribble, 2015; Jin et al., 2024).

The presence of naturally occurring brominated phenols in food has been shown to cause an unpleasant taste in a number of marine seafoods, such as crustaceans and fish (EFSA CONTAM Panel, 2012a), and have also been associated with an effect on taste and odour in water from desalination plants (Albaladejo et al., 2012). Brominated phenols have also been found in whisky (Bendig et al., 2014).

Degradation of Brominated Phenols

There are several reports in the literature about biodegradation of brominated phenols or detailing methods of decontamination either in contaminated sites or in order to decontaminate products where brominated phenols were used prior to disposal (e.g. Bidleman et al., 2019; Huang et al., 2021; Wang et al., 2024; Oh & Seo, 2019; Thue et al., 2021; Tian et al., 2022; Wang et al., 2023, 2024; Xu et al., 2018).

Bacteria have been identified that can dehalogenate brominated phenols (e.g. Li et al., 2013; Liu et al., 2017), and details of the interaction between green rust and **2,4,6-TBP** under anoxic, oxic and anoxic-to-oxic conditions resulting in oxidative degradation to less toxic derivatives have been described (Zhang, Jia, et al., 2022).

The review by Michałowicz et al. (2022) reports that brominated phenols are degraded by bacteria in both aerobic and anaerobic conditions, but the presence of oxygen enhances the degradation efficiency (Yadu et al., 2016). In aerobic conditions, brominated phenols may be converted to hydroquinones, and then hydroxyquinoles, which may then be degraded to produce maleylacetate and beta-ketoadipate (Sánchez & González, 2007). Brominated phenols (like chlorophenols) may be converted to catechol derivatives which can be easily degraded (Golan et al., 2019).

Brominated phenols are transformed by reductive dehalogenation in anaerobic conditions. For example, **2,4-DBP** and **2,4,6-TBP** have been shown to be debrominated to **4-BP** and **2,4-DBP**, and then dehalogenated to phenol (Kunze et al., 2017).

Abiotic transformation of brominated phenols usually results in the formation of products with high toxicity that persist in the environment. Zhao et al. (2017) showed that UV phototransformation of **2,4,6-TBP** resulted in the formation of dihydroxylated dibromobenzene, hydroxy-PBDEs and dihydroxylated polybrominated biphenyls (di-OH-PBBs). Combustion of brominated phenols results in the formation of various products. Polybrominated dibenzo-*p*-dioxins and polybrominated dibenzofurans (PBDFs) were shown to be formed during the combustion of e-wastes containing BFRs, including **2,4,6-TBP** (Dopico & Gómez, 2015; Michałowicz et al., 2022).

It has also been shown that both 2,3,7,8-substituted and non-2,3,7,8-substituted PBDD/Fs can be generated from **2,4,6-TBP**, and under laboratory conditions, the effects of the catalyst on the Br substituted position of 2,3,7,8-substituted PBDD/Fs were much lower than the Br-substituted position on brominated phenol (Die et al., 2022).

1.3.3.2 | *Occurrence in the environment*

There are several studies in the scientific literature on the occurrence of the brominated phenols considered in this update in the environment, in particular in sediments and aquatic systems. There is less information about brominated phenols in terrestrial wildlife and vegetation.

Aquatic environment, including biota, wildlife and marine mammals

The presence of brominated phenols in the aquatic environment was included in the review by Michałowicz et al. (2022). The review reported that widespread occurrence of synthetic brominated phenols in fresh water and marine ecosystems leads to bioaccumulation of these substances in aquatic organisms, and noted that some naturally produced brominated phenols, i.e. **2,4-DBP** and **2,4,6-TBP**, which are formed as secondary metabolites by diverse marine organisms, are also accumulated in the food chain (Dong et al., 2020; Gribble, 2010; Haldén et al., 2010; Haraguchi et al., 2010). Fish that consume algae and a variety of invertebrates that accumulate brominated phenols have concentrations that range from a few to few hundreds µg/kg.

The amounts of **2,4-DBP** and **2,4,6-TBP** detected in marine fish have been shown to be higher than in freshwater fish (EFSA CONTAM Panel, 2012a; Oliveira et al., 2009), which may be due to much higher content of bromine in ocean water in comparison to inland waters. It is the bromine content of water that acts as a precursor for bromophenols formation in aquatic ecosystems, including in fish and invertebrates that live in them (Wang et al., 2016).

The review by Michałowicz et al. (2022) also reported that marine sponges are natural sources of brominated organic compounds, including brominated phenols that may comprise up to 12% of the sponge dry weight. Seasonal growth of seaweed synthesising brominated phenols affects the total content of these compounds in fish, oyster crabs and shrimps, which varies depending on the season (Chung, Ma, & Kim, 2003). In addition, Haldén et al. (2010) observed that **2,4,6-TBP** level in the tissue of marine organisms was associated with their diet. **2,4,6-TBP** has been found in macroalgae (0.5–107 µg/kg), sponges (0.2–240 µg/kg) and hydroid (29 µg/kg) (Boyle et al., 1992; Haraguchi et al., 2010). Bidleman et al. (2019) reported **2,4,6-TBP** in Antarctic krill (*Euphausia superba*) in low concentrations (57–398 ng/kg), while Chung, Ma, and Kim (2003) found high concentrations of **2,4,6-TBP** (mean of 2.36 mg/kg) in clams from Hong Kong. In another study, Haldén et al. (2010) found huge concentration of **2,4,6-TBP** of 8.3 g/kg in marine polychaetes.

Only a few studies reporting concentrations of brominated phenols in aquatic wildlife have been published since the previous Opinion (EFSA CONTAM Panel, 2012a). In a study investigating molluscs in order to reveal the temporal–spatial variations and trophic transferring of brominated phenols in the Bohai Sea, China (Li, Song, et al., 2023), out of 19 brominated phenols that were identified as potentially present in molluscs, only three, **4-BP**, **2,4-DBP** and **2,4,6-TBP**, were detected in 150 molluscs samples, with a detection frequency of 98.7%, 86.7% and 98.0%, respectively. The concentration of the three detectable congeners (sum of 3 brominated phenols), ranged from 0.152 to 703 µg/kg dry weight, with a median value of 8.08 µg/kg dry weight. The median concentration of **2,4,6-TBP** was 4.27 µg/kg dry weight (range: < LOD–698 µg/kg dry weight), followed by **4-BP** (1.89 µg/kg dry weight; range: < LOD–58.4 µg/kg dry weight) and **2,4-DBP** (0.625 µg/kg dry weight; range: < LOD–9.13 µg/kg dry weight).

Svihlikova et al. (2015) investigated halogenated compounds in fish from the upper Labe River basin in the Czech Republic. Concentrations of **2,4,6-TBP** in fish ($n = 59$) ranged from 1.76 to 107 µg/kg lipid weight.

In a study by Boudjellaba et al. (2016) on chlorination by-product concentration levels in seawater and fish of an industrialised bay (Gulf of Fos, France) exposed to multiple chlorinated effluents, **2,4,6-TBP** was the only one of 15 halogenated chlorination by-products that was found at measurable concentrations. This was consistent with the bioconcentration factors (BCF) predicted by QSAR (quantitative structure–activity relationship) where **2,4,6-TBP** was assessed to be the most susceptible to be bioaccumulated. **2,4,6-TBP** was found in 10 of the 15 fish muscle samples with concentrations ranging from 2.80 to 10.39 µg/kg ww. Concentrations in three samples of conger eel (*Conger conger*) were 2.92, 7.74 and 8.13 µg/kg ww.

Gustavsson et al. (2018) reported on a range of organic flame retardants in Swedish river water. The total daily flux of flame retardants into the Baltic Sea was estimated to be ~31 kg and consisted mainly of TBBPA, 3,4,5,6-tetrabromophthalic anhydride (TEBP-Anh), and **2,4,6-TBP**.

Dron et al. (2022) investigated the contamination by **2,4,6-TBP** of marine waters and organisms exposed to chlorination discharges. The study was conducted in the Gulf of Fos (north-western Mediterranean Sea, France) and clearly showed that industrial chlorination discharges resulted in **2,4,6-TBP** in water, at concentrations of 1–10 ng/L on average with some concentrations reaching up to 580 ng/L near the outlets. Concentrations found in European conger muscle tissues from these locations were 140–1000 ng/g lipid; on average, purple sea urchin gonads were found to contain 830–880 ng/g lipid, on average, and Mediterranean mussel body concentrations averaged 1500–2000 ng/g lipid.

Polyakova et al. (2023) reported that bromophenols, and particularly **2,6-DBP**, is responsible for the smell of 'stinky' Grey whales (*Eschrichtius robustus*). **2,6-DBP** was measured in various tissues from a whale and the maximum concentration was found in liver with a value of 38 ng/g.

Kim et al. (2023) investigated the occurrence and distribution of phenolic compounds, including bromophenols, in freshwater environments. The focus was on crucian carp (*Carassius auratus*) tissues, specifically the muscle, gills, brain, blood, liver and gonads, to assess their potential to bioaccumulate bromophenols in fish and humans and associated health risks. Most other phenolic compounds found in crucian carp samples were also detected in freshwater and sediment, but **2,4,6-TBP** was only found in crucian carp tissues.

Sun et al. (2024) reported on the bioaccumulation, biotransformation and trophic transfer of typical TBBPA analogues including **TBBPS** along a simulated aquatic food chain. It was shown that **TBBPS** could be readily accumulated by brine shrimp (*Artemia salina*), and the estimated bioconcentration factor (BCF) value of **TBBPS** was 5.68 L/kg ww, which was higher than that of TBBPA-di(allyl ether) (1.04 L/kg ww).

Sediments

The review by Michałowicz et al. (2022) also covered sediment and reported that brominated phenols have also been found in concentrations ranging from a few µg up to several mg/kg (Ganci et al., 2019; Han et al., 2013; Harju et al., 2013; Remberger et al., 2002; Tolosa et al., 1991).

The studies reviewed showed that brominated phenols, mostly **2,4,6-TBP**, were found in freshwater sediments. Xiong et al. (2016) assessed the presence of **2,4,6-TBP** and PBP in sediments of Beijiang River water (South China). Low concentrations of **2,4,6-TBP** from detection limit (< LOD) up to 0.410 µg/kg were found. In another study, much higher concentrations of **2,4,6-TBP** (0.2–36 µg/kg) were determined in the sediments collected from freshwater ecosystems of Osaka Prefecture, Japan (Watanabe et al., 1985). The highest concentrations of **2,4,6-TBP** ranging from 26 µg/kg to 3690 µg/kg were detected by Tolosa et al. (1991) in the sediments of the Rhone estuary (France). Marine sediments may also contain significant concentrations of brominated phenols, for example, Remberger et al. (2002) detected **2,4-DBP** in the concentrations range from 5 to 13 µg/kg in the sediments of the Baltic Sea. The study of Manasfi et al. (2019) showed that sediment samples collected from various locations of Gulf of Fos (France) contained **2,4,6-TBP** (only 2 of 24 samples) at 2.1 µg/kg and 1.5 µg/kg. Similar concentrations of **2,4,6-TBP** (1.6–9 µg/kg) were found by Sim et al. (2009) in marine sediments from South Korea.

Soil, vegetation and the terrestrial environment

The review by Michałowicz et al. (2022) reported that high concentrations of brominated phenols of up to several mg/kg were found in soil adjacent to wastes of electrical and electronic equipment (e-wastes) (Han et al., 2013; Remberger et al., 2002; Tolosa et al., 1991). Han et al. (2013) showed that soil adjacent to e-wastes was contaminated with **2,4-DBP** (0.17–2.10 µg/kg) and **2,4,6-TBP** (0.64–2.64 µg/kg). Sewage usually contains high concentrations of brominated phenols,

e.g. high mean concentrations of **2,4-DBP** (1.69 µg/L) and **2,4,6-TBP** (7063 µg/L) were measured in discharge sewage of a factory producing flame retardants in China (Chi et al., 2017).

Very little information was found about brominated phenols in vegetation in the terrestrial environment. Wu et al. (2023) described a method to identify metabolites of **2,4-DBP** in plants. Eight metabolites were identified in the plant callus tissues after 120 h of incubation. The metabolites were said to be formed by direct conjugation with glucose or amino acids. Zhang et al. (2021) exposed **2,4,6-TBP** to rice for 5 days both in vivo (intact seedling) and in vitro (suspension cell) to systematically characterise the fate of its sulfation and glycosylation conjugates in rice. The **2,4,6-TBP** was rapidly transformed to produce 6 (rice cells, 3 h) and 8 (rice seedlings, 24 h) sulfated and glycosylated conjugates. The sulfated conjugates could be vertically transported into the leaf sheath and leaf, while the glycosylated conjugates were sequestered in cell vacuoles and walls, which resulted in exclusive compartmentalisation within the rice roots. These results showed that glycosylation and sulfation of the phenolic hydroxyl groups during plant excretion and Phase III metabolism may reduce the accumulation of **2,4,6-TBP** and its conjugates in rice plants.

Air

Only limited information is available for **2,4,6-TBP** in air and no information could be identified for the other brominated phenols covered in this Opinion. de Wit et al. (2010) reported that **2,4,6-TBP** was found in air samples from 18 houses and 14 offices in Tokyo, Japan, in 2002 (Saito et al., 2007). **2,4,6-TBP** air concentrations ranged from not detectable levels to 6800 pg/m^3. For outdoor air, **2,4,6-TBP** concentrations were all below the detection limit.

Sha et al. (2018) measured the concentrations of a variety of contaminants in indoor air from occupational and home environments. **2,4,6-TBP** was always detected in indoor air and was found in concentrations up to 310 pg/m^3 in a sample that was taken in a computer room.

Cousins (2012) investigated the effect of the indoor environment on the fate of organic chemicals in the urban landscape. Concentrations were not reported as such, but it was concluded that the outdoor environmental concentrations of **2,4,6-TBP** were predicted to be lower if emitted to indoor air than if emitted to outdoor air because of the additional indoor removal pathways of dust and indoor film, leading to loss of chemical from the system.

In a review of halogenated natural products in Arctic, Subarctic and Nordic ecosystems, **2,4-DBP** and **2,4,6-TBP** were found in low concentrations (few pg/m^3) in air (Bidleman et al., 2019), and Schlabach et al. (2011) measured the same two brominated phenols at similar low concentrations in air from both urban and background sites in Nordic environments.

Dust

For most BFRs, and other POPs, the biggest source of non-dietary exposure for non-occupationally exposed individuals is from dust. There are no European studies reporting concentrations of brominated phenols and derivatives in dust, but studies from other parts of the world are collated in Appendix A (Table A.1).

For **2,4,6-TBP**, concentrations up to 2000 ng/g have been reported in dust samples taken from an e-waste recycling industrial park in Central China, although the mean concentration was 352 ng/g and the median was 263 ng/g. Concentrations found in suburban residential homes in the same study were used as reference values and had a high value of 181 ng/g and a mean of 66.2 ng/g and median of 63.9 ng/g. These and were taken from Guangzhou, China, which is around 1000 km away from the e-waste dismantling park (Lan et al., 2023).

Dust from an e-waste recycling facility in Canada was found to have **2,4,6-TBP** at a mean concentration of 174 ng/g, a median of 145 ng/g with a standard deviation of 157 ng/g (Guo et al., 2018).

Dust from residential homes in the USA was found to contain **2,4,6-TBP** with a mean concentration of 17.9 ng/g, a median of 6.69 ng/g with a standard deviation of 31.8 ng/g (Guo et al., 2018).

Concentrations in house dust from Japan have been reported at the same order of magnitude (Suzuki et al., 2008; Takigami et al., 2009) and concentrations in Japanese office dust was found to have a median concentration of 90 ng/g with a range of 27–620 ng/g (Suzuki et al., 2008).

There is one study reporting concentrations of **TBBPS** in dust from China (Lan et al., 2023). Concentrations in samples taken from an e-waste recycling area had a mean concentration of 2.60 ng/g; a median of 1.31 ng/g with a range from < LOQ–15.5 ng/g. All samples from suburb residential homes from this study had concentrations < LOQ.

Levasseur et al. (2021) studied young children's exposure to phenols including brominated phenols in the home in a study conducted in central North Carolina (USA). They looked for associations between house dust, hand wipes, silicone wristbands and urinary biomarkers. **2,4,6-TBP** was found to have a median concentration in dust ($n = 186$) of 46 ng/g, and a maximum concentration of 1967 ng/g. Based on correlations with urinary biomarkers, both wristbands and hand wipes demonstrated better estimates of ambient environmental brominated phenols exposures in children than house dust. The results suggested that wristbands and hand wipes captured the primary pathways of exposure for several environmental brominated phenols or their precursors where diet was not considered the main pathway.

Terrestrial animals including birds

No new studies were identified that reported brominated phenols and derivatives in terrestrial wildlife or birds since the previous Opinion (EFSA CONTAM Panel, 2012a), but some studies were identified that reported levels in pets. Norrgran

et al. (2012) reported on BFRs including brominated phenolic compounds in the serum of cats diagnosed with the endocrine disease feline hyperthyroidism. One dibromophenol (**2,4-DBP**), two tribromophenols (**2,4,6-TBP** and 2,4,5-TBP) and four hydroxylated PBDEs were identified among the halogenated phenolic compounds analysed in cat serum. The estimated concentration for **2,4,6-TBP** in the cat serum sample was 250 ng/g fat. Norrgran Engdahl et al. (2017) reported on cats' internal exposure to several BFRs including brominated phenols from house dust and cat food. Serum levels were significantly correlated with concentrations found in cat food for **2,4,6-TBP** ($p < 0.035$).

Mizukawa et al. (2017) investigated anthropogenic and naturally produced brominated phenols in pet blood (cats and dogs) and pet food in Japan. Concentrations were higher in cat blood than in dog blood, with statistically insignificant differences ($p = 0.07$). Among the congeners, **2,4,6-TBP** constituted the majority of brominated phenols (> 90%) detected in both species. Analysis of commercial pet food to estimate exposure routes showed that the most abundant congener in all pet food samples was **2,4,6-TBP**, accounting for > 99% of total brominated phenols. No significant differences ($p = 0.07$) were found between the median concentrations of total brominated phenols in the cat blood (median: 260 pg/g ww; range: 91–1300) and dog blood (median: 93 pg/g ww; range: 2.7–2700). 2,4,5-TBP, 2,3,4,6-TeBP, 2,3,5,6-TeBP and PBP were found in dog blood and 2,4,5-TBP, 2,3,5-TBP, 2,3,4,6-TeBP, 2,3,5,6-TeBP, 2,3,4,5-TeBP and PBP were found in cat blood.

1.3.4 | Sampling and methods of analysis

Sampling

There are no specific guidelines for the sampling of foods specifically for the determination of brominated phenols, and so basic rules for sampling of organic contaminants or pesticides should be followed. The EU Reference Laboratory for persistent organic pollutants (EURL-POPs) in food and feed produced a guidance document[3] in 2023 on the 'Determination of Organobromine Contaminants with a focus on Analytical Parameters in food and feed'. While this document deals primarily with PBDEs and HBCDDs, much of the information contained is applicable for the wider class of organobromine compounds.

Analysis

The general principles of the analytical approach for brominated phenols and derivatives were described in the previous opinion (EFSA CONTAM Panel, 2012a). Compounds with only one or two bromine atoms are considered as volatile whereas those with more bromines are semi-volatile. Volatile brominated phenols are found in seafood and are considered as flavour components, and several methods release the analytes from the matrix by steam distillation. Methods for a wider range of brominated phenols and derivatives generally use a similar approach to those used for PBDEs and HBCDDs (EFSA CONTAM Panel, 2012a).

While liquid chromatography (LC) with ultraviolet (UV) detection has been used in the past (EFSA CONTAM Panel, 2012a), more advanced methods use either gas chromatography (GC) or LC with mass spectrometry (MS) detection (see below).

Over the past decade, most published papers detailing analytical methods have focussed on **2,4,6-TBP** (e.g. Allard et al., 2018; Bernstein et al., 2019; Li, Gao, et al., 2023). Several also measure **2,4-DBP** (e.g. Sun et al., 2015; Wang et al., 2017) and a few measure **2,6-DBP** and **4-BP** in addition (e.g. Bartosova et al., 2014). Fewer publications detail methodology for **2,6-DBP**, **4-BP** or **TBBPS** with one paper giving a method for **TBBPS-BME** (Liu et al., 2015).

Of these published papers, only a few focus on food or feed, and these are described below.

Malysheva et al. (2018) reported on the development and validation of a quantitative ultra-high-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS) method for selected brominated flame retardants in food. The method covered **2,4,6-TBP**, **2,4-DBP**, **2,6-DPB** and **4-BP** which were analysed together with PBDEs and HBCDDs, and used UPLC-MS/MS. The method was applied to samples of fish, meat, chicken eggs, cow milk, baby food, oils, cheese and vegetables. The lack of isotopically labelled standards for **2,6-DPB** was stated to be a limitation of the method. The method was sufficiently sensitive to uncover low-level contamination of **4-BP** in egg and fish samples.

Paseiro-Cerrato, De Jager, et al. (2021) investigated the migration of a range of phenolic BFRs including **2,4,6-TBP** from contaminated food contact articles into food simulants and food. The method used a direct analysis in real-time ionisation high-resolution mass spectrometry (DART-HRMS) screening technique and GC–MS for confirmation. The DART-HRMS screening method was able to identify **2,4,6-TBP** in several repeat use food contact articles, although it was not possible to use the GC–MS method for confirmation.

TBBPS and **TBBPS-BME** were among compounds identified as metabolites of tetrabromobisphenol-S bis(2,3-dibromopropyl ether) (TBBPS-BDBPE), and were measured in molluscs by Liu et al. (2015) using HPLC coupled with Orbitrap Fusion HRMS.

Zhang et al. (2016) used gas purge microextraction coupled with stable isotope labelling-LC/MS for the analysis of brominated phenols in aquatic products.

[3]https://eurl-pops.eu/user/pages/05.news/09.Guidance-Document-BCon-Parameters/Guidance-Document-on-the-Determination-of-Organobromine-Contaminants_Analytical-Parameters-in-food-and-feed_V1.2.pdf?g-64cde584.

Liu et al. (2024) were able to determine 19 brominated phenols by GC–MS. Optimal chromatographic separation, selectivity, sensitivity and linearity were achieved after derivatisation using acetic anhydride.

TBBPS was included in a method using functional melanin nanoparticles-assisted laser desorption ionisation mass spectrometry in a sensitive method for contaminations in animal-derived foodstuffs. The method was applied to milk products where the LOD was 200 pg/mL, and also bass, catfish and meat (Chen et al., 2024).

Quality control studies

No commercial proficiency test schemes could be identified for brominated phenols and their derivatives, and they have not been the subject of inter-laboratory studies organised by the EURL for POPs. Dvorakova et al. (2021) included **2,4,6-TBP** in their interlaboratory comparison investigations and external quality assurance schemes (EQUASs) for flame retardant analysis in biological matrices, but few laboratories reported results and it was not possible to conduct formal statistical analysis. The authors concluded that there was low analytical capacity in Europe for the analysis of this compound.

1.3.5 | Previous assessments

In 2012, the EFSA CONTAM Panel published its first risk assessment on brominated phenols and their derivatives in food (EFSA CONTAM Panel, 2012a). At that time, the Panel noted that oral toxicity studies were scarce and the only two repeated dose studies related to **2,4,6-TBP**. From these limited two studies, which included dosing for periods up to 48 days, the Panel identified liver and kidney as the main targets for toxicity of **2,4,6-TBP**, and identified a no-observed-adverse-effect level (NOAEL) of 100 mg/kg bw per day in rats from the study by Tanaka et al. (1999, as cited in WHO, 2005, OECD, 2005). This was a repeated dose toxicity study combined with a reproduction/developmental toxicity screening test, in which rats were dosed by gavage **2,4,6-TBP** at 0, 100, 300 or 1000 mg/kg bw per day.

The Panel concluded that **2,4,6-TBP** did not induce mutations in bacteria but induced chromosomal aberrations in mammalian cells in vitro. It did not induce micronuclei in bone marrow of mice in vivo.

Due to the limitations and uncertainties in the database, the CONTAM Panel did not find it appropriate to establish a health-based guidance value for **2,4,6-TBP**, and instead used a margin of exposure (MOE) approach for the risk characterisation.

At the time of the previous Opinion, no data on brominated phenols or their derivatives were submitted to EFSA. A limited number of occurrence data, covering the food group 'Fish and other seafood', were identified in the literature, and data from European sampling showed that **2,4,6-TBP** predominated over other brominated phenols. Since these data from the literature covered one food group only, a meaningful exposure assessment for the general population was not possible. In order to provide some indication of whether there could be a possible health concern with respect to dietary exposure to **2,4,6-TBP**, the CONTAM Panel made a tentative exposure estimate for the specific group of 'adult high consumers of fish, molluscs and crustaceans' using the data identified in the literature and estimated a worst-case exposure estimate of 40 ng/kg bw per day.

Comparison of the NOAEL for **2,4,6-TBP** of 100 mg/kg bw per day with the worst-case dietary exposure estimate of 40 ng/kg bw per day for high consumers of fish, molluscs and crustaceans, resulted in an estimated MOE of about six orders of magnitude. This MOE was so large that the CONTAM Panel concluded that it was unlikely that current dietary exposure to **2,4,6-TBP** in Europe would raise a health concern.

Due to lack of data, a risk assessment of the other brominated phenols or their derivatives considered in the previous opinion was not possible.

The WHO (2005) in its evaluation of **2,4,6-TBP** also concluded on a NOAEL of 100 mg/kg bw per day based on the same study by Tanaka et al. (1999), but could not establish a reliable tolerable daily intake for **2,4,6-TBP** for drinking water or food. It was concluded that exposure of the general population to **2,4,6-TBP** was through drinking water and the consumption of seafood (WHO, 2005).

In 2009, the US Environmental Protection Agency (US-EPA) published a report on provisional peer-reviewed toxicity values for **2,4,6-TBP** (US-EPA, 2009), which was not described in the previous Opinion. US-EPA recognised that the number of toxicological studies identified for this compound were limited at that time, and based on the duration of the studies retrieved, it concluded that a provisional subchronic oral reference dose (RfD) could be derived. The repeated-dose reproductive/developmental screening toxicity study (Tanaka et al., 1999) and a pilot teratology study (International Research and Development Corporation, 1978) were identified as the critical studies, both performed in rats exposed to **2,4,6-TBP** by gavage. A LOAEL for short-term oral exposure was considered at 300 mg/kg bw per day based on the increase in serum creatinine in male rats. The serum creatinine data were also used for benchmark dose (BMD) modelling and a $BMDL_{1SD}$ of 92 mg/kg bw per day was calculated. The subchronic RfD was established at 0.09 mg/kg bw per day, applying a composite uncertainty factor (UF) of 1000 to the BMDL, accounting for interspecies extrapolation (UF of 10), intraspecies differences (UF of 10) and database deficiencies (UF of 10). No chronic RfD was derived for **2,4,6-TBP**; however, a screening value that may be useful in certain instances was defined at 0.009 mg/kg per day (applying a composite UF of 10,000 to the BMDL, the additional UF of 10 was applied for extrapolation from subchronic to chronic exposure).

No other (risk) assessments have been identified.

1.3.6 | Legislation

In this Opinion, where reference is made to European legislation (Regulations, Directives, Recommendations, Decisions), the reference should be understood as relating to the most recent amendment at the time of publication of this Opinion, unless otherwise stated.

In order to protect public health, Article 2 of Council Regulation (EEC) No 315/93[4] of 8 February 1993 laying down Community procedures for contaminants in food stipulates that, where necessary, maximum tolerances for specific contaminants shall be established. The brominated phenols and their derivatives considered in this Opinion are not regulated under any specific legislations within the EU for food or feed, e.g. Commission Regulation (EU) 2023/915 of 25 April 2023 and Council Directive 2002/32/EC.

2,4,6-TBP is registered under Regulation (EC) No 1907/2006[5] of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation), and is manufactured in and/or imported to the European Economic Area, at 100–1000 tonnes per annum. In 2016, Norway published the report of the evaluation of this substance[6] as required by REACH Article 48. Concerns originally raised regarding this substance were about potential carcinogenicity, mutagenicity and/or toxicity to reproduction and persistent, bioaccumulative and toxic properties. Nevertheless, the substance evaluation was terminated as this substance no longer had any active registration. The Norwegian Competent Authority concluded that hazards remained unverified, and in case of possible future activation of registrations or new registrations, a further assessment should be undertaken. In March 2024, in accordance with Article 44(2) of the Regulation (EC) No 1907/2006 (REACH), the French competent authority (CA), ANSES, published a Justification Document for the Selection of **2,4,6-TBP** for evaluation.[7] The concerns raised by the French CA refer to suspected reproductive toxicity and persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM), potential endocrine disruptor properties. The remaining brominated phenols considered in this Opinion (Table 1) are pre-registered substances, except for **TBBPS-BME**. Brominated phenols have not been restricted under REACH, however, according to ECHA's regulatory strategy for flame retardants,[8] discussions are ongoing for a wide and generic restriction for all aromatic brominated flame retardants, that are confirmed or will be confirmed to be PBT/vPvB through harmonised classification or identification as SVHCs.

According to the WHO (2005), **2,4,6-TBP** is registered as a wood preservative in South America. For example, the pesticide register for Chile reveals that three products based on the sodium tribromophenol salt are approved for use as a fungicide (two manufacturers in Chile and one in Brazil). However, it is not registered as a pesticide in the EU. If a pesticide is not registered in the EU and thus not included in any of the Annexes of Regulation (EC) No. 396/2005,[9] according to Art. 18 (1b) of this Regulation, a default maximum residue level (MRL) of 0.01 mg/kg applies.

None of the brominated phenols in the TORs are regulated under the Stockholm or long-range transboundary air pollution (LRTAP) conventions.

2 | DATA AND METHODOLOGIES

The current updates of the EFSA risk assessments on BFRs, including this one on brominated phenols and their derivatives, were developed applying a structured methodological approach, which involved developing a priori the protocol or strategy of the full risk assessments and performing each step of the risk assessment in line with the strategy and documenting the process. The protocol in Annex A of this Opinion contains the method that was used for all the steps of the risk assessment process, including any subsequent refinements/changes made.

The CONTAM Panel used its previous risk assessment on brominated phenols and their derivatives in food (EFSA CONTAM Panel, 2012a) as a starting point for drafting the current Opinion.

2.1 | Supporting information for the assessment

Information on physicochemical properties, production and industrial use, environmental fate and levels, analytical methods, previous assessments and legislation was gathered from the previous EFSA Opinion on brominated phenols and their derivatives (EFSA CONTAM Panel, 2012a), assessment by international bodies (by checking the original websites of the relevant organisations), and from current EU legislation. Literature searches were conducted to identify new information in

[4]Council Regulation (EEC) No 315/93 of 8 February 1993 laying down Community procedures for contaminants in food. OJ L 37, 13.2.1993, p. 1.

[5]Regulation (Ec) No 1907/2006 Of The European Parliament And Of The Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006, pp. 1–849.

[6]https://echa.europa.eu/documents/10162/fd19d44e-7365-c189-d263-d3b0f4cc7dd9.

[7]https://echa.europa.eu/documents/10162/91956f4a-4612-34f6-15fa-0155e7237874.

[8]https://echa.europa.eu/documents/10162/2082415/flame_retardants_strategy_en.pdf/.

[9]Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC Text with EEA relevance. OJ L 70, 16.3.2005, pp. 1–16.

reviews and other peer-reviewed publications. Details about the literature searches are given in Appendix B. The information was summarised in a narrative way based on expert knowledge and judgement.

The draft Scientific Opinion underwent a public consultation from 13 June 2024 to 1 August 2024. The comments received were taken into account when finalising the Scientific Opinion and are presented and addressed in Annex E.

2.2 | Hazard identification and characterisation

Information relevant for the sections under hazard identification and characterisation was identified by an outsourced literature search. EFSA outsourced a call for 'Identifying and collecting relevant literature related to the toxicity of polybrominated diphenyl ethers (PBDEs), Tetrabromobisphenol A (TBBPA) and brominated phenols'. The call was launched as a reopening competition for a specific contract under multiple framework contract CT/EFSA/AMU/2014/01 Lot 2. The Technical University of Denmark (DTU) was awarded the contract and a final project report was delivered in October 2019. The aim of the assignment was to identify and collect all relevant literature related to the toxicity of brominated phenols and their derivatives (as well as PBDEs and TBBPA and its derivatives) to support the preparatory work for the hazard identification and characterisation steps in the human health risk assessment of these substances. Literature searches were designed and performed to retrieve all potentially relevant studies within the following four areas: Area 1: Data on toxicokinetics in experimental animals and humans and from in vitro studies, Area 2: Data on toxicity in experimental animals, Area 3: Data on in vitro and in vivo genotoxicity and mode of action and Area 4: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure). Details of the methodology and the results are reported in Bredsdorff et al. (2023).

Additional literature searches to identify studies published since October 2019 were made in October 2023 and April 2024 as reported in Appendix B.

The selection of the scientific papers for inclusion or exclusion was based on consideration of the extent to which the study was relevant to the assessment or on general study quality considerations (e.g. sufficient details on the methodology, performance and outcome of the study, on dosing, substance studied and route of administration and on statistical description of the results), irrespective of the results. Limitations in the information used are documented in this Scientific Opinion.

Benchmark dose (BMD) analysis was carried out according to the EFSA Scientific Committee Guidance on BMD modelling (EFSA Scientific Committee, 2022). The Bayesian BMD Modelling web-app (https://zenodo.org/record/7334435#.Y5osYXbMLD4) available at the EFSA R4EU platform (https://efsa.openanalytics.eu/). All analyses were performed using Bridge sampling because of the higher level of accuracy with respect to Laplace approximation set as default (EFSA Scientific Committee, 2022; Hoeting et al., 1999; Morales et al., 2006).

2.3 | Occurrence data submitted to EFSA

2.3.1 | Data collection

Following a mandate from the European Commission, a call for annual collection of chemical contaminant occurrence data in food was issued by EFSA in December 2010. Since then, data have been submitted every year by a deadline agreed with the EFSA Scientific Network on Chemical Monitoring Data collection.[10]

The data submission to EFSA follow the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010a) and the EFSA Guidance on Standard Sample Description 2 (EFSA, 2013). Occurrence data are managed following the EFSA standard operation procedures (SOPs) on 'Data collection and validation' and on 'Data analysis of food consumption and occurrence data'.

2.3.2 | Data validation and analysis

Following EFSA's Technical Report on handling of occurrence data for dietary exposure assessment (EFSA, 2021) to guarantee an appropriate quality of the data used in the exposure assessment, the initial data set was carefully evaluated by applying several data cleaning and validation steps. Special attention was paid to the identification of duplicates and to the accuracy of different parameters, such as 'Sampling strategy', 'Sampling year', 'Sampling country', 'Analytical methods', 'Result express' (expression of results, e.g. fat weight), 'Reporting unit', 'Limit of detection/quantification' and the codification of analytical results under FoodEx2 classification (EFSA, 2011a, 2011b, 2015).

Left-censored data were treated using the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO/IPCS, 2009, updated in 2020). This is the same method as indicated in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010b). The guidance suggests that the lower bound (LB) and upper bound (UB) approach should be used for chemicals likely to

[10]Current call: https://www.efsa.europa.eu/en/call/call-continuous-collection-chemical-contaminants-occurrence-data-food-and-feed-2023.

be present in the food (e.g. naturally occurring contaminants, nutrients and mycotoxins). The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as lower than the LOD (< LOD) or LOQ (< LOQ). The UB is obtained by assigning the numerical value of LOD to values reported as < LOD and LOQ to values reported as < LOQ (maximum possible value), depending on whether LOD or LOQ is reported by the laboratory.

A mean LB and UB occurrence value was then calculated at each level of the FoodEx2 classification.

Means for specific food categories calculated on less than six analytical results were not used in the dietary exposure assessment. However, these analytical results were included in the calculation of averages for categories at higher levels of the FoodEx2 classification in case at least six were available.

Specific food subcategories with 100% left-censored results were included with mean LB and UB concentration of the closest parent FoodEx2 categories for which quantified results were available if there was no reason to exclude the presence of the compound in the subcategory.

Similarly, specific food subcategories for which there were no occurrence data available were attributed with the concentration of the parent FoodEx2 category where contamination could not be excluded, e.g. the mean concentration for 'Marine fish' was attributed to 'Sea bass', subcategory for which there were no specific occurrence data.

2.4 | Food consumption data

Food consumption data from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) were used for the dietary exposure assessment. This database contains national data on food consumption at the individual level, which are the most complete and detailed data currently available in the EU.

The food consumption data gathered in the Comprehensive Database were collected using repeated 24-h or 48-h dietary recalls or dietary records covering 3 or 7 days per individual. Owing to the differences in the methods used for data collection, direct country-to-country comparisons of the exposure estimates should be avoided.

Details of how the Comprehensive Database is used to assess the dietary exposure to food chemicals are published in a 2011 EFSA Guidance (EFSA, 2011b). The latest version of the Comprehensive Database was published in December 2022 and contains results from 53 dietary surveys carried out in 24 Member States covering 95,410 individuals. Six surveys provide information on 'Pregnant women', two on 'Lactating women' and one on Vegetarians. When two different dietary surveys are available for one country and age class, the most recent one is used in the dietary exposure assessment.

A chronic dietary exposure assessment is relevant in the context of the terms of reference. For such an assessment, surveys in which food consumption data were collected over only 1 day are not considered appropriate. Exclusion of these surveys resulted in a total of 49 dietary surveys carried out in 22 Member States covering 84,676 individuals. Table 2 provides an overview of the population groups and countries included in the dietary exposure assessment.

According to the EFSA Scientific Committee Guidance on the risk assessment of substances present in food intended for infants under 16 weeks of age, the exposure assessment for these infants should be carried out separately from that for older infants, following the procedure described in the guidance (EFSA Scientific Committee, 2017). Based on this guidance, infants under 16 weeks of age should be excluded from the dietary exposure estimation of the infants age group. However, due to uncertainty in the reported individual ages of infants in the Comprehensive Database, the cut-off age was based on a validated existing age group in this database corresponding to 12 weeks of age. Thus, food consumption data of infants between 12 and 16 weeks of age were also included in the exposure assessment. As the number of children within this age range in the database is limited, it is not expected that this will have affected the exposure estimate for infants of 16 weeks up to 12 months of age.

Annex B (Table B.1) provides details on the dietary surveys included in the dietary exposure assessment.

TABLE 2 Population groups and countries included in the chronic dietary exposure assessment.

Population group	Age range	Countries with food consumption surveys covering more than 1 day
Infants	> 12 weeks to < 12 months	Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Portugal, Slovenia, Spain
Toddlers	≥ 12 to < 36 months	Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Portugal, Slovenia, Spain
Other children	≥ 36 months to < 10 years	Austria, Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Netherlands, Portugal, Spain, Sweden
Adolescents	≥ 10 to < 18 years	Austria, Belgium, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Netherlands, Portugal, Romania, Slovenia, Spain, Sweden
Adults	≥ 18 to < 65 years	Austria, Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Portugal, Romania, Slovenia, Spain, Sweden
Elderly	≥ 65 to < 75 years	Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Portugal, Romania, Slovenia, Spain, Sweden
Very elderly	≥ 75 years	Austria, Belgium, Denmark, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Portugal, Romania, Sweden

2.5 | Food classification

Consumption and occurrence data were codified according to the FoodEx2 classification system (EFSA, 2011a, 2011b). Since 2018, all consumption records in the Comprehensive Database as well as all occurrence data submitted to EFSA have been codified according to the FoodEx2 classification system (EFSA, 2015). The FoodEx2 classification system consists of a large number of standardised basic food items aggregated into broader food categories in a hierarchical parent–child relationship. Additional descriptors, called facets, are used to provide additional information about the codified foods (e.g. information on food processing and packaging material).

2.6 | Exposure assessment

Due to the limited, or lack of, toxicological and occurrence data on **2,4-DBP**, **2,6-DBP**, **4-BP**, **TBBPS** and **TBBPS-BME** (see Section 3.1), the Panel deemed it not possible to perform a risk assessment for these brominated phenols, and an exposure assessment was only performed for **2,4,6-TBP** (see Section 3.1.5).

For calculating the chronic dietary exposure to **2,4,6-TBP**, food consumption and body weight data at the individual level were retrieved from the Comprehensive Database. Occurrence data and consumption data were linked at the relevant FoodEx2 level.

Chronic dietary exposures were calculated by combining mean **2,4,6-TBP** occurrence values for food samples collected in different countries (pooled European occurrence data) with the average daily consumption for each food at the individual level in each dietary survey and age class. Consequently, individual average exposures per day and body weight were obtained for all individuals. The following formula describes the calculation made:

$$\bar{e}_i = \frac{\sum_{d \in D_i} \sum_{f \in F} \bar{x}_f \cdot c_{f,d,i}}{|D_i| \cdot \mathrm{bw}_i},$$

where $\bar{e}_i$ is the average exposure of individual i; $\bar{x}_f$ is the mean **2,4,6-TBP** concentration in each food or food group f (belonging to set of foods F_i for individual i); $c_{f,d,i}$ is the consumed amount of food f by individual i on day d; bw_i is individual body weight of individual i; d is the survey day (belonging to the set of survey days D_i for individual i); $|D_i|$ represents the number of survey days of individual i.

The distributions of individual exposures were then used to calculate the mean and high (95th percentile) exposure per survey and per age class. These exposure estimates were obtained using the LB and UB mean concentration of **2,4,6-TBP**.

All analyses were run using the SAS Statistical Software (SAS enterprise guide 8.3 Update 5).

2.7 | Risk characterisation

The general principles of the risk characterisation for chemicals in food as described by the WHO/IPCS (2009, updated in 2020) will be applied as well as the different EFSA guidance documents relevant to this step of the risk assessment (see Annex A).

3 | ASSESSMENT

3.1 | Hazard identification and characterisation

3.1.1 | Toxicokinetics

3.1.1.1 | *Toxicokinetic studies in experimental animals*

In the previous Opinion, the limited toxicokinetics data suggested that, following oral administration to rats, radiolabelled **2,4,6-TBP** was rapidly absorbed, distributed in different tissues, such as kidney, lung and liver, and eliminated, via urine (70%–90%) and faeces (4%–6%), within 48 h. The reported half-life was 2 h in blood. No information was found on metabolic pathways of **2,4,6-TBP** (for details, see EFSA CONTAM Panel, 2012a). No data on the other brominated phenols considered in the previous opinion were identified.

Since the previous Opinion, two in vivo studies with direct administration of **2,4,6-TBP** have been identified (Knudsen et al., 2019, 2020).

Knudsen et al. (2019) performed a toxicokinetic study on female Sprague–Dawley rats dosed with [^{14}C]-**2,4,6-TBP** by gavage at 0.033–330 mg/kg bw, or by intravenous (iv) route at 3.3 mg/kg bw. The authors reported an oral bioavailability of 30%, based on the area under the curve (AUC) (comparison oral vs. iv route).

Following the single oral administration of [^{14}C]-**2,4,6-TBP** to the female Sprague–Dawley rats, **2,4,6-TBP** was excreted mainly via urine at 24 h (88%–89%) whereas 7%–9% of the dose was excreted in faeces. The authors studied also the biliary excretion (using bile duct cannulated female Sprague–Dawley rats) and found that 11% of the dose was recovered in bile.

The authors also investigated the distribution and potential accumulation of **2,4,6-TBP** by administration over 5 consecutive daily doses of [^{14}C]-**2,4,6-TBP** and collecting excreta at 24-h intervals. Additional male Sprague–Dawley rats and B6C3F1 male and female mice were exposed to a single dose of 3.3 mg/kg bw (4 mL/kg bw) by gavage to assess sex and species differences. The following tissues and samples were collected: adipose, adrenals, brain, heart, kidneys, stomach, stomach contents, large intestine, large intestine contents, liver, lung, muscle (quadriceps), pancreas, ovaries/testes, skin (ears), spleen, thymus, thyroid, urinary bladder, uterus and epididymis. The authors did not detect changes in either excretion patterns or bioaccumulation in tissues in rats and mice. The percentage of [^{14}C]-radioactivity recovered in tissues at 24-h post-dose in male and female Sprague–Dawley rats and male and female B6C3F1 mice was less than 1%. The authors compared the disposition of **2,4,6-TBP** after a single oral dose and concluded that rats and mice (both sexes) had similar kinetic profile (elimination, blood concentration, …).

2,4,6-TBP-glucuronide and 2,4,6-TBP-sulfate metabolites were detected in urine. The mass spectral analysis of urine revealed that the major metabolite was 2,4,6-TBP-glucuronide (more than 90% of the [^{14}C]-radioactivity), a trace of 2,4,6-TBP-sulfate was also detected. The elimination half-life was 4.5 h.

In another study, Knudsen et al. (2020) performed a toxicokinetic study on female Sprague–Dawley rats dosed by gavage [^{14}C]-**2,4,6-TBP** at 3.3 mg/kg bw on gestation day (GD) 12 and 20, or postnatal day (PND) 12. The authors measured radioactivity in embryos and dam tissues in the following order according to concentrations: kidney (dam) = plasma (dam) > liver (dam) > embryos at GD12. At GD20, the tissue concentrations were in the following order: kidney (dam) > plasma (dam) > liver (dam) > placenta > fetus. The tissue concentrations in pups at PND12 were stomach contents > kidney > liver. The authors demonstrated that there is evidence of maternal transfer during gestation and lactation. At GD12 and PND12, 70% of the total radioactivity measured in plasma was in the form of phase II metabolites (the authors did not differentiate between glucuronide and sulfate metabolites) whereas the percentage was less at GD20 (Knudsen et al., 2020). The authors reported an elimination half-life of 3, 5 and 2 h at GD12, GD20 and PND12, respectively.

The CONTAM Panel acknowledged that **2,4-DBP** and 2,4,5-TBP and their metabolites measured in rodents could be due to the metabolism of PBDEs. Sanders et al. (2006) and Chen et al. (2006) measured two glutathione conjugates and a glucuronide and sulfate conjugate of **2,4-DBP** and 2,4,5-TBP in the bile and urine, respectively, in rats treated with BDE-47 and BDE-99 (as cited in EFSA CONTAM Panel, 2024a).

Xu et al. (2019) detected **2,4-DBP** in urine of C57BL/6J *gpt* delta transgenic mice after oral administration of BDE-47 at 0, 1.5, 10 and 30 mg/kg bw per day, 6 days/week for 6 weeks.

In summary, after oral administration, the bioavailability of **2,4,6-TBP** was around 30% in rats and is distributed in different organs without accumulation. It is mainly excreted in urine. There is evidence of maternal transfer during gestation and lactation. **2,4,6-TBP** is metabolised into sulfate and glucuronic acid conjugates, with an elimination half-life of less than 5 h. There appears to be no major difference between rats and mice regarding disposition after a single oral dose exposure.

3.1.1.2 | *Toxicokinetic studies in humans*

No data were identified in the previous opinion (EFSA CONTAM Panel, 2012a).

Since then, Erratico et al. (2015) studied the in vitro metabolism of **2,4-DBP** and **2,4,5-TBP** using human liver microsomes and cytosolic fractions. The authors found that these two brominated phenols were metabolised either into sulfate or glucuronic acid conjugates.

Zhang et al. (2024) performed an in vitro study (with human liver microsomes) to identify which UGT isoforms were involved in the biotransformation of brominated phenols. The authors showed that UGT1A1, UGT1A8 and UGT2B4 play crucial roles as UGT isoforms in the glucuronidation of **2,4,6-TBP**.

It seems that brominated phenols are able to affect UGT expression and/or function. Zhang et al. (2024) reported induction of UGT1A1 and UGT2B7 in Hep G2 cells exposed to **2,4,6-TBP** (50 μM). In another study, Wang et al. (2020) reported that human UGT isoforms in human liver microsomes were competitively inhibited by **2,4,6-TBP**, where UGT1A7 was more sensitive than UGT1A3 or UGT2B7.

2,4,6-TBP and other brominated phenols have been detected in human samples, e.g. human milk, serum, urine (see Section 3.1.1.3), as well as urinary sulfate and glucuronic acid conjugates. Ho et al. (2012, 2015) detected **2,4-DBP**, 2,4,5-TBP and **2,4,6-TBP** in plasma human samples (from 100 voluntary donors in Hong Kong), and in urine, glucuronide and sulfate conjugates of **2,4-DBP** and **2,4,6-TBP** were also measured. The authors found a correlation between the brominated phenol conjugates with the sum of PBDEs in blood and also suggested that these conjugates could be metabolites of PBDEs.

No data on absorption or elimination were identified.

In summary, there are no data regarding the absorption and elimination of **2,4-DBP** or **2,4,6-TBP** in humans. There are some data showing that **2,4,6-TBP** was detected in human samples, e.g. human milk and serum. **2,4-DBP** and **2,4,6-TBP** are metabolised either into sulfate or glucuronic acid conjugates.

3.1.1.3 | *Levels in human samples*

The previous Opinion on brominated phenols and their derivatives (EFSA CONTAM Panel, 2012a) summarised the occurrence data in human milk and other human samples from European countries published in the literature until its publication in 2012. The number of studies was limited to one study on the levels of **2,4,6-TBP** in human milk samples from Norway (Thomsen, Leknes, et al., 2002), two studies on the levels of **2,4,6-TBP** in plasma from workers (Thomsen, Janák, et al., 2001; Thomsen, Lundanes, et al., 2001) and in **serum** from the general population (Thomsen, Lundanes, et al., 2002), and one study on the levels of **2,4,6-TBP** in adipose tissue from routine medico-legal autopsies from Finland (Smeds & Saukko, 2003).

Data from non-European countries were limited to one study on the levels of **2,4,6-TBP** in human milk samples from Japan (Ohta et al., 2004), one study on the levels of **2,4,6-TBP** in maternal blood and cord blood, and umbilical cord from Japan (Kawashiro et al., 2008), and one study on the levels of **2,4-DPB** and **2,4,6-TBP** in plasma from Nunavik Inuit adults from the Canadian Arctic (Dallaire et al., 2009).

Since then, a limited number of studies in European and non-European countries have become available and are summarised in Table 3.

No studies in human milk from European countries on the levels of any of the brominated phenols considered have been identified since the previous Opinion. Three studies investigating the levels of **2,4,6-TBP** in serum samples from Belgium were identified (Dufour et al., 2016, 2017, 2020).

In a first study, Dufour et al. (2016) described the validation of an analytical method for the simultaneous determination of phenolic organohalogen compounds, including **2,4,6-TBP**, in human serum samples. The method was applied for the analysis of 20 serum samples from adult blood donors in which **2,4,6-TBP** was not detected >LOQ (15 pg/mL) in any of the samples.

In a later study, the same authors analysed 274 serum samples from adult volunteers living in the province of Liège (Belgium) with the same validated method. **2,4,6-TBP** was detected in 64% of the samples, with a mean (median) level of 81.2 (57.3) pg/mL. As a comparison, in that study, the mean levels of TBBPA and two other brominated phenols (2,3,6-TBP and 2,4,5-TBP) were <LOQ (4.1, 2.4 and 5 pg/mL, respectively).

In another study, Dufour et al. (2020) assessed the blood levels of several halogenated compounds, including **2,4,6-TBP**, in hypothyroid and hyperthyroid volunteers ($n=70$) and individuals from the general population designated as controls ($n=90$), to assess the association between organic pollutants and thyroid pathologies. **2,4,6-TBP** was detected in 56% of the samples, with a mean (median) level of 74.6 (53.3) pg/mL. As a comparison, in that study, the detection frequency of TBBPA was lower (39%, mean levels not reported by the authors for compounds with a detection frequency lower than 40%).

TABLE 3 Concentration of brominated phenols and their derivatives in **serum** samples from European countries.

Country year	Number of samples	Concentration (ng/g lipid)	Detection frequency	Reference
Serum				
Belgium NR	**2,4,6-TBP** $n=20$ adults (21–69 years old)	<LOQ	0% LOQ = 15 pg/mL	Dufour et al. (2016)
Belgium 2015	**2,4,6-TBP** $n=274$ adults (18–76 years old)	Mean (SD): 81.2 (108) pg/mL Median (range): 57.3 (<LOQ–1277 pg/mL)	63.8% LOQ = 49.6 pg/mL	Dufour et al. (2017)
Belgium 2015–2018	**2,4,6-TBP** $n=160$ adults (17–74 years old)	Mean: 74.6 pg/mL Median (range): 53.3 (< LOQ–1276.6) pg/mL	56.3% LOQ = 49.6 pg/mL	Dufour et al. (2020)[a]

Abbreviations: LB, lower bound; LOD, limit of detection; LOQ, limit of quantification; ND, not detected; NR, not reported; UB, upper bound.

[a]There is some overlap between some of the participants in Dufour et al. (2017) and the controls population in Dufour et al. (2020) (P Dufour, 2024, personal communication).

Data on several of the brominated phenols considered in this Opinion have been reported in human milk, serum, placenta, urine and hair samples from non-European countries. These are captured in Appendix C (Table C.1) and also include the brominated phenol level data reported in the three publications on the available epidemiological studies (Eguchi et al., 2015; Leonetti, Butt, Hoffman, Hammel, et al., 2016; Miranda et al., 2015) (see Section 3.1.3). Regarding human milk, in Japan, the mean level of **2,4,6-TBP** in samples collected in the years 2005–2006 was 1.17 ng/g lipid (Fujii, Nishimura, et al., 2014), while it was 0.82 ng/g lipid in samples collected in the years 2008–2010 (Fujii et al., 2018). A mean value of 0.58 ng/g lipid was reported in the USA for samples collected in 2019 (Schreder et al., 2023). In serum, mean levels of **2,4,6-TBP** in Japan were reported to be 40.2 pg/g ww for samples collected in 2006 (Fujii, Nishimura, et al., 2014), while it was 350 pg/g ww in samples collected in 2010 (Fujii, Harada, et al., 2014). In China, mean levels in serum were 146 ng/g lipid (Lin et al., 2023), and in India, they were 360 pg/g ww (Eguchi et al., 2012). In Vietnam, total brominated phenol concentrations measured in 2010–2011 were significantly higher at an occupational exposure setting (e-waste recycling site) than in donors from reference sites (mean, 310 vs. 220 pg/g ww) and congener profiles for brominated phenols were dominated by **2,4,6-TBP** (mean, SD, pg/g ww; 220, 80, reference site; 270, 230, e-waste recycling site). 2,3,4,6-TetraBP, 2,4,5-TBP,

2,3,5,6-TetraBP and PBP were more frequently present at the e-waste recycling site (4.5%, 2.8%, 2.3% and 2.2%, respectively), than in participants from the control site and the total levels of non-**2,4,6-TBP** in donors from the e-waste recycling site were significantly higher than at the reference site (median: 36 vs. 0.27 pg/g ww) (Eguchi et al., 2015). In adipose tissue, Gao et al. (2015) reported a mean value of 5.05 ng/g lipid, while in placental tissue, levels of around 15 ng/g lipid were reported (Leonetti, Butt, Hoffman, Hammel, et al., 2016; Leonetti, Butt, Hoffman, Miranda, et al., 2016). Levels of brominated phenols in urine have been reported in several studies in China, with mean values of **2,4,6-TBP** ranging from 1.69 to 2.35 µg/g creatinine (Feng et al., 2016; Lin et al., 2023).

3.1.1.4 | *Toxicokinetic modelling*

No data were identified.

3.1.1.5 | *Transfer from feed to food of animal origin*

No data were identified.

3.1.2 | Toxicity in experimental animals

3.1.2.1 | *Acute toxicity studies*

The previous Opinion (EFSA CONTAM Panel, 2012a) reported **2,4-DBP** and **2,4,6-TBP** to be of low toxicity, both with LD50 values in excess of 1000 mg/kg body weight (bw). No data were available for the other brominated phenols that are the subject of this update.

Since then, Shi et al. (2013) reported an oral LD50 of **4-BP** in mice of 2410 mg/kg bw. On day 7, there was no change in relative liver weight in mice exposed by gavage to a single dose of 0, 100, 500, 2000 and 5000 mg **4-BP**/kg bw. There was a slight significant increase in relative kidney weight at 5000 mg/kg bw 7 days after the dosing.

No data on **2,6-DBP**, **TBBPS** or **TBBPS-BME** have been identified.

3.1.2.2 | *Repeated dose toxicity studies*

In the previous Opinion (EFSA CONTAM Panel, 2012a), it was concluded that the main targets in the limited available repeated dose toxicity studies on **2,4,6-TBP** in rats were liver and kidney.

In a 28-day gavage study in Wistar rats, the NOAEL for systemic toxicity was 150 mg **2,4,6-TBP**/kg bw per day and a LOAEL of 1000 mg **2,4,6-TBP**/kg bw per day (as cited by ECHA, 2012 in EFSA CONTAM Panel, 2012a).

The critical study in the previous Opinion was a repeated-dose toxicity study (Tanaka et al., 1999, which was reported by WHO, 2005), with a NOAEL of 100 mg **2,4,6-TBP**/kg bw per day for both sexes (see Section 1.3.5). Since then, more detailed information from this study have been identified in the US-EPA (2009) evaluation of **2,4,6-TBP** to support the current evaluation. In this study, Sprague–Dawley rats were exposed by gavage to 0 (vehicle: corn oil), 100, 300 or 1000 mg **2,4,6-TBP**/kg bw per day. The dosing period for males was 48 days starting from 14 days before mating, and that for females was 41–45 days starting from 14 days before mating to day 3 of lactation. For females unsuccessfully mated, the dosing period was 48 days. Body weight was statistically significantly decreased (about 10% compared to controls) in the high-dose males and females (about 6% relative to controls). Food consumption was reduced in high-dose animals during the first week of exposure. There were statistically significant, dose-related increases in serum creatinine in males at 300 (22%) and 1000 mg/kg bw per day (74%), and a statistically significant increase in serum protein, albumin and alkaline phosphatase (ALP) activity in males at 1000 mg/kg bw per day. At this dose, there was also an increase (not statistically significant) in blood urea nitrogen (BUN). No biochemical examinations were performed in females. At the highest dose, increased absolute and relative liver weights and increased relative kidney weights were observed in both sexes and a significant decrease in absolute thymus weight was noted in males. Also at the highest dose but in males only, increased number of animals with hepatocyte hypertrophy was observed, as well as kidney papillary necrosis, dilatation of tubules, lymphocyte infiltration, basophilic tubular epithelium and hyaline casts in kidney. Slight atrophy of the thymus was seen in 3/12 high-dose males. No histopathological studies were performed on females exposed to 100 and 300 mg/kg bw per day and no effects were observed at 1000 mg/kg bw per day.

No data were available on the toxicity of the remaining brominated phenols considered in the current opinion.

Studies published since the previous EFSA assessment

The details of the new studies published since the previous opinion are provided in Table 4.

2,4,6-TBP

Male C57BL/6J mice were exposed through drinking water (Ultrapure Water for in vivo studies) to 0, 0.5, 10 or 200 µg **2,4,6-TBP**/L (equivalent to 0, 0.075, 1.5 or 30 µg/kg bw per day applying the default conversion factor of 0.15 according

to EFSA Scientific Committee, 2012) for 12 weeks (Miao et al., 2022). Only final water consumption estimates according to the author's laboratory records were reported (approximately 0.36 L per 12 weeks per mouse). Slight renal congestion was observed. In the kidney, the authors reported an increase in the cumulative diameter of congested vessels per field (from 0.5 µg/L), the number of glomerular cells per mm^2 (at 10 and 200 µg/L), the glomerular cross-section area (at 10 and 200 µg/L) and the number of glomeruli per field (at 200 µg/L). The urine protein content (detected by urine test strips and semi-quantitatively analysed) increased slightly when exposed to 0.5 µg/L and increased significantly in the 10 and 200 µg/L exposure groups. The CONTAM Panel considered that due to the limitations of the method used for detecting urine protein content and the absence of clear renal lesions, the results of this study are not convincing.

A similar experimental study design was reported in another publication by the same research group, focusing on the evaluation of liver toxicity (Jiang et al., 2022). Water consumption was reported per cage and per week. The authors reported a statistically significant decrease in body weight gain (22% and 50%) at 0.5 µg/L on week 4 and 8, and a non-dose-related increase at all doses at week 12. The CONTAM Panel noted this might be a consequence of unexpected lack of growth of the control group at week 12. Statistically significant increases in serum levels of ALP (c. 50% at all doses) and albumin (c. 25% at all doses) were reported, however, without a dose–response relationship. Slight liver inflammation was reported at 10 and 200 µg/L. The CONTAM Panel noted the absence of clear liver damage.

The CONTAM Panel noted that, in these two studies, the concentrations in the drinking water were not confirmed by analysis of **2,4,6-TBP**.

Effects on thyroid hormones and on morphology of the thyroid gland were investigated in female ICR mice after sc injection of 0, 40 or 250 mg **2,4,6-TBP**/kg bw for 20 days from PND21 (Lee et al., 2016). On PND42, there were dose-related decreases in serum FT3 levels and non-dose-related decreases in serum FT4 levels at both doses. No morphological changes were observed in the follicle shape, follicular epithelium, mesenchyme and adjunct blood vessels of the thyroid gland. However, partially large follicles and reduced epithelia were seen at both doses. The overall thyroid activation index (which represents the ratio of the volume density of follicular epithelium to the volume density of colloid, Kalisnik, 1972) reflecting changes in thyroid function caused by alterations in TSH level, was reduced in the **2,4,6-TBP** groups (0.62-fold and 0.78-fold, respectively) (Lee et al., 2016).

TBBPS

Male C57BL/6 mice were exposed for 5 weeks by gavage to 0, 0.002, 0.02, 2 and 20 mg **TBBPS**/kg bw per day. In addition, females were exposed to 0, 0.002 and 0.02 mg/kg bw per day (Hu et al., 2023). A statistically significant increase in serum TSH level was observed in males at 2 mg/kg bw per day only. Increases in TSH levels were also seen in female mice at the two lowest doses, but not significantly. There was no significant effect on the serum TT3 and TT4 levels in either male or female mice. An increased height of thyroid follicular epithelial cells was observed in male mice after exposure to 20 mg/kg bw per day indicating impairment of the thyroid gland structure. This effect was not investigated at 2 mg/kg bw per day. No significant increase was observed in male or female mice at the two lowest doses. The CONTAM Panel noted limitations and contradictions in the reporting of the study, and therefore, the study was not considered adequate for an identification of a NOAEL/LOAEL.

In summary, the main targets in repeated-dose subacute toxicity studies in rats exposed by gavage to **2,4,6-TBP** are the liver and kidney. There were increases in organ weights and also histopathological changes at 1000 mg/kg bw per day. There were also statistically significant, dose-related increases in serum creatinine in males at 300 and 1000 mg/kg bw per day. The studies identified since the publication of the previous Opinion does not provide an adequate basis for identification of NOAELs/LOAELs.

In the study with **TBBPS** effects in the thyroid were observed, but the study was not considered adequate for an identification of a NOAEL/LOAEL.

No data on **4-BP**, **2,4-DBP**, **2,6-DBP** or **TBBPS-BME** were identified.

3.1.2.3 | *Developmental and reproductive toxicity studies*

In the previous Opinion, it was noted that reduced neonatal viability and lower neonatal body weights were observed at 1000 mg **2,4,6-TBP**/kg bw per day in the combined repeated-dose toxicity study in rats with a reproduction/developmental toxicity screening test (Tanaka et al., 1999, as cited in WHO, 2005) (EFSA CONTAM Panel, 2012a). No reproductive or developmental effects were observed at 300 mg/kg bw per day.

In a developmental toxicity study in pregnant Charles River CD rats exposed by gavage from GD6–15, an increase in post-implantation loss and a slight decrease in the number of viable fetuses (no further details available) were observed at 1000 mg **2,4,6-TBP**/kg bw per day (IRDC, 1978 as cited in EFSA CONTAM Panel, 2012a). The NOAELs for maternal and developmental toxicity were considered to be 1000 and 300 mg/kg bw per day, respectively (IRDC, 1978, as cited in EFSA CONTAM Panel, 2012a).

Since the previous Opinion, no further data have been identified on **2,4,6-TBP** or the other brominated phenols considered in this Opinion.

3.1.2.4 | *Genotoxicity studies*

In the previous Opinion, it was reported that **2,4,6-TBP** did not induce gene mutations in Salmonella Typhimurium but induced chromosomal aberrations in three studies in mammalian cells in vitro, with and without metabolic activation (EFSA CONTAM Panel, 2012a) (see Table 5).

In vivo in mice after ip administration of 75, 150 and 300 mg **2,4,6-TBP**/kg bw, no increase in micronuclei formation in bone marrow was observed (DSBG/BCL, 2002, as cited in WHO, 2005; EFSA CONTAM Panel, 2012a and ECHA website[11]). The CONTAM Panel considered that the lack of access to the primary information is a limitation.

Studies published since the previous EFSA assessment

2,4,6-TBP

2,4,6-TBP was tested in an alkaline Comet assay in human peripheral blood mononuclear cells (PBMCs) exposed for 24 h to concentrations of 0, 0.01, 0.1, 1 or 10 µg/mL. Concentration-related increases in DNA strand breaks (as measured by the % DNA in the Comet tail) were observed at 1 and 10 µg/mL. Small but significant increases ($p < 0.05$) in double strand breaks (DSB) were also observed only at 10 µg/mL in the neutral version of the Comet assay. **2,4,6-TBP** induced oxidative damage to DNA pyrimidines (at 1 µg/mL, $p < 0.05$) or purines (at 0.1 and 1 µg/mL, $p < 0.05$) as detected by a modified comet assay using the enzymes endo III or hOGG1, respectively, in the alkaline Comet assay (Barańska, Woźniak, et al., 2022).

TBBPS

TBBPS was tested in an alkaline Comet assay in human peripheral blood mononuclear cells (PBMCs) exposed for 24 h to concentrations of 0, 0.01, 0.1, 1 or 10 µg/mL. Increases in DNA strand breaks (as measured by the % DNA in the Comet tail) were observed at 10 µg/mL. Small but significant increases ($p < 0.05$) in DSB were also observed at 10 µg/mL in the neutral version of the Comet assay. **TBBPS** induced oxidative damage to DNA pyrimidines or purines (at 1 µg/mL, $p < 0.05$) as detected by a modified comet assay using the enzymes endo III or hOGG1, respectively, in the alkaline Comet assay (Barańska, Woźniak, et al., 2022).

In summary, **2,4,6-TBP** did not induce mutations in bacteria but induced chromosomal aberrations in mammalian cells in vitro. In in vitro Comet assays, **2,4,6-TBP** induced SSB and DSB as well as oxidised DNA bases in human peripheral blood mononuclear cells. These changes may be indicative for ROS involvement in vitro as shown in Section 3.1.4.4. It did not induce micronuclei in bone marrow of mice in vivo after ip injection up to the maximum tolerated dose of 300 mg/kg bw per day. Although no toxicity in the bone marrow was demonstrated, systemic exposure is generally expected after ip injection and clinical signs of toxicity were reported (e.g. lethargy, ataxia and tremors, see Table 5). Based on the overall evidence, the CONTAM Panel considered in vivo genotoxicity of **2,4,6-TBP** to be unlikely.

In in vitro Comet assays, **TBBPS** induced SSB and DSB as well as oxidised DNA bases in human peripheral blood mononuclear cells. Due to the limited data available, the CONTAM Panel could not conclude on the genotoxicity of **TBBPS**.

No data on **4-BP**, **2,4-DBP**, **2,6-DBP** or **TBBPS-BME** were identified.

3.1.2.5 | *Carcinogenicity*

No long-term toxicity or carcinogenicity studies on brominated phenols and their derivatives have been identified.

[11] https://echa.europa.eu/registration-dossier/-/registered-dossier/5191/7/7/2.

TABLE 4 Summary of the outcomes of toxicological studies on brominated phenols and their derivatives (**2,4,6-TBP** and **TBBPS**) in experimental animals.

Test compound Purity Supplier (lot number)	Species tested (strain) Number of animals per dose group Age Gender	Route of administration Exposure doses Vehicle Study duration	Parameter(s) studied and effects reported	NO(A)EL or LO(A)EL	Reference
2,4,6-TBP Purity: NR	Rat (Sprague Dawley) Number: 12 M and 12 F/dose Age: NR M, F	Oral (gavage) 0, 30, 100, 300, 1000 mg/kg bw per day Vehicle: corn oil Duration: M: 48 days, F: 41–45 days Dosing period for M was 48 days starting from 14 days before mating, and that for F was 41–45 days starting from 14 days before mating to day 3 of lactation. For F unsuccessfully mated, the dosing period was 48 days No biochemical examinations were performed in F and no urinalysis has been performed No histopathological studies were performed on F exposed to 100 and 300 mg/kg bw per day	– Statistically significant decrease in body weight in the high-dose M (about 10% compared to controls) and F (about 6% relative to controls) – Reduction of food consumption in high-dose animals during the first week of exposure – Statistically significant, dose-related increases in serum creatinine in M at 300 mg/kg bw per day (22%) and 1000 mg/kg bw per day (74%) – Statistically significant increase in serum protein, albumin and in alkaline phosphatase (ALP) activity in M at 1000 mg/kg bw per day. At this dose, there was also an increase (not statistically significant) in blood urea nitrogen (BUN) – At the highest dose, increased absolute (16% in M and 15% in F) and relative liver weights (35% in M and 24% in F) and increased relative kidney weights (22% in M and 14% in F) in both sexes and significant decrease in absolute thymus weight in M – In high-dose M, enlargement of liver, increase in the number of animals with hepatocyte hypertrophy and decreased fat storage in the liver, as well as kidney papillary necrosis, dilatation of tubules, lymphocyte infiltration, basophilic tubular epithelium and hyaline casts in kidney. Slight atrophy of the thymus in 3/12 high-dose M. No histopathological effects were observed in F at 1000 mg/kg bw per day – Reduced neonatal viability on day 4 of lactation (~50%) and lower neonatal body weights on days 0 and 4 of lactation (17–19% in M and 19%–25% in F) at 1000 mg/kg bw per day	NOAEL = 300 mg/kg bw per day	Tanaka et al. (1999, as cited by WHO, 2005; US-EPA, 2009)[a]
2,4,6-TBP Purity: NR Sigma-Aldrich	Mouse (ICR) Number: 5/group Age: PND21 F	sc 0, 40, 250 mg/kg bw per day Vehicle: corn oil Duration: 20 days	– Dose-related decreased FT3 at both doses – Non-dose-related decrease FT4 levels at both doses – Morphological changes of thyroid (partially large follicles and reduced epithelia) at both doses but not dose-related	Not applicable due to sc route of administration	Lee et al. (2016)

(Continues)

TABLE 4 (Continued)

Test compound Purity Supplier (lot number)	Species tested (strain) Number of animals per dose group Age Gender	Route of administration Exposure doses Vehicle Study duration	Parameter(s) studied and effects reported	NO(A)EL or LO(A)EL	Reference
2,4,6-TBP Purity: > 99% Sigma-Aldrich (catalogue number T0349)	Mice (C57BL/6) 8 mice/group Age: 4 weeks at the start of dosing M	Drinking water (Ultrapure water for in vivo studies) 0, 0.5, 10, 200 μg/L (equivalent to 0, 0.075, 1.5, 30 μg/kg bw per day) (equivalent dose applying default value for conversion 0.15) Duration: 12 weeks	No **2,4,6-TBP**-related deaths Statistically significant decrease in body weight gain at 0.5 μg/L on week 4 and 8 and a non-dose-related increase at all doses at week 12 Slight liver inflammation at 10 and 200 μg/L (no quantitative data reported). No changes in ALT and AST levels Statistically significant increases in serum levels of ALP (c. 50% at all doses) and albumin (c. 25% at all doses), which are not clearly adverse, in view of the lack of dose–response	No NOAEL/LOAEL was identified	Jiang et al. (2022)
2,4,6-TBP Purity: ≥ 99% Sigma-Aldrich (Catalogue number 137715)	Mice (C57BL/6) 6 mice/group Age: 4 weeks at the start of dosing M	Drinking water (Ultrapure water for in vivo studies) 0, 0.5, 10, 200 μg/L (equivalent to 0, 0.075, 1.5, 30 μg/kg bw per day, equivalent dose applying default value for conversion of 0.15, EFSA Scientific Committee, 2012) Duration: 12 weeks	No **2,4,6-TBP**-related deaths Kidney: slight renal congestion at all doses. Increase in the cumulative diameter of congested vessels per field (from 0.5 μg/L), the number of glomerular cells per mm^2 (at 10 and 200 μg/L), the glomerular cross-section area (at 10 and 200 μg/L) and the number of glomeruli per field (at 200 μg/L). The urine protein content increased slightly when exposed to 0.5 μg/L and increased significantly in the 10 and 200 μg/L exposure groups	No NOAEL/LOAEL was identified	Miao et al. (2022)
TBBPS Purity: NR Pansine Chemical Company (NR)	Mice (C57BL/6) 10 mice/group Age: 6–8 week-old M, F	Gavage M: 0, 0.002, 0.02, 2, 20 mg/kg bw per day F: 0, 0.002, 0.02 mg/kg bw per day Vehicle: corn oil Study duration: 5 weeks	No significant changes in serum T3 and T4 levels in both M and F mice Increase in TSH levels at 2 mg/kg bw per day but not at other doses in M (1.20-fold). Increases in TSH levels were also seen in female mice at the two lowest doses, but not statistically significant Thyroid follicle histopathological changes in M mice only at 20 mg/kg bw per day (increase of the height of thyroid follicular epithelial cells from 3.46 μm to 4.71 μm)	No NOAEL/LOAEL was identified	Hu et al. (2023)

Abbreviations: 2,4,6-TBP, 2,4,6-tribromophenol; ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate aminotransferase; bw, body weight; CAT, catalase; F, female; LOAEL, Lowest-observed-adverse-effect level; M, male; MDA, malondialdehyde; NOAEL, no-observed-adverse-effect level; NR, not reported; sc, subcutaneous administration; T3, Triiodothyronine; T4, Thyroxine; TBBPS, tetrabrominated bisphenol S; TSH, Thyroid-stimulating hormone.

[a]This study was cited in the previous Opinion, but due to the limited number of studies and for completeness, it is also included in this table.

TABLE 5 In vitro and in vivo genotoxicity studies on the brominated phenols and their derivatives considered in the current assessment.

Type of test experimental test system	Test substance	Exposure conditions	Result	Reference
Reverse mutation assay in *S.* Typhimurium TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvr*A	**2,4,6-TBP**	Preincubation test With and without S9 mix (rat) Up to 500 µg/plate in TA98, TA100, TA1535 Up to 1000 µg/plate in TA1537 Up to 5000 µg/plate in *E. coli* WP2 *uvr*A Solvent: DMSO Positive and negative controls responded appropriately	**Negative**	Tanaka et al. (1999, as cited by US-EPA, 2009)
Reverse mutation assay in *S.* Typhimurium TA98, TA100, TA1535, TA1537 TA1538	**2,4,6-TBP**	With and without S9 mix (rat) Up to 1500 µg/plate Concurrent solvent and positive controls	**Negative**	DSBG/BCL (2002, as cited by WHO, 2005; EFSA CONTAM Panel, 2012a)
Reverse mutation assay in S. Typhimurium TA98, TA100, TA1535 and TA1537 and *E. coli* WP2 *uvr*A	**2,4,6-TBP**	With and without S9 mix (rat) Up to 1000 µg/plate in S. Typhimurium Up to 5000 µg/plate in *E. coli* concurrent solvent and positive controls	**Negative**	Shibuya et al. (1999, as cited by WHO, 2005; EFSA CONTAM Panel, 2012a)
Reverse mutation assay in S. Typhimurium TA98, TA100, TA1535, TA1537, TA1538	**2,4,6-TBP**	Plate incorporation assay With and without S9 mix (rat) Up to 1000 µg/plate Concurrent solvent and positive controls	**Negative**	Litton Bioetics (1978, as cited by WHO, 2005; EFSA CONTAM Panel, 2012a; US-EPA, 2009)
Reverse mutation assay in S. Typhimurium TA98, TA100, TA1535, TA1537	**2,4,6-TBP**	Preincubation test With and without S9 mix (rat and hamster)	**Negative**	Zeiger et al. (1987, as cited in US-EPA, 2009)
Chromosomal aberration Chinese hamster lung cells According to TG473	**2,4,6-TBP**	Up to 1.6 mg/mL with and without S9 mix	**Positive**	Sasaki et al. (1999, as cited in WHO, 2005, EFSA CONTAM Panel, 2012a)
Chromosomal aberration Chinese hamster lung cells (CHL/IU)	**2,4,6-TBP**	With and without S9 mix Solvent: DMSO S9: phenobarbital and 5,6-benzoflavone induced rat liver	**Positive** Lowest effective concentrations: w/o S9: 0.050 µg/mL w S9: 0.10 µg/mL	Tanaka et al. (1999, as cited by US-EPA, 2009)
Chromosomal aberration Human lymphocytes	**2,4,6-TBP**	Up to 500 µg/mL in the absence of S9-mix Up to 450 µg/mL in the presence of S9-mix	**Positive** -S9: statistically significant, dose dependent increase in the number of cells with chromosome aberrations at all concentrations tested +S9: significant, in the number of cells with chromosome aberrations at 400 and 450 µg/mL Cytotoxicity: dose dependent reduction of the mitotic index -S9: reduced to 38% of the control +S9: reduced to 48% of the control	As cited in EFSA CONTAM Panel (2012a)

(Continues)

TABLE 5 (Continued)

Type of test experimental test system	Test substance	Exposure conditions	Result	Reference
Comet assay (alkaline) Human peripheral blood mononuclear cells	**2,4,6-TBP** Purity: ≤ 100%	-S9 mix 0, 0.01, 0.1, 1, 10 μg/mL Exposure: 24 h Positive control: H_2O_2 Vehicle: DMSO	**Positive** Concentration-related increases in SSB or DSB (as measured by the % DNA in the Comet tail) at 1 and 10 μg/mL Oxidative damage to DNA pyrimidines (at 1 μg/mL) or purines (0.1 and 1 μg/mL) using the enzymes endo III or hOGG1, respectively	Barańska, Woźniak, et al. (2022)
Comet assay (neutral) Human peripheral blood mononuclear cells	**2,4,6-TBP** Purity: ≤ 100%	-S9 mix 0, 0.01, 0.1, 1, 10 μg/mL Exposure: 24 h Vehicle: DMSO	**Positive** Increases in DSB at 10 μg/mL Information on cytotoxicity was reported in a previous paper (Włuka et al., 2020) Cell viability after treatment at 10 μg/mL was 83.4% ± 2.47	Barańska, Woźniak, et al. (2022)
Micronucleus test NMRI Mice (5M + 5F/dose) Bone marrow According to TG474 GLP	**2,4,6-TBP** Purity: 99.79%	Single ip dose 0, 75, 150, 300 mg/kg bw Sampling time: 24 h and 48 h for 300 mg/kg bw, 24 h for 75 and 150 mg/kg bw and 48 h for CP Negative control: corn oil Posiive control: cyclophosphamide 2000 PCE analysed/dose	**Negative** The MTD (maximum tolerance dose) was 300 mg/kg After dosing, all animals at 300 mg/kg bw were lethargic, showed ataxia and tremors. Within 17 h, all animals had recovered from the treatment No decrease in the ratio of polychromatic to normochromatic erythrocytes compared to the vehicle controls, which reflects a lack of toxic effects of this compound on the erythropoiesis	DSBG/BCL (2002, as cited in WHO, 2005; EFSA CONTAM Panel, 2012a, ECHA[a])
Comet assay (alkaline) Human peripheral blood mononuclear cells	**TBBPS** Purity: 98.8%	-S9 mix 0, 0.01, 0.1, 1, 10 μg/mL Exposure: 24 h Positive control: H_2O_2 Vehicle: DMSO	**Positive** Concentration-related increases in SSB or DSB (as measured by the % DNA in the Comet tail) at 10 μg/mL Oxidative damage to DNA pyrimidines (at 1 μg/mL) or purines (0.1 and 1 μg/mL) using the enzymes endo III or hOGG1, respectively	Barańska, Woźniak, et al. (2022)
Comet assay (neutral) Human peripheral blood mononuclear cells	**TBBPS** Purity: 98.8%	-S9 mix 0, 0.01, 0.1, 1, 10 μg/mL Exposure: 24 h Vehicle: DMSO	**Positive** Increases in DSB at 10 μg/mL Information on cytotoxicity was reported in a previous paper (Włuka et al., 2020) Cell viability after treatment at 10 μg/mL was 85.4% ± 1.98	Barańska, Woźniak, et al. (2022)

Abbreviations: bw, body weight; DSBG/BCL, Dead Sea Bromine Group/Bromine Compounds Ltd.; F, female; GLP, good laboratory practice; M, male; MTD, maximum tolerance dose.

[a]https://echa.europa.eu/registration-dossier/-/registered-dossier/5191/7/7/2.

3.1.3 | Observations in humans

In the previous EFSA Opinion on brominated phenols and their derivatives, no epidemiological studies were identified (EFSA CONTAM Panel, 2012a).

Since then, four publications on three studies have been identified on the association between thyroid function and disease and birth outcomes (Dufour et al., 2020; Eguchi et al., 2015; Leonetti, Butt, Hoffman, Hammel, et al., 2016; Miranda et al., 2015).

3.1.3.1 | *Thyroid function and disease*

Leonetti, Butt, Hoffman, Hammel, et al. (2016) using the Healthy Pregnancy, Healthy Baby birth cohort study setting in the USA assessed the cross-sectional correlation between levels of PBDEs and **2,4,6-TBP** in placental tissue and placental thyroid hormone profile (T4, T3, rT3, deiodinase (DIO3) activity, TH sulfotransferase (SULT); $n = 95$; 68% non-Hispanic black) in a cross-sectional fashion. Detection frequencies for **2,4,6-TBP** were > 50% and the geometric mean concentration of **2,4,6-TBP** was 15.4 ng/g lipid (range: 1.31–316 ng/g lipid). Overall, no statistically significant associations were observed either in the correlation or the adjusted regression analyses. Multiple other analyses were performed; in female offspring ($n = 46$), a statistically significantly positive correlation was observed between placental T3 levels and placental **2,4,6-TBP** concentrations, and increased **2,4,6-TBP** levels (1st vs. 3rd tertile comparison) were associated with increased T3 in the adjusted regression analysis.

Dufour et al. (2020) in a small hypothesis-generating case–control study in Belgium with a cross-sectional exposure assessment evaluated the association between serum levels of **2,4,6-TBP**, 2,3,6-TBP, 2,4,5-TBP and 2,3,4,6-TeBP (among 50 other persistent organic pollutants) and hypothyroidism ($n = 35$) and hyperthyroidism ($n = 44$) using a control sample of 160 volunteers from the general population. Overall, **2,4,6-TBP** was detected in 56%, 2,3,6-TBP was detected in 2% and 2,3,4,6-TeBP was detected in 16% of the evaluated samples. Only chemicals with detection frequencies > 40% were further evaluated and, for pollutants detected in frequencies between 40% and 70%, the contamination status (detected vs. non-detected) was used in the analyses. For the 19 pollutants that were detected in more than 40% of the individuals, weighted quantile sum (WQS) regressions were performed and the WQS index was statistically significantly associated with an increased odds of hypothyroidism with the highest weights attributed to PCB 138, 3-OH-CB 180, 4-OH-CB 146 and 4′,4-DDE while there were no evidence of an association with increased odds of hyperthyroidism. In the monopollutant models adjusted for age, sex, smoking status, body mass index and delay between sampling and start of the recruitment, 23 associations gave a statistically significant signal with ORs ranging from 0.10 to 13.7. **2,4,6-TBP** was inversely statistically significantly associated with hyperthyroidism (OR, 95% CI; 0.20, 0.04–0.91), while the associations between **2,4,6-TBP** and hypothyroidism (OR, 95% CI; 0.65, 0.16–2.72) and any thyroid disease (OR, 95% CI; 0.43, 0.16–1.18) were also inverse but did not reach statistical significance. Overall, the signals detected in this small exploratory study with a cross-sectional exposure assessment, are hindered by the multiple comparisons performed and by the within-study inconsistency in results considering that increased **2,4,6-TBP** levels were associated with reduced odds of both hyper- and hypothyroidism.

Eguchi et al. (2015) in a small cross-sectional study in Vietnam involved workers at an e-waste recycling site ($n = 77$) and donors who were residents from a rural area ($n = 34$). They assessed the association between the serum levels of **2,4,6-TBP**, other brominated phenols (2,3,4,6-tetraBP and PBP), along with other compounds (PCBs, OH-PCBs, PBDEs, MeO-PBDEs and OH-PBDEs) and thyroid hormone profile, i.e. TSH, TT3, TT4, FT3 and FT4. Across the whole study population, the sum of 2,4,5-TBP, 2,3,4,6-tetraBP, 2,3,5,6-tetraBP and PBP was statistically significantly associated with a lower TSH. In females, the sum of 2,4,5-TBP, 2,3,4,6-tetraBP, 2,3,5,6-tetraBP and PBP was statistically significantly associated with a lower TSH, and **2,4,6-TBP** as well as the sum of all assessed brominated phenols were both statistically significantly associated with an increase in FT4.

3.1.3.2 | *Birth outcomes*

In the study by Miranda et al. (2015), using the Healthy Pregnancy, Healthy Baby birth cohort study setting in the USA, **2,4,6-TBP** was measured in serum from a subsample of 55 pregnant women in the third trimester of pregnancy (out of full study sample of 137). **2,4,6-TBP** was detected in 38% of the samples. No further analyses were done by the authors in relation to health outcomes (e.g. birth outcomes) since only compounds with over 50% detection frequency were included in the statistical analyses.

In summary, in the available limited body of epidemiological evidence, a few statistically significant associations between increased **2,4,6-TBP** levels and altered thyroid hormones are reported. However, among other limitations, the lack of prospective epidemiological evidence, the small number of studies, the small study sample sizes, the heterogeneity in study settings and in the exposure assessment matrices, the use of multiple comparisons, the assessment of multiple contaminants frequently without appropriate adjustments and the lack of within-study consistency of the associations under study render this body of evidence insufficient for further hazard identification and risk characterisation.

3.1.4 | Mode of action

The 2012 Opinion concluded from the studies in experimental animals that the critical effects for **2,4,6-TBP** were in the liver and kidney and that disruption of thyroid hormone signalling was the most sensitive in vitro effect of **2,4-DBP** and **2,4,6-TBP**. Possible oestrogenic effects were suggested by studies reporting induction of aromatase activity by **2,4-DBP** and **2,4,6-TBP**, and inhibition of oestradiol sulfotransferase by **2,4,6-TBP**. A possible developmental effect of **2,4,6-TBP** was indicated by increased differentiation of neuroblastoma cells in vitro. One in vitro study found no effect of **TBBPS** on thyroid hormone receptor-mediated gene expression.

Since then, more mode of action studies have been published, but the in vivo toxicology of brominated phenols is still not well characterised. Therefore, the CONTAM Panel also evaluated the in vitro studies as possible indicators of other hazards.

The vast majority of studies were for **2,4,6-TBP** and **TBBPS** and these studies are summarised below with details reported in Appendix D (Tables D.1–D.3). Few studies have been identified on **4-BP**, **2,4-DBP** and **2,6-DBP** for which no toxicity studies in rodents have been identified, and these are summarised in Appendix D (Table6 D.3).

3.1.4.1 | *Liver*

2,4,6-TBP

No studies of direct relevance to liver toxicity were identified, except those reporting oxidative stress (see below).

TBBPS

Human embryonic stem cells were exposed to 10 nM **TBBPS** as they differentiated for 12 days into liver cells (Yang et al., 2021). Transcriptomics analysis indicated that **TBBPS** promoted the expression of neural-related genes at day 4, possibly via inhibiting Apelin signalling, and genes involved in proliferation at day 12 possibly by upregulating the FGF10 pathway.

Exposure to **TBBPS** attenuated proliferations of THLE-2 and AML12 cells, which are derived from liver of human and mouse, respectively (Yin et al., 2024). **TBBPS** increased expression of pro-inflammatory cytokines, such as TNFα, IL-1β and IL-6. **TBBPS** induced necroptosis through reactive oxygen species formation, and expression of RIP3 and pMLKL. It also suppressed mitochondrial autophagy mediated by the PINK1-PARKIN signalling pathway.

3.1.4.2 | *Kidney*

2,4,6-TBP

No studies of direct relevance to kidney toxicity were identified, except those reporting oxidative stress (see below).

TBBPS

No studies of direct relevance to kidney toxicity were identified.

3.1.4.3 | *Thyroid hormone signalling*

2,4,6-TBP

2,4,6-TBP inhibited the activity of thyroid hormone (TH) sulfotransferases (SULTs) in a choriocarcinoma placenta cell line (BeWo, Leonetti et al., 2018), and of deiodinase (DI) activity in human liver microsomes at μM concentrations (Butt et al., 2011). In juvenile mice dosed sc **2,4,6-TBP** treatment decreased deiodinase 1 (Dio1) and thyroid hormone receptor isoform 2 (Thrβ2) mRNA in the pituitary gland. In the liver, deiodinase 2 (Dio2) and growth hormone (Gh) mRNA levels were increased, with no effect on Dio1 and Thrβ1 expression (Lee et al., 2016). It has been found to bind to the human and zebrafish thyroid receptor β (TRβ) (Kollitz et al., 2018), and to downregulate transcription of corticotrophin-releasing hormone, TRH and TSH in zebrafish (Fu et al., 2020). Michałowicz et al. (2022) suggested that the effects of brominated phenols on thyroid are due to their structural similarity to thyroid hormones.

TBBPS

Downregulation of TSHR, NIS, TPO (protein abundance) at 0.02 and at 20 mg/kg bw per day in mouse was reported, and expression of TG was downregulated at 20 mg/kg bw per day in mouse (Hu et al., 2023). **TBBPS** showed dose-dependent binding to the ligand-binding domain of TRβ at **TBBPS** concentrations ranging from 1 to 20 μM (Lu et al., 2018). Computer simulations were successful in docking **TBBPS** to the ligand binding site of TRβ and the decomposition of binding free energy,

ΔG of −42.28 kcal/mol indicated stable binding (Lu et al., 2018). A two-hybrid yeast assay for TRβ showed that, under the experimental conditions, **TBBPS** has antagonistic activity towards TRβ, with an IC10 of 10.1 nM in the presence of a very high concentration of T3 (100 μM). The TRβ gene was upregulated in zebrafish larvae but not in a concentration-related manner (Lu et al., 2018).

3.1.4.4 | *Oxidative stress, apoptosis and mitochondrial dysfunction*

2,4,6-TBP

Two studies have reported that **2,4,6-TBP** induces ROS formation in CaCo2 and SH-SY5Y cells (Liu et al., 2022) and lipid peroxidation in human PBMCs (Włuka et al., 2020), but without indication of possible mechanisms leading to these effects. Li, Gao, et al. (2023) reported that **2,4,6-TBP** induced ROS in HepG2 cells associated with differential expression of genes involved in antioxidant, immune and endocrine associated systems. A weighted gene correlation network analysis (WGCNA) indicated that the MAPK signalling pathway, which can be activated by ROS, played a key role. A series of studies performed with human erythrocytes reported that **2,4,6-TBP** induced ROS and caspase-3 activation and decreased antioxidant enzymes (SOD, CAT and GSH-Px) and GSH. Haemolysis and methemoglobin formation were also demonstrated (Jarosiewicz et al., 2017; Jarosiewicz, Krokosz, et al., 2019; Jarosiewicz, Michałowicz, et al., 2019).

De Souza Salgado et al. (2018) found that low concentrations of **2,4,6-TBP** (0.06 and 6 μM) did not induce levels of ROS in murine melanoma B16F1 cells, but increased expression of genes related to membrane ABC transporters (ABCB5). **2,4,6-TBP** (25 and 50 μM) was found to induce apoptosis in human peripheral blood mononuclear cells. Elevation of the cytosolic calcium ion level, depleted the ΔΨm, activated caspase-8, -9 and -3 and PARP-1 cleavage, DNA fragmentation and chromatin condensation indicated that the mitochondrial (intrinsic) pathway was mainly involved (Barańska, Sicińska, et al., 2022).

TBBPS

Oxidative stress caused by **TBBPS** exposure was indicated in a study using human PBMCs (Włuka et al., 2020). PBMCs were exposed for 24 h to **TBBPS** (100 μg/mL), resulting in decreased ATP levels and cell viability. At lower concentrations, lipid peroxidation (0.1–20 μg/mL) and protein oxidation (0.01–20 μg/mL) were seen; however, the latter was not concentration related. **TBBPS** concentrations of 100 μM and higher stimulated formation of ROS in mouse embryonic stem cells (mESC; Yin et al., 2018). The exposure was at, or at least close, to cytotoxic concentrations as the 72-h IC50 of cell viability (formazan dye method) for **TBBPS** was 172 μM. Exposure of red blood cells to **TBBPS** resulted in increased abundance of thiol groups and an increase in lipid peroxidation along with a reduced level of ATP (Jarosiewicz et al., 2021).

TBBPS (0.01–50 mg/L) induced apoptosis in human PBMCs, with responses in a number of apoptosis markers, but primarily through the mitochondrial pathway (Barańska, Bukowska, et al., 2022). The most sensitive marker of apoptosis was cytosolic [Ca^{2+}] which was elevated at **TBBPS** concentrations of 0.1 mg/L and above.

Mode of action studies of **TBBPS** have addressed diverse effects of **TBBPS**, including effects on the cardiovascular system by acting on endothelial nitric oxide synthase (eNOS) (Hu et al., 2024) and stimulation of angiogenesis (Lu et al., 2023); changes in lipid and energy metabolism including stimulation of preadipocyte differentiation (Yu et al., 2022, 2024); and effects on membrane fluidity (Jarosiewicz et al., 2021).

Other brominated phenols

Similar to **2,4,6-TBP**, Li, Song, et al. (2023) reported that **2,6-BP** induced ROS in HepG2 cells associated with differential expression of genes involved in antioxidant, immune and endocrine-associated systems. A weighted gene correlation network analysis (WGCNA) indicated that the MAPK signalling pathway, which can be activated by ROS, played a key role. A series of studies performed with human erythrocytes reported that **2,4-DBP** induced ROS and apoptosis associated with caspase-3 activation and decreased antioxidant enzymes (SOD, CAT and GSH-Px) and GSH. Haemolysis and methemoglobin formation were also demonstrated (Jarosiewicz et al., 2017; Jarosiewicz, Krokosz, et al., 2019; Jarosiewicz, Michałowicz, et al., 2019).

3.1.4.5 | *Reproductive/developmental effects*

2,4,6-TBP

Two studies have reported possible developmental effects of **2,4,6-TBP** with observations of cytotoxicity and altered differentiation in human extended pluripotent stem (EPS) cells (Liu et al., 2021) and morphological changes and apoptosis in cultured mouse embryos (Zhao et al., 2022). 20 μM **2,4,6-TBP** altered the composition of protein components of exosomes in human placental explants, with proteomic analysis indicating inhibition of pathways associated with cell survival, tissue repair and proliferation, as well as activation of cell death pathways (Sheller-Miller et al., 2020).

Antioestrogenic and antiandrogenic activity of **2,4,6-TBP** was demonstrated using reporter gene assays, in which IC50 values of 14.1 and 9.2 μM were determined for decreased transcriptional activity of the human oestrogen receptor, and 3.9 μM for decreased transcriptional activity of the androgen receptor (Ezechiáš et al., 2012). Li, Song, et al. (2023) reported

that **2,4,6-TBP** exhibited oestrogenic and antiandrogenic activity in MDA-kb2 cells and an MCE-7-derived cell line (MVLN). In zebrafish, testosterone and oestradiol levels were increased in males and decreased in females by **2,4,6-TBP** exposure, leading to an increased male/female ratio in offspring.

TBBPS

TBBPS was found not to be oestrogenic in the E-screen assay or a reporter gene assay (Cao et al., 2017). It did also not inhibit CYP19A1 in rat placental microsomes at concentrations up to 100 μM (Zheng et al., 2024).

Other brominated phenols

Li, Song, et al. (2023) reported that **2,6-DBP** exhibited oestrogenic and antiandrogenic activity in MDA-kb2 cells and in MVLN.

3.1.4.6 | *Neurotoxicity*

2,4,6-TBP

One study investigated the inhibition by **2,4,6-TBP** of the blood–brain barrier transporters P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2) (Trexler et al., 2019). P-gp transport was decreased by low concentrations (pM–nM) of **2,4,6-TBP** in brain capillaries isolated from male and female rats and mice, with males of both species being more sensitive than females. Following in vivo dosing, decreased P-gp transport activity and expression were observed at 0.132 mg/kg bw, but not at 0.331 or 1.654 mg/kg bw. Further studies suggested that **2,4,6-TBP** did not directly interact with P-gp. **2,4,6-TBP** had no effect on MRP2 activity (Trexler et al., 2019).

One study reported an IC50 value for **2,4,6-TBP** in SH-SY5Y cells of 155 μM (Liu et al., 2020), but provided no information on possible mode of action.

TBBPS

The new studies identified to address mode of action of **TBBPS** effects on the nervous system have all utilised embryonic stem cells (ESC) differentiated into various systems representing the central nervous system.

Human ESC were induced to differentiate into neural ectoderm in the presence of 1 or 5 μM **TBBPS** and four other halogenated flame retardants (BDE-47, BDE-209, TBBPA and TCBPA), individually or in combination (Liang, Liang, Yin, et al., 2019). Transcriptome analysis (RNAseq with follow-up quantitative RT-PCR) was used to identify biological processes that were affected by these chemicals. The most significantly enriched gene ontology terms in the set of differentially regulated genes related to 'neural system development', 'neuron differentiation', 'neuron migration' Wnt signalling and positive regulation of transcripts from genes with 'RNA-polymerase II promoter'. Transcripts for transcription factors of importance for neural development, such as ZIC1, ZIC3, HES3, IGFBP3 and DLX5, were evaluated in follow-up experiments and found to be dysregulated by **TBBPS** with significance apparent at 10 nM. In addition, **TBBPS** might influence axon growth/guidance and neuron transmission-related processes, as evidenced by dysregulating genes for CNTN2, SLIT1, LRRC4C, RELN, CBLN1, CHRNB4 and GDF7.

TBBPS also decreased expression of mRNA for human neural stem cell (hNSC) identity markers SOX2, SOX3 and NES, at concentrations ranging from 1 to 100 nM, without effects on cell viability or proliferation (Liang, Liang, Zhou, et al., 2019). Further experiments indicated that the effects were mediated in part by modulating glycogen synthase kinase 3 beta (GSK3β) signalling and the NOTCH pathway. hNSC differentiation may also be mediated by altering triiodothyronine (T3) cellular signalling as indicated by concentration-dependent 10–100 nM **TBBPS** increase in *SOX3* expression in the presence of T3 at 3 nM. Expression of mRNA for SOX3 was significantly increased at 10 and 100 nM **TBBPS** but with no effect at 1 nM **TBBPS**.

A mouse embryonic stem cell (mESC) system was used as an in vitro model to evaluate developmental neurotoxicity of **TBBPS**, TBBPA and TCBPA (Yin et al., 2018). Influence of expression of genes of importance for neurodifferentiation (*Pax6*, *Sox1*, *Sox3*, *Map2* and *NeuroD*) was measured and these were upregulated by non-cytotoxic concentrations of **TBBPS** (1–100 nM), but the dose–response was unclear. **TBBPS** inhibited Wnt signalling which is a negative regulator of cell differentiation. Overall, the data suggest that, in the mESC system, **TBBPS** has the potential to stimulate neural differentiation, potentially by inhibition of the proliferative Wnt pathway.

A study in zebrafish indicated effects of **TBBPS** on circadian rhythms, which was associated with changes in expression of genes and proteins (Cry2 and Per3) involved in the circadian rhythm network (Ding et al., 2022). The effects were observed at internal concentrations of **TBBPS** of 2, 4.9 and 12.3 μg/g tissue.

In summary, **TBBPS** has the potential to alter differentiation of ESC into neural tissue at nanomolar concentrations. This involves changes in expression of numerous genes known to be involved in development of the central nervous system. A recurring finding is changes in the Wnt signalling pathway, which in general promotes stem cell proliferation and inhibits differentiation. There may also be a T3-dependent component to the effects.

3.1.4.7 | *Immunotoxicity*

2,4,6-TBP

Three studies have investigated possible immunotoxic effects of **2,4,6-TBP**. Differential expression of M1 and M2 markers of polarisation were reported in the mouse macrophage cell line RAW264.7, together with increased expression pro-inflammatory cytokines (Xie et al., 2019). Decreased expression of the pro-inflammatory marker Ly6C and resistance to bacterial infection in RAW264.7 were reported by Qin et al. (2023) with increased RNA N6-methyladenosine (m6A) methyltransferases and total RNA m6A levels, which are implicated in anti-infection immunity and were also increased in freshly isolated mouse peritoneal macrophages and human PBMCs (Qin et al., 2023). Changes in the hepatic transcriptome and serum metabolomic profiles in mice after exposure to **2,4,6-TBP** indicated disturbed immune responses. Gut microbiome changes were also reported (Jiang et al., 2022).

TBBPS

As described above, the transcriptome in ESC induced to form retinal tissue was statistically enriched (overrepresentation) in genes with Gene Ontology annotations relating to cytokine–cytokine receptor interaction, TNF signalling, IL-17 signalling (Li et al., 2022).

In summary, these studies do not provide evidence on the possible mode of action of **2,4,6-TBP** or **TBBPS** in relation to liver or kidney toxicity, with the exception of induction of oxidative stress and apoptosis, which could also be involved in other endpoints. In vitro studies support the plausibility of **2,4,6-TBP** and **TBBPS** having effects on thyroid hormone signalling, possibly mediated by inhibition of SULTs and deiodinase-2, and binding to TRβ. The available data suggest that **2,4,6-TBP** could have developmental and antiandrogenic effects, but are insufficient for **TBBPS**. Inhibition of expression, and of transport mediated by, P-gp by **2,4,6-TBP** in the central nervous system of rats has been reported. Studies with ESC suggest the potential of **TBBPS** to alter development of the CNS, mediated via changes in the Wnt signalling pathway, which in general promotes stem cell proliferation and inhibits differentiation. There may also be a T3-dependent component to the effects. **2,4,6-TBP** has also been found to cause changes in expression of pro-inflammatory cytokines implicated in disturbed immune responses.

While the available data indicate that **2,4,6-TBP** and **TBBPS** may have some common effects, the data are insufficient to conclude on relative potency. There were insufficient data on the mode of action of the other brominated phenols included in the TORs to allow a comparison with **2,4,6-TBP**.

3.1.5 | Considerations of critical effects and dose–response analysis

3.1.5.1 | *Consideration of critical effects*

In the previous Opinion (EFSA CONTAM Panel, 2012a), the CONTAM Panel concluded that the main targets of **2,4,6-TBP** were liver and kidneys. The critical study was a subacute repeated-dose toxicity study in rats exposed by gavage combined with a reproduction/developmental toxicity screening test (Tanaka et al., 1999, which was reported by the WHO, 2005), with a NOAEL of 100 mg/kg bw per day (see Section 1.3.5).

No reproductive or developmental effects were observed at 300 mg/kg bw per day but reduced neonatal viability and lower neonatal body weights were noted at 1000 mg/kg bw per day (Tanaka et al., 1999, as cited by WHO, 2005). In a developmental toxicity study in Charles River CD rats exposed by gavage from GD6–15, an increase in post-implantation loss and a slight decrease in the number of viable fetuses were observed at 1000 mg **2,4,6-TBP**/kg bw per day (IRDC, 1978, as cited in EFSA CONTAM Panel, 2012a). The NOAEL for developmental toxicity was considered to be 300 mg/kg bw per day.

Since the previous Opinion, only two new oral exposure studies were identified. In these sub-acute toxicity studies, mice were exposed via drinking water to **2,4,6-TBP** (Jiang et al., 2022; Miao et al., 2022). The authors reported effects on the liver and kidney at low levels (1.5 µg/kg bw per day). The CONTAM Panel considered that, due to the limitations in the study design and the absence of clear renal or liver lesions, the results of these studies are not convincing. In these two studies, the concentrations in the drinking water were not confirmed by analysis of **2,4,6-TBP**. Based on this, the CONTAM Panel considered that no NOAEL/LOAEL could be identified from those studies.

One sc exposure study indicated slight effects on the thyroid (decreases in FT3 and FT4 levels and minor morphological changes), but cannot be used to identify a reference point because of the route of administration. Effects on thyroid were not investigated in oral studies but were supported by mode of action studies (see Section 3.1.4.3).

No long-term/carcinogenicity studies, one- or two-generation reproductive toxicity studies, neurotoxicity/neurodevelopmental or immunotoxicity studies in experimental animals were available. Mode of action data indicated possible effects on neurodevelopment and immunotoxicity (see Section 3.1.4). Moreover, in a study where pregnant Wistar rats were exposed through inhalation to **2,4,6-TBP** from GD1 to 21, behavioural effects (grooming behaviour, behaviour in an emotionality test) were observed in pups on PND30 (Lyubimov et al., 1998, as cited in EFSA CONTAM Panel, 2012a).

2,4,6-TBP did not induce mutations in bacteria but induced chromosomal aberrations in mammalian cells in vitro. In in vitro Comet assays, **2,4,6-TBP** induced SSB and DSB as well as oxidised DNA bases in human peripheral blood

mononuclear cells. These changes may be indicative for ROS involvement in vitro as shown in Section 3.1.4.4. It did not induce micronuclei in bone marrow of mice in vivo after ip injection up to the maximum tolerated dose of 300 mg/kg bw per day. Although no toxicity in the bone marrow was demonstrated, systemic exposure is generally expected after ip injection and clinical signs of toxicity were reported (e.g. lethargy, ataxia and tremors, see Table 5). Based on the overall evidence, the CONTAM Panel considered in vivo genotoxicity of **2,4,6-TBP** to be unlikely.

The CONTAM Panel confirmed that the Tanaka et al. (1999, as cited by the WHO, 2005) study in rats is the critical study, and re-evaluated it considering additional data identified in the US-EPA (2009) evaluation of **2,4,6-TBP**. At 1000 mg/kg bw per day (the highest dose tested), adverse effects were reported in the liver and kidneys. In the liver, there were increases in absolute and relative weights in both sexes and increases in the number of male animals with hepatocyte hypertrophy. There were increases in relative kidney weights in both sexes and kidney papillary necrosis, dilatation of tubules, lymphocyte infiltration, basophilic tubular epithelium and hyaline casts in males only. There was also a dose-related statistically significant increase in serum creatinine (marker of renal function) in males at 300 and 1000 mg/kg bw per day, but no parallel increase in serum BUN. A NOAEL of 300 mg/kg bw per day and a NOEL of 100 mg/kg bw per day were identified. However, the Panel noted some limitations in this study: Urinalysis was not performed, haematological and blood chemistry analyses were not performed in females and lack of a number of standard parameters to be examined (according to the test guideline OECD TG 422 reported to have been applied in this study). The limitations have been considered in Section 3.1.6.

The observations in experimental animal studies are not corroborated in the studies in humans due to limited data (see Section 3.1.3).

The CONTAM Panel confirmed that the critical effects of **2,4,6-TBP** are on liver and kidney and modelled the relevant data from Tanaka et al. (1999), to identify reference points for the human hazard characterisation.

There were insufficient or no data on the toxicity of any other brominated phenols considered in the TORs to identify reference points.

3.1.5.2 | *Dose response analysis*

The panel performed benchmark dose (BMD) modelling according to the 2022 EFSA Guidance on the use of the BMD approach in risk assessment (EFSA Scientific Committee, 2022, see Section 2.2).

The results of the BMD modelling for the critical study in rats exposed by gavage (Tanaka et al., 1999, detailed data available from US-EPA, 2009) are summarised in Table 6. Details of the BMD analyses, including the individual reports of the modelling, are shown in Annex C.

For quantal data, the default benchmark response (BMR) of 10% was applied as recommended in the EFSA BMD guidance (EFSA Scientific Committee, 2022). For continuous data, the EFSA guidance recommends estimating the 90% credible interval by using a BMR that takes into account biological relevance. For organ weights (increased relative liver and kidney weight), the CONTAM Panel agreed to use a BMR of 15% based on the consideration in the JMPR guidance document that an increase of less than 15% of relative liver or kidney weight might be non-adverse (JMPR, 2015). For increased serum creatinine, the CONTAM Panel applied a BMR based on the standard deviation of the control groups, i.e. 10%.

The CONTAM Panel selected the $BMDL_{10}$ of 353 mg/kg bw per day for kidney papillary necrosis as the reference point for the risk characterisation.

TABLE 6 Benchmark dose (BMD) modelling for the critical study of **2,4,6-TBP** (for details of the BMD analyses, see Annex C).

Reference	Observed effect	$BMDL_{15}$ (mg/kg bw per day)	BMD_{15}	$BMDU_{15}$
Tanaka et al. (1999)[a]	Increased relative liver weight, M rats[e]	416	603	858
	Increased relative liver weight, F rats[e]	573	802	980
	Increased relative kidney weight, M rats[e]	593	848	1001
	Increased relative kidney weight, F rats[d,e]	730	1039	1992
	Observed effect	**$BMDL_{10}$**	**BMD_{10}**	**$BMDU_{10}$**
	Increased serum creatinine, M rats	116[b]	417	1016
	Hepatocyte hypertrophy, M rats (quantal)	321[c]	502	795
	Kidney papillary necrosis, M rats (quantal)	353	694	1059

[a]Detailed data available from US-EPA (2009).

[b]Marker of renal function.

[c]Acceptance criteria not satisfied if none of the BMD model fits sufficiently well, as reported in the EFSA 2022 BMD guidance (EFSA Scientific Committee, 2022).

[d]Relative increase of 14% at the highest dose group of 1000 mg/kg bw per day.

[e]For both relative kidney and liver weights covariate analysis was also performed and gave similar results (see Annex E).

3.1.6 | Approach for risk characterisation

The CONTAM Panel concluded that, due to the limitations and uncertainties in the current database, the establishment of a health-based guidance value for **2,4,6-TBP** was not appropriate. Instead, the margin of exposure (MOE) approach was used for the risk characterisation.

Usually, an MOE of 100, covering 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 $3.2 \times 3.2 = 10$), is considered sufficient to conclude that there is no health concern.

An additional factor was applied to account for the shorter duration of the critical study (48 days) compared to a lifetime exposure. The EFSA Guidance on default factors indicates that the size of this factor should be determined on a case-by-case basis (EFSA Scientific Committee, 2012), while ECHA (2012) suggested using a factor of 6. The Panel decided to apply a factor of 6, while noting the uncertainty about the precise value that would be appropriate.

According to the EFSA Scientific Committee Guidance on selected default values, an additional factor can be considered in case of deficiencies in the database on a case-by-case basis. A default value has not been proposed, as it will be directly dependent on the data set available (EFSA Scientific Committee, 2012). The WHO/IPCS (1994, 1999) has recommended a factor of 3 or 5 if there are minor deficiencies in the database and a factor of 10 if there are major deficiencies in the database. Major deficiencies in the database for **2,4,6-TBP** included lack of studies on reproductive toxicity, carcinogenicity, neurotoxicity, developmental neurotoxicity and immunotoxicity. No studies with exposure during a critical period (gestation and lactation), as was the case for other BFRs evaluated, were identified. Limitations in the key study from which the reference point has been derived included that haematological and clinical chemistry parameters were not examined in females, urinalysis was not performed, and lack of a number of standard parameters. The CONTAM Panel considered an additional factor of 10 to be appropriate for deficiencies in the database.

As a result, the CONTAM Panel considered that MOEs ≥ 6000 do not raise a health concern.

There were insufficient or no data on the toxicity of any other brominated phenols considered in the TORs to identify reference points. Furthermore, there were insufficient data on the mode of action to allow a comparison with **2,4,6-TBP**.

3.2 | Occurrence data

3.2.1 | Occurrence data on food submitted to EFSA

In the previous EFSA Opinion on brominated phenols and their derivatives (EFSA CONTAM Panel, 2012a), no occurrence data on any brominated phenol had been submitted to EFSA. Data available for the current Opinion are described in this section.

By the 1st of December 2022, a total of 87,535 analytical results were available for **2,4,6-TBP** ($n = 87{,}390$), **2,4-DBP** ($n = 52$), **2,6-DBP** ($n = 42$) and **4-BP** ($n = 51$) in the EFSA database between year 2011 and 2021. No data were available for other brominated phenols considered. The raw occurrence data set on brominated phenols in food as extracted from the EFSA data warehouse is available at the EFSA Knowledge Junction community.[12]

The occurrence data reported by 10 Member States were carefully evaluated, and a list of validation steps was applied before being used to estimate dietary exposure. Data providers were contacted to clarify inconsistencies identified during the data check. The following paragraphs describe modifications that were made to the initial data set based on the feedback received and/or expert judgement.

Where analytical results were reported as not corrected for recovery, the reported result was multiplied by the reported recovery factor. When no indication was provided on the application of a correction factor, it was assumed that the result was reported as corrected. A recovery factor equal to one was assumed to indicate 100% recovery. A number of analytical results were reported as not corrected for recovery and no recovery factor was provided ($n = 10{,}309$). In this case, the recovery was assumed to be 100%.

Analytical results reported to be related to 'suspect sampling' ($n = 9162$ all for **2,4,6-TBP**) were excluded based on the fact that sampling strategy cannot be considered randomised.

Analytical results reported for pooled samples ($n = 59$) were excluded as information on sample size was missing and it was not possible to ensure a proportionate representation of the individual samples by weighting the reported analytical results for the number of samples pooled.

The majority of the results referred to GC–MS. For 10,253 analytical results (11.7%), no information on analytical method was available. All analytical results were retained.

After the described cleaning procedure, 9221 analytical results were excluded and 78,314 analytical results were included in the final dataset.

The number of analytical results per year and country in this final data set is presented in Table 7. Most results for **2,4,6-TBP** were provided by France (52%), Sweden (18%) and Finland (12%) with 5 to 12% of the analytical results submitted each year. Ireland was the only Member State providing data on brominated phenols other than **2,4,6-TBP**, but only for 2015.

[12] https://doi.org/10.5281/zenodo.13850547.

Out of the 78,314 analytical results, 24,606 were reported as of non-EU origin (31%) while 2569 samples were of unknown origin (3%).

Table 8 shows data availability and summary statistics for each Level 1 of the FoodEx2 classification of the occurrence data submitted to EFSA on **2,4,6-TBP**, **2,4-DBP**, **2,6-DBP** and **4-BP**.

Analytical results were 100% left-censored for all food categories with the following exceptions:

- Quantified results were found for **2,4,6-TBP** in 'Fish and seafood' ($n = 8$ various types of 'Marine fish meat' from the EU and from unknown origin with concentration range from 0.1 to 0.3 μg/kg, overall 90% left censorship), 'Fruit and fruit products' ($n = 1$ lemon from Spain, $n = 2$ crab apple from Brazil, $n = 1$ gooseberry from India, $n = 1$ banana from Ecuador, with concentration range from 49 to 290 μg/kg, 99.98% left censorship) and 'Spices' ($n = 1$ marjoram dry herb from Turkey with concentration of 11 μg/kg 99.8%).
- Quantified results were found in 'Fish and seafood' for **2,4-DBP** and **4-BP** (same 2 positive samples for both compounds with a range of 0.47–0.98 μg/kg, overall, 80% left-censorship). All 12 samples of 'Hen eggs' from various production methods had quantified results for **4-BP** with a range of 0.28–0.63 μg/kg.

The limited occurrence data for **2,4-DBP**, **2,6-DBP** and **4-BP** were not further used as the CONTAM Panel deemed it not possible to identify a reference point or perform a risk assessment for them due to lack of, or limited, toxicological studies on these brominated phenols (see Section 3.1.5).

For the assessment of dietary exposure to **2,4,6-TBP**, the CONTAM Panel decided to include food categories that had 100% left-censored results at the Level 1 of the FoodEx2 classification if in the literature there was evidence of a possible contamination from **2,4,6-TBP** within these categories (see Appendix E, Table E.1). This allows UB estimates of the dietary exposure that include the uncertainty linked to the sensitivity of the analytical method in what could be considered a 'worst-case scenario' where it is assumed that **2,4,6-TBP** is present in the concerned food categories at the level of the reported LODs and LOQs.

To be noted (Table 8) that most of the samples were analysed with an LOQ of 0.01 mg/kg based on the default MRL set according to Art. 18 (1b) of EC Regulation 396/2005 on pesticides (see Section 1.3.6), or even higher. These LOQs result in very conservative UB dietary exposure estimates, and for that reason, these estimates should not be considered representative of the true exposure to **2,4,6-TBP** (see Section 3.3.1).

TABLE 7 Number of analytical results per year and country in the final data set for **2,4,6-TBP**, **2,4-DBP**, **2,6-DBP** and **4-BP**.

	Country/ year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
2,4,6-TBP	Austria	1											1
	Denmark				10	20	10						40
	Finland	1437	1798		1807	1888	1769	1553					10,252
	France	3055	3909	3704	4068	4288	3678	4303	5196	4934	3576	4439	45,150
	Germany	275	220	275	381	425	525	1695	1380	753	362	380	6671
	Ireland					50							50
	Luxembourg									129			129
	Sweden	1591	1581		1672	1862	1691	1682	1711	1695	1560	831	15,876
	Total	**6359**	**7508**	**3979**	**7938**	**8533**	**7673**	**9233**	**8287**	**7511**	**5498**	**5650**	**78,169**
2,4-DBP	Ireland					51							**51**
	Italy								1				**1**
2,6-DBP	Ireland					42							**42**
4-BP	Ireland					51							**51**
Total		**6359**	**7508**	**3979**	**7938**	**8677**	**7673**	**9233**	**8288**	**7511**	**5498**	**5650**	**78,314**
% by year		8%	10%	5%	10%	11%	10%	12%	11%	10%	7%	7%	100%

TABLE 8 Number of analytical results, % of left-censored analytical results, number of quantified samples, LB and UB mean concentrations and maximum quantified concentrations (μg/kg) for each Level 1 of the FoodEx2 classification calculated from occurrence data submitted to EFSA on **2,4,6-TBP**, **2,4-DBP**, **2,6-DBP** and **4-BP**.

	FOODEX2_L1_ID	*N* results	% LC	*N* quant.	Mean LB	Mean UB	Max quant.	Min LOQ	Max LOQ	Median LOQ
2,4,6-TBP	**Grains and grain-based products**	8670	100%	0	0	8.9	0	10	100	10
	Vegetables and vegetable products	27,551	100%	0	0	15.3	0	10	50	10
	Starchy roots or tubers and products thereof, sugar plants	3214	100%	0	0	15.6	0	10	50	10
	Legumes, nuts, oilseeds and spices	4364	99.98%	1	0.003	10.3	11	10	100	10
	Fruit and fruit products	28,213	99.98%	5	0.022	19.7	290	10	50	10
	Meat and meat products	13	100%	0	0	2.7	0	0.15	10	0.63
	Fish and seafood	82	90%	8	0.022	1.5	0.442	0.05	30	0.5
	Milk and dairy products	79	100%	0	0	5.3	0	0.03	30	10
	Eggs and egg products	62	100%	0	0	5.6	0	1.35	30	10
	Sugar and similar, confectionery and water-based sweet desserts	400	100%	0	0	10.1	0	10	100	10
	Animal and vegetable fats and oils and primary derivatives thereof	504	100%	0	0	14.8	0	0.006	50	10
	Fruit and vegetable juices and nectars (including concentrates)	424	100%	0	0	12.0	0	10	50	10
	Water and water-based beverages	23	100%	0	0	6.7	0	10	30	10
	Coffee, cocoa, tea and infusions	1623	100%	0	0	10.9	0	10	50	10
	Alcoholic beverages	1195	100%	0	0	7.0	0	10	50	10
	Food products for young population	1375	100%	0	0	23.7	0	10	50	25
	Products for non-standard diets, food imitates and food supplements	97	100%	0	0	7.3	0	10	30	10
	Composite dishes	117	100%	0	0	13.1	0	10	50	10
	Seasoning, sauces and condiments	112	100%	0	0	7.1	0	10	60	10
	Major isolated ingredients, additives, flavours, baking and processing aids	41	100%	0	0	5.1	0	10	10	10
	Other ingredients	10	100%	0	0	6.0	0	10	30	10
2,4-DBP	**Meat and meat products**	7	100%	0	0	0.2	0	0.24	0.81	0.48
	Fish and seafood	10	80%	2	0.145	1.0	0.98	0.27	5.1	2.97
	Milk and dairy products	10	100%	0	0	0.0	0	0.03	0.12	0.09
	Eggs and egg products	13	100%	0	0	0.7	0	0.72	2.94	1.59
	Animal and vegetable fats and oils and primary derivatives thereof	12	100%	0	0	0.7	0	0.006	7.2	1.605

(Continues)

TABLE 8 (Continued)

	FOODEX2_L1_ID	*N* results	% LC	*N* quant.	Mean LB	Mean UB	Max quant.	Min LOQ	Max LOQ	Median LOQ
2,6-DBP	**Meat and meat products**	6	100%	0	0	0.8	0	1.17	3.9	2.28
	Fish and seafood	6	100%	0	0	2.0	0	2.4	10.5	5.55
	Milk and dairy products	10	100%	0	0	0.2	0	0.3	0.87	0.6
	Eggs and egg products	11	100%	0	0	2.6	0	2.49	12	7.8
	Animal and vegetable fats and oils and primary derivatives thereof	9	100%	0	0	3.5	0	3.6	20.7	10.2
4-BP	**Meat and meat products**	7	100%	0	0	0.1	0	0.09	0.63	0.3
	Fish and seafood	10	80%	2	0.167	0.5	0.91	0.3	3.15	1.035
	Milk and dairy products	10	100%	0	0	0.01	0	0.03	0.06	0.03
	Eggs and egg products	12	0%	12	0.480	0.5	0.63	0.3	0.3	0.3
	Animal and vegetable fats and oils and primary derivatives thereof	12	100%	0	0	0.2	0	0.006	1.32	0.33

The following food categories that had 100% left-censored analytical results were included based on literature findings of possible contamination of raw primary commodities, ingredients and/or its derivatives: 'Grains and grain-based products', 'Vegetables and vegetable products', 'Starchy roots or tubers and products thereof, sugar plants', 'Meat and meat products', 'Milk and dairy products', 'Alcoholic beverages', 'Food products for young population', 'Composite dishes', 'Seasoning, sauces and condiments', 'Animal and vegetable fats and oils and primary derivatives thereof', 'Fruit and vegetable juices and nectars (including concentrates)', 'Water and water based beverages'.

The following food categories having 100% left-censored analytical results were excluded because there was no evidence of possible contamination from **2,4,6-TBP** in the literature: 'Major isolated ingredients, additives, flavours, baking and processing aids', 'Coffee, cocoa, tea and infusions', 'Products for non-standard diets, food imitates and food supplements', 'Sugar and similar, confectionery and water-based sweet desserts', 'Eggs and egg products', 'Other ingredients'.

In addition, as there were no occurrence data available for drinking water in the EFSA occurrence database, while in the literature, it is reported that drinking water could be contaminated by **2,4,6-TBP** and be an important contributor to the exposure (see Section 1.3.2), the highest occurrence on **2,4,6-TBP** documented in literature for drinking water, 0.0013 µg/kg (OECD, 2005), was used for both the LB and UB concentration estimates.

For the food category 'Fish and seafood' only data for 'Fish meat' were available. As there is evidence that **2,4,6-TBP** concentration in fish liver, crustaceans and mussels could be higher, the highest occurrence values available in the literature were used for these food categories in the dietary exposure assessment. In particular, for 'Fish liver', a **2,4,6-TBP** concentration of 86 µg/kg was used, and for 'Crustaceans' and all 'Molluscs' categories other than 'Squids, cuttlefishes, octopuses', a concentration of 13 µg/kg (see Section 3.2.2) were used for both the LB and UB estimates.

Table 9 shows the ranges across various food categories at the Level 2 of the FoodEx2 classification of **2,4,6-TBP** LB mean concentrations, used for the dietary exposure assessment, obtained from occurrence data submitted to EFSA and from the literature (only categories with LB different than 0 are shown).

Table B.2 in Annex B contains the mean LB and UB occurrence values used in the dietary exposure assessment for each of the 3940 FoodEx2 food categories for which a mean concentration could be calculated from the available data and that is reported in the consumption database.

TABLE 9 **2,4,6-TBP** LB mean concentration (µg/kg) ranges across various food categories at the Level 2 of the FoodEx2 classification used for the dietary exposure assessment, obtained from occurrence data submitted to EFSA and from the literature (only categories with LB > 0 are shown, *n* = number of food subcategories).

FOODEX2_L1_ID	FOODEX2_L2_ID	*N* FC*	Min LB	Median LB	Max LB
Fish and seafood	**Crustaceans**	18	13	13	13
	Fish (meat)	129	0.017	0.070	0.115
	Fish and seafood processed	30	0.022	0.022	0.022
	Fish offal	9	86	86	86
	Molluscs	21	0.022	13	13
	Sea urchins and other echinoderms	1	0.022	0.022	0.022

TABLE 9 (Continued)

FOODEX2_L1_ID	FOODEX2_L2_ID	*N* FC*	Min LB	Median LB	Max LB
Fruit and fruit products	**Fruit and fruit products**	1	0.022	0.022	0.022
	Fruit used as fruit	135	0.007	0.022	1.4
	Processed fruit products	81	0.022	0.022	0.022
Legumes, nuts, oilseeds and spices	**Spices**	53	0	0	1.222
Water and water-based beverages	**Drinking water**	15	0.001	0.001	0.001

**N* FC = Number of food subcategories within the foodex2 level 2 classification included in the dietary exposure assessment.

3.2.2 | Food processing

No relevant data were identified in the scientific literature with respect to the effects of cooking and processing on the levels of the brominated phenols considered in the TORs in food.

3.2.3 | Previously reported occurrence data in the open literature

Occurrence data on brominated phenols and their derivatives in the open literature until 2011 were summarised in the previous EFSA Opinion (EFSA CONTAM Panel, 2012a). A limited number of occurrence data were identified in the literature until 2011, and data from European sampling showed that **2,4,6-TBP** predominated over the other brominated phenols. Levels of **2,4,6-TBP** in fish meat of perch and Arctic char from < 0.03 to 3.5 ng/g ww were reported. Higher levels were reported for blue mussels (3.2–13 ng/g ww) and cod liver (86 ng/g ww) (Nordic Council of Ministers, 2011).

Since then, only few studies published in peer-reviewed journals have been retrieved reporting data on the occurrence of brominated phenols and their derivatives in food samples from European countries; however, this information may not be exhaustive. Data retrieved from the studies identified are summarised in Appendix E (Table E.1). Moreover, some of the data reported in the current Opinion, might have been submitted to EFSA since authors noted that the studies were performed in response to Commission Recommendation 2014/118/EU on the monitoring of BFRs in foodstuff.

Two studies from Belgium (Malysheva et al., 2018; Poma et al., 2018) reported occurrence of five brominated phenols (**4-BP**, **2,4-DBP**, **2,6-DBP**, **2,4,6-TBP** and **TBBPS**) in a variety of Belgian food commodities ($n = 207$ samples). A low detection frequency was observed for the majority of cases, as shown in Table E.1. **2,4,6-TBP** was mainly detected in oils (range: 227–318 pg/g ww), molluscs and crustaceans (range: < 4–4216 pg/g ww), cheese and dairy products (range: < 10–289 pg/g ww) and few meat (range: < 50–83 pg/g ww) samples. **2,4-DBP** was principally found in fish (range: < 15–4637 pg/g ww) and molluscs and crustacean samples (range: < 45–8259 pg/g ww). **4-BP** was detected in different fish and meat products in ranges of < 75–21,042 pg/g ww and < 215–710 pg/g ww, respectively, with higher concentrations in molluscs and crustaceans (range: < 75–22,915 pg/g ww). **2,6-DBP** (LOQ: 320–10,000 pg/g ww) and **TBBPS** (LOQ: 150–1800 pg/g ww) were not detected in any of the sample analysed.

Garcia Lopez et al. (2018) assessed the concentration of brominated phenols in foodstuffs from Ireland, a total number of 53 food samples including eggs, milk, fish, fat and offal. The highest detection frequency was reported for **4-BP** in egg samples (12/12) and the concentration measured in these samples ranged between 0.28 to 0.63 µg/kg ww. In white fish samples, **4-BP** and **2,4-DB** were detected in two out of the four samples tested. The concentrations measured for **4-BP** and **2,4-DB** were reported in the ranges of < 0.1 (LOQ)–0.91 and < 0.09 (LOQ)–0.98 µg/kg ww, respectively.

Bendig et al. (2014) analysed 20 whisky samples from different brands and reported concentrations of brominated phenols. The highest detection frequency was reported for **2,6-DBP** (12 out of the 20 samples) followed by **2,4-DBP** (3 out of the 20 samples) and **2,4,6-TBP** (2 out of the 20 samples). Ranges of **2,6-DBP**, **2,4-DBP** and **2,4,6-TBP** were < 0.010–398, < 0.010–44 and < 0.010–112 ng/L, respectively.

Since 2010, few studies published report occurrence data on brominated phenols and their derivatives in fish and seafood collected both from marine and freshwater regions. A summary of the information reported in some of these studies identified in the literature is presented in Table E.1.

Aznar-Alemany et al. (2017) analysed **2,4,6-TBP** in 42 samples from 10 species of fish and seafood consumed in Europe. Samples were collected from the Mediterranean Sea, the North Sea and the north-east Atlantic Ocean, while three samples were imported from the Pacific Ocean and one from India. **2,4,6-TBP** was detected only in all 10 mussel samples (mean value of 99.1 ng/g lipid) and one place sample analysed (23.6 ng/g lipid, respectively).

Dahlberg et al. (2016) measured **2,4-DBP** and **2,4,6-TBP** in Baltic herring samples (12 samples per site) collected from the southern Bothnian Sea (Ängskärsklubb) and the Northen Baltic Proper (Askö). At Ängskärsklubb the geometric mean concentration of the sum of **2,4-DBP** and **2,4,6-TBP** was 9.6 ng/g lipid (0.71 ng/g ww) and at Askö, 4.3 ng/g lipid (0.23 ng/g ww).

In the Czech Republic, Lankova et al. (2013) reported concentrations of **2,4-DBP** and **2,4,6-TBP** in three out of the four blue mussel samples tested from Spain and Denmark, in the range of 19.6–43.5 µg/kg ww and 2.3–7.5 µg/kg ww, respectively. No **2,4-DBP** or **2,4,6-TBP** were detected in 32 fish samples tested from European and non-European countries, both wild and from aquaculture.

Studies on the levels of brominated phenols in samples from non-European countries are summarised in Table E.2 (Appendix E).

3.3 | Dietary exposure assessment for humans

3.3.1 | Current dietary exposure

The CONTAM Panel assessed the dietary exposure to **2,4,6-TBP** following the methodology described in Section 2.6. A summary of the **2,4,6-TBP** occurrence data including the number of results and concentrations across the FoodEx2 level food categories as used for the dietary exposure assessment is presented in Section 3.2.1.

3.3.1.1 | *Mean and high dietary exposure*

As described in Sections 2.3 and 2.6, dietary exposure to **2,4,6-TBP** was calculated using the LB and UB concentration estimates. Due to the very high number of left-censored results and the LOQs reported in the analysis of **2,4,6-TBP** in most of the food categories (see Section 3.2.1), the difference between LB and UB estimates was up to three orders of magnitude.

The CONTAM Panel noted that, while the LB estimates are expected to be a potential underestimation of the true exposure, the UB estimates are likely to be a large overestimation. However, UB dietary exposure estimates represent worst-case scenarios to be compared to the identified reference point that could be informative for the purpose of risk assessment although not representative of the true exposure to **2,4,6-TBP**.

Table 10 shows the summary statistics of the estimated chronic dietary exposure to **2,4,6-TBP** for each age group. Detailed mean and 95th percentile dietary exposure estimates for all age group and population groups and dietary surveys are presented in Annex B (Table B.3). The special population groups 'Pregnant women', 'Lactating women' and 'Vegetarians' resulted in mean and P95 exposure estimates within the range of the adult population group and thus will not be further discussed.

The LB mean dietary exposure to **2,4,6-TBP** ranged across surveys from 0.078 ng/kg bw per day in very elderly to 3.1 ng/kg bw day in adults. LB P95 dietary exposure to **2,4,6-TBP** ranged across surveys from 0.34 ng/kg bw per day in the elderly to 16 ng/kg bw day in adults and very elderly.

The UB mean dietary exposure to **2,4,6-TBP** ranged across surveys from 140 ng/kg bw per day in adults and elderly to 1600 ng/kg bw day in infants. UB P95 dietary exposure to **2,4,6-TBP** ranged across surveys from 270 ng/kg bw per day in elderly and very elderly to 2400 ng/kg bw day in infants.

TABLE 10 Mean and P95 dietary exposure (LB and UB) to **2,4,6-TBP** (range across surveys).

	Mean dietary exposure (ng/kg bw day)					P95 dietary exposure (ng/kg bw day)				
		LB		UB[a]			LB		UB[a]	
Age group	***N***	**Min**	**Max**	**Min**	**Max**	***N***	**Min**	**Max**	**Min**	**Max**
Infants[b]	12	0.17	1.1	670	1600	11	0.66	2.7	1300	2400
Toddlers	15	0.38	1.5	670	1100	14	0.89	5.6	1100	2000
Other children	19	0.29	1.2	380	720	19	0.71	5.1	710	1200
Adolescents	21	0.15	1.4	190	440	20	0.42	6.9	360	670
Adults	22	0.16	3.1	140	230	22	0.38	16	280	400
Elderly	19	0.19	2.6	140	240	19	0.34	13	270	400
Very elderly	14	0.078	2.7	160	230	10	0.37	16	270	420

[a]UB values should be considered worst-case scenario estimates linked to the LOQs reported (see Section 3.2.1).

[b]The age group of 'Infants' covers subjects from 12 weeks to < 12 months of age (see Section 2.4). Infants below 16 weeks of age are considered in Section 3.3.1.3.

3.3.1.2 | *Contribution of different food groups to the dietary exposure*

The percentage contribution of each individual food category at the Level 1 and 3 of the FoodEx2 classification to the total mean LB chronic dietary exposure of **2,4,6-TBP** was estimated across dietary surveys and is presented in Annex B (Tables B.4 and B.5).

Contribution of the respective food groups was calculated over LB exposure estimates to avoid that the high contribution of certain food groups could be artificially driven by the treatment of the left-censored data.

The food categories with the highest number of surveys in which the contribution to the dietary exposure was higher than 10% are 'Fruits and fruit products', 'Fish and seafood' and 'Drinking water' for all age groups. To be noted that these are also three of the four food categories with quantified analytical results. The fourth category 'Spices' had only one quantified result and contributed to the total dietary exposure only up to 1.5% across surveys. In addition, for drinking water, the highest concentration value of **2,4,6-TBP** found in literature was used in the dietary exposure assessment (see Section 3.2.1). For these reasons, the identification of main contributors to the dietary exposure to **2,4,6-TBP** is subject to large uncertainty. Within the 'Fruit and fruits products' category, 'Pome fruits' and 'Bananas' were the main contributors while in the 'Fish and seafood' category, the main contributor was the category 'Fish offal', 'Crustaceans' and 'Molluscs'.

3.3.1.3 | *Breastfed and formula-fed infants*

The CONTAM Panel concluded that the data on human milk from European countries (see Section 3.1.1.3) and on infant formula are too limited to carry out a useful dietary exposure assessment.

3.3.2 | Previously reported dietary exposure

In the literature, information on dietary exposure to brominated phenols is very limited. Only one study was identified reporting estimation of dietary exposure to organohalogenated compounds, including **2,4,6-TBP**, among infants in Japan. Exposure estimates were based on 24-h duplicate diet method in infants and the median dietary intake of **2,4,6-TBP** was reported at 3.5 ng/day ranging between 0.33 and 109 ng per day. Correlations between intake of organohalogenated compounds and food consumption were investigated and intake of **2,4,6-TBP** was found to be moderately correlated with the intake of seaweed, suggesting that seaweed is a potential source of exposure to **2,4,6-TBP** (Fujii et al., 2021).

3.3.3 | Non-dietary sources of exposure

For most BFRs, the biggest source of exposure after food for non-occupationally exposed individuals is from dust. There are no European studies reporting concentrations of brominated phenols and derivatives in dust, but studies from other parts of the world are collated in Appendix A (Table A.1). The studies listed in the table all report occurrence levels in dust, and those below also make exposure estimates.

Lan et al. (2023) measured eight BFRs in indoor and outdoor dust samples from an E-waste recycling industrial park, and made estimates of human exposure, including for **2,4,6-TBP**. For e-waste dismantling workers, the median estimate was 0.0298 ng/kg bw per day, and the maximum was 0.836 ng/kg bw per day. For residents in a nearby suburb, adult exposure was estimated to be 0.0199 ng/kg bw per day (median value) with a maximum estimate of 0.049 ng/kg bw per day. For children, the median estimate was 0.033 ng/kg bw per day and the maximum was 0.0812 ng/kg bw per day.

Takigami et al. (2009) reported on BFRs and other polyhalogenated compounds in indoor air and dust from two houses in Japan. For adults, using a mean dust ingestion rate of 4.16 mg per day, a mean value for ingestion of **2,4,6-TBP** of 62 pg per day was calculated, and using a high dust ingestion rate of 50 mg per day, the value was 1500 pg per day. For children with an assumed mean dust ingestion rate of 55 mg per day, the estimate was 830 pg per day, and using a high dust ingestion rate of 200 mg per day, the estimate was 3000 pg per day.

Given that dietary exposure estimates range from 0.078 ng/kg bw per day (LB mean) to 2400 ng/kg bw per day (UB 95), the figures above for total ingestion of **2,4,6-TBP** from dust can be seen to be much lower than exposure from the diet.

In addition, from exposure to dust, there are reports in the literature about the potential for exposure to **2,4,6-TBP** from food contact materials (Paseiro-Cerrato, Ackerman, et al., 2021), from textiles as a result of the use of preservatives (Ping et al., 2015) and on the general presence in consumer products Kajiwara et al. (2011).

Gallistl et al. (2017) reported on several classes of polyhalogenated compounds including **2,4,6-TBP** in dishcloths after their regular use in households. **2,4,6-TBP** was found in 68% of samples with a mean of 290 ng per dishcloth and a median value of 29 ng per dishcloth.

Simonetti et al. (2023) conducted a survey on bio-based food packaging material for the presence and migration of flame retardants including **2,4-DBP** and **2,4,6-TBP**. The results showed that except in one case (baking paper), the concentration of migrated brominated phenols was very low. For the baking paper sample, up to 34% migration of brominated phenols was found to migrate in a test using a simulant.

3.4 | Risk characterisation

Comparison of the exposure estimates (see Section 3.3.1) and the $BMDL_{10}$ of 353 mg/kg bw per day for kidney papillary necrosis as the reference point for **2,4,6-TBP** resulted in MOEs of about 22,000,000 at the maximum P95 LB exposure, and of about 145,000 at the maximum P95 UB exposure.

The CONTAM Panel noted that these MOEs are far above 6000 (see Section 3.1.6), and therefore, current dietary exposure to **2,4,6-TBP** does not raise a health concern.

No conclusion could be made for breastfed or formula-fed infants due to insufficient occurrence data.

No conclusion could be made for brominated phenols other than **2,4,6-TBP** due to lack of toxicological and occurrence data.

3.5 | Uncertainty analysis

The aim of the uncertainty analysis is to identify uncertainties affecting the risk assessment for **2,4,6-TBP** in food and quantify their combined impact on the main conclusions, as recommended in the EFSA Guidance on uncertainty analysis

(EFSA Scientific Committee, 2018a). This was restricted to the risk assessment for the general population. Due to the limited occurrence data for human milk and infant formula, no exposure or risk assessment and hence no uncertainty analysis was performed for exposure of breastfed and formula-fed infants (see Sections 3.1.1.3 and 3.3.1.3). No risk characterisation or uncertainty analysis could be performed for any of the other compounds included in the TORs, due to lack of data both on the toxicity and occurrence (see Sections 3.1.5 and 3.2.1).

As the risk assessment for **2,4,6-TBP** followed the normal approach of the CONTAM Panel, including standardised elements to address some sources of uncertainty, e.g. default uncertainty factors and use of EFSA's Comprehensive Database on consumption, the uncertainty analysis followed the approach for a standardised assessment (Section 3 of the Guidance).

The combined impact of the identified uncertainties was quantified in a tiered approach. Considering the large margin between the reference point and the estimates of exposure (Section 3.3.1), it was considered appropriate to quantify the combined impact of all the uncertainties affecting the risk characterisation in a single judgement, as described in Section 3.2 of the Guidance (EFSA Scientific Committee, 2018a). This proved sufficient to reach a clear conclusion for the present assessment. The combined impact of uncertainties affecting the conclusion on the genotoxic potential of **2,4,6-TBP** was quantified separately.

The following sections report the methods and results for each step in the uncertainty analysis. Further details of the expert knowledge elicitation (EKE) that was performed for the risk characterisation are documented in Annex D.

3.5.1 | Identification of sources of uncertainty

Sources of uncertainty related to the exposure assessment, hazard assessment and risk characterisation for the current **2,4,6-TBP** assessment were listed and discussed (see Appendix F). It was then considered which of these were non-standard[12] sources of uncertainty and which would have most impact on the outcome of the risk assessment. Standard sources of uncertainty[13] were not considered further in the uncertainty analysis, as explained in Section 3 of the EFSA Guidance on uncertainty analysis (EFSA Scientific Committee, 2018a).

Uncertainties affecting the exposure assessment for the general population are described and prioritised in Table F.1 (Appendix F). Most of the non-standard sources of uncertainty were judged to have negligible or low impact on the exposure assessment. The only exception was uncertainty relating to the high proportion of left-censored data for some food categories. This was addressed by using the substitution method in the exposure assessment. However, the LOQs reported for those foods resulted in UB estimates of exposure that are likely to be a great overestimation, with a high impact on uncertainty of the exposure assessment.

Most of the non-standard uncertainties affecting the hazard assessment were judged to have negligible or low impact on the hazard assessment (Table F.2, Appendix F). Those with higher impact were as follows:

- High impact: Only subacute toxicity studies (including a screening of reproductive effects) and one developmental toxicity study have been conducted in rats exposed by gavage. The Panel noted some limitations in the critical study Tanaka et al. (1999, as reported by WHO, 2005; US-EPA, 2009): urinalysis was not performed, haematological and blood chemistry analyses were not performed in females, and lack of a number of standard parameters to be examined. One sc study indicated dose-related effects on the thyroid, but cannot be used to identify a Reference Point because of the route of administration. Effects on thyroid were not investigated in gavage studies. Major deficiencies in the database for **2,4,6-TBP** included lack of studies on subchronic and chronic toxicity/carcinogenicity, reproductive toxicity, neurotoxicity/developmental neurotoxicity and immunotoxicity. No studies with exposure during a critical period (gestation and lactation), as was the case for other BFRs evaluated, were available.
- Medium impact: The mode of action studies provide indication of toxic effects (neurotoxicity, immunotoxicity, thyroid toxicity) not investigated in the identified experimental animal studies. Except for oxidative stress no investigation of mechanisms for genotoxicity, liver or kidney toxicity have been identified.

Two non-standard uncertainties affecting risk characterisation were each judged to have low impact on the assessment (see Table F.3 in Appendix F).

3.5.2 | Genotoxicity

Uncertainties affecting the evidence on the genotoxic potential of **2,4,6-TBP** (see Section 3.1.2.6) were assessed to have low impact on the assessment (Table F.2, Appendix F). **2,4,6-TBP** did not induce mutations in bacteria but induced

[12]Non-standard uncertainties are defined by EFSA Scientific Committee (2018a) as 'Any deviations from a standardised procedure or standardised assessment element that lead to uncertainty regarding the result of the procedure. For example, studies that deviate from the standard guidelines or are poorly reported, cases where there is doubt about the applicability of default values, or the use of non-standard or 'higher tier' studies that are not part of the standard procedure.'

[13]Standard uncertainties are defined by EFSA Scientific Committee (2018a) as 'Sources of uncertainty that are considered (implicitly or explicitly) to be addressed by the provisions of a standardised procedure or standardised assessment element. For example, uncertainties due to within and between species differences in toxicity are often addressed by a default factor of 100 in chemical risk assessment.'

chromosomal aberrations in mammalian cells in vitro. **2,4,6-TBP** did not induce micronuclei in bone marrow of mice in vivo after ip injection up to the maximum tolerated dose of 300 mg/kg bw per day. Although no toxicity in the bone marrow was demonstrated, systemic exposure is generally expected after ip injection and clinical signs of toxicity were reported (e.g. lethargy, ataxia and tremors, see Table 5).

Based on the overall evidence, and following an expert group discussion, the CONTAM Panel considered there is < 5% probability that **2,4,6-TBP** is genotoxic in vivo. This implies at least 95% probability that **2,4,6-TBP** is *not* genotoxic in vivo.

3.5.3 | Risk characterisation

In view of the large MOEs obtained for **2,4,6-TBP**, all far above an MOE of 6000 that does not raise a health concern (see Section 3.4), it was considered appropriate to quantify the combined impact of all the uncertainties affecting the risk characterisation in a single judgement. This was done by a semi-formal process of expert knowledge elicitation (semi-formal EKE, Annex B.8 of EFSA Scientific Committee (2018b)).

The question to be addressed in the EKE was formulated as follows:

What is your % probability that, if all of the identified non-standard uncertainties affecting the assessment were resolved (e.g. by obtaining more or better data), current dietary exposure to **2,4,6-TBP** would raise a health concern for at least one type of health effect for at least one of the population groups and surveys that were included in the exposure assessment, at the P95 of chronic exposure?

Nine experts (five toxicology experts, two epidemiology experts and two exposure assessment experts) provided judgements and reasoning on this question. Their individual judgements of the required probability ranged from 1% to 25%; the judgements are documented in Annex D together with a description of the EKE procedure.

After discussing and refining their individual judgements and reasoning, the experts worked toward a consensus conclusion, which was based on the following considerations:

- The lowest MOE values based on the Reference Point of 353 mg/kg bw per day were about 22,000,000 at the maximum P95 LB exposure, and about 145,000 at the maximum P95 UB exposure. These MOEs are far above the value of 6000 identified by the CONTAM Panel that does not raise a health concern.
- The Panel noted some limitations in the critical study Tanaka et al. (1999, as reported by WHO, 2005; US-EPA, 2009): Urinalysis was not performed, haematological and blood chemistry analyses were not performed in females and lack of a number of standard parameters to be examined.
- Major deficiencies in the toxicological database include lack of studies on subchronic and chronic toxicity, reproductive toxicity, carcinogenicity, neurotoxicity, developmental neurotoxicity and immunotoxicity.
- An increase in serum creatinine was observed in the critical study at a dose threefold below the reference point. Serum creatinine is a marker of renal function. Slight effects on the thyroid were observed in a sc exposure study but could not be used in the risk assessment due to the route of exposure (see Section 3.1.5.1).
- The mode of action studies provided indications of toxic effects (e.g. neurotoxicity, immunotoxicity, thyroid toxicity) that were not investigated in the identified experimental animal studies.
- There was a limited body of epidemiological evidence.
- The MOE that would not raise a health concern that would be appropriate to take account of the potential for effects to occur at lower doses could be anywhere between 1000 and 100,000, given the limitations of the toxicological data and the indications from MOA studies, noted above. However, even the upper end of this range is below the lowest MOE obtained for P95 UB exposure (about 145,000).
- The UB exposures were considered to be great overestimates due to the large proportion of left-censored occurrence data with the LOQs reported: Resolving this uncertainty would lead to higher MOEs.
- It was judged that there was at least 95% probability that **2,4,6-TBP** is not genotoxic in vivo (Section 3.5.2).

Based on these considerations, the experts agreed on a consensus judgement of < 5% probability that current dietary exposure to **2,4,6-TBP** would raise a health concern for any of the surveys and population groups considered. This implies at least 95% probability that current dietary exposure to **2,4,6-TBP** does *not* raise a health concern.

3.5.4 | Summary of the uncertainty analysis

Uncertainties affecting each part of the assessment were systematically identified and prioritised, and their combined impact on the main conclusions was quantified by expert judgement.

The CONTAM Panel concluded with at least 95% probability that **2,4,6-TBP** is not genotoxic in vivo.

Considering the large margin between the exposure estimates and the reference point, and taking account of all associated uncertainties, the CONTAM Panel concluded with at least 95% probability that current dietary exposure to **2,4,6-TBP** would not raise a health concern.

Due to gaps and limitations in the available data, no risk assessment and therefore no uncertainty analysis was performed for breastfed or formula-fed infants, nor for any of the other compounds included in the TORs.

4 | CONCLUSIONS

Brominated phenols have been used since the 1920s as flame retardants and for applications including the synthesis of other brominated flame retardants (BFRs), pigments, herbicides, germicides and antifungal agents. They can be released into the environment through transformation of TBBPA, PBDEs and other BFRs. In the past, **2,4,6-TBP** was used as a wood preservative due to its fungicidal properties. Brominated phenols, along with some other brominated aromatic compounds can be naturally produced by marine organisms. This, along with the fact that brominated phenols are used for applications other than as flame retardants make it difficult to assess the relative proportions that may be found in the environment as a result of their use as a BFR and from other sources. While action has been taken to restrict the production and use of some classes of BFRs, this is not the case specifically for brominated phenols.

This assessment is an update of the EFSA CONTAM Panel Opinion on brominated phenols and their derivatives in Food published by EFSA in 2012. This update considered the following compounds: 2,4,6-tribromophenol (**2,4,6-TBP**), 2,4-dibromophenol (**2,4-DBP**), 4-bromophenol (**4-BP**), 2,6-dibromophenol (**2,6-DBP**), tetrabrominated bisphenol S (**TBBPS**) and the derivative tetrabromobisphenol S bismethyl ether (**TBBPS-BME**). It takes into account the occurrence data in food and biological samples submitted to EFSA after the publication of the previous Opinion, as well as the newly available scientific information of relevance to hazard identification and characterisation.

No risk characterisation could be performed for any brominated phenols or derivative included in the TORs other than **2,4,6-TBP**, due to insufficient or lack of data both on the toxicity and occurrence (see Sections 3.1.5 and 3.2.1).

4.1 | Hazard identification and characterisation

4.1.1 | Toxicokinetics

- In rodents, **2,4,6-TBP** has an oral bioavailability of 30% and is distributed in different organs without accumulation. It is mainly excreted in urine. There is evidence of maternal transfer during gestation and lactation. **2,4,6-TBP** is metabolised into sulfate and glucuronic acid conjugates, with an elimination half-life of less than 5 h. There appears to be no major difference between rats and mice regarding disposition after a single oral dose exposure.
- In humans, there are no data regarding the absorption and elimination of **2,4-DBP** or **2,4,6-TBP**. Several studies have measured concentrations of **2,4,6-TBP** in human samples, including human milk and serum. **2,4-DBP** and **2,4,6-TBP** are metabolised either into sulfate or glucuronic acid conjugates.

4.1.2 | Toxicity in experimental animals

- The main targets in repeated-dose subacute toxicity studies in rats exposed by gavage to **2,4,6-TBP** are the liver and kidney. There were increases in organ weights and also histopathological changes at 1000 mg/kg bw per day. There were also statistically significant, dose-related increases in serum creatinine in males at 300 and 1000 mg/kg bw per day.
- No reproductive effects were observed at 300 mg/kg bw per day in a subacute toxicity study in rats. However, in a developmental toxicity study where rats were exposed by gavage from GD6–15, an increase in post-implantation loss, and a slight decrease in the number of viable fetuses were observed at 1000 mg **2,4,6-TBP**/kg bw per day. The NOAEL for developmental toxicity was 300 mg/kg bw per day.
- **2,4,6-TBP** did not induce mutations in bacteria but induced chromosomal aberrations in mammalian cells in vitro. It did not induce micronuclei in bone marrow of mice in vivo after ip injection up to the maximum tolerated dose of 300 mg/kg bw per day. Overall, the CONTAM Panel considered in vivo genotoxicity of **2,4,6-TBP** to be unlikely.

4.1.3 | Observations in humans

- The volume of the available epidemiological evidence on brominated phenols and their derivatives is very limited and is mostly related to the association between **2,4,6-TBP** levels and thyroid hormones. A few signals coming from statistically significant association were reported, but the confidence in a true underlying effect is low due to methodological issues.

4.1.4 | Mode of action

- **2,4,6-TBP** and **TBBPS** can induce oxidative stress and apoptosis.
- There is evidence that **2,4,6-TBP** and **TBBPS** can have effects on thyroid hormone signalling, possibly mediated by inhibition of sulfotransferase and deiodinase-2, and binding to thyroid hormone receptor β (TRβ).

- The available data suggest that **2,4,6-TBP** might have antiandrogenic effects and exhibit effects on neurodevelopment and immune function.

4.1.5 | Critical effects and dose–response analysis

- The evidence from the available human data did not provide a sufficient basis for the risk assessment. Thus, the CONTAM Panel considered the data from studies in experimental animals to identify reference points for the human risk characterisation.
- The CONTAM Panel concluded that liver and kidney toxicity observed in a subacute oral toxicity study in rats were the critical effects for the hazard characterisation.
- Dose–response modelling was performed and a $BMDL_{10}$ of 353 mg/kg bw per day for kidney papillary necrosis was identified as the most appropriate reference point for **2,4,6-TBP** risk characterisation.
- There were insufficient or no data on the toxicity of any of the other compounds included in the TORs to derive reference points.
- There were insufficient data to assess if **2,4,6-TBP** and other compounds included in the TORs have a common mode of action or otherwise contribute to common adverse outcomes. It was therefore not possible to assign the brominated phenols in the TOR to assessment groups for the purposes of combined risk assessment.

4.2 | Occurrence and exposure for the European population

4.2.1 | Occurrence in food

- Following data cleaning, 78,169 analytical results were made available for inclusion in the assessment of dietary exposure to **2,4,6-TBP**.
- The limited number of analytical results for **2,4-DBP**, **2,6-DBP** and **4-BP** ($n = 51$ for **2,4-DBP** and **4-BP** and $n = 42$ for **2,6-DBP**) was not used as the CONTAM Panel deemed not possible to identify a reference point or perform a risk assessment for them due to lack of, or limited, toxicological studies on these brominated phenols
- For **2,4,6-TBP**, analytical results were 100% left-censored for all food categories with very few exceptions. Quantified results were found in 'Fish and seafood' ($n = 8$, 90% left censorship), 'Fruit and fruit products' ($n = 5$, 99.98% left censorship) and 'Spices' ($n = 1$, 99.8% left censorship).
- For 'Drinking water' and some subcategories of fish and seafood, occurrence data (including quantified results) extracted from the literature were used.
- For the assessment of dietary exposure to **2,4,6-TBP**, the CONTAM Panel decided to include food categories that had 100% left-censored results at the Level 1 of the FoodEx2 classification if in the literature there was evidence of a possible contamination from **2,4,6-TBP** within these categories.

4.2.2 | Exposure assessment

- Dietary exposure to **2,4,6-TBP** was calculated using the LB and UB concentration estimates.
- Due to the very high number of left-censored results and the LOQ reported in the analysis of **2,4,6-TBP** in most of the food categories, the difference between LB and UB estimates was up to three orders of magnitude.
- The LB mean dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 0.078 to 3.1 ng/kg bw per day. LB P95 dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 0.34 to 16 ng/kg bw day.
- The UB mean dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 140 to 1600 ng/kg bw per day. UB P95 dietary exposure to **2,4,6-TBP** ranged across surveys and age groups from 270 to 2400 ng/kg bw day.
- The CONTAM Panel noted that while the LB estimates are expected to be an underestimation of the true exposure, the UB estimates are likely to be a large overestimation. The UB dietary exposure estimates represent worst-case scenarios, not representative of the true exposure to **2,4,6-TBP**.
- The main contributors to the dietary exposure to **2,4,6 TBP** were 'Fruits and fruit products', 'Fish and seafood' and 'Drinking water'. This is subject to uncertainty because only four food categories had quantified values (the three main contributors plus 'Spices'), and for 'Drinking water' the highest concentration value of **2,4,6-TBP** found in literature was used.
- No exposure assessment could be performed for breastfed or formula-fed infants due to lack of occurrence data.
- The available data suggest that for most of the population, diet represents the largest source of exposure to **2,4,6-TBP**.
- No relevant data were identified in the scientific literature with respect to the effects of cooking and processing on the levels of brominated phenols and the derivative considered.

4.3 | Risk characterisation

- Due to limited information on hazard for **2,4,6-TBP**, the derivation of a health-based guidance value (HBGV) was not considered appropriate. Instead, the margin of exposure (MOE) approach was applied to assess possible health concerns.
- The CONTAM Panel considered that MOEs ≥ 6000 do not raise a health concern. This MOE would cover variability with respect to kinetic and dynamic differences between animal species and humans and within the human population (factor of 100), account for the shorter duration of the critical study compared to a lifetime exposure (factor of 6), and account for major deficiencies in the database (factor of 10).
- Comparison of the exposure estimates to the reference point identified for **2,4,6-TBP** resulted in MOEs of about 22,000,000 at the maximum P95 LB exposure, and of about 145,000 at the maximum P95 UB exposure.
- The CONTAM Panel noted that these MOEs are far above 6000, and therefore, current dietary exposure to **2,4,6-TBP** does not raise a health concern.
- No conclusion could be made for breastfed or formula-fed infants due to insufficient occurrence data.
- No conclusion could be made for the compounds other than **2,4,6-TBP** included in the TORs due to lack of toxicological and occurrence data.

4.4 | Uncertainty analysis

- An uncertainty analysis was performed. The CONTAM Panel concluded with at least 95% probability that **2,4,6-TBP** is not genotoxic in vivo. Considering the large margin between the exposure estimates and the reference point, and taking account of all associated uncertainties, the CONTAM Panel concluded with at least 95% probability that current dietary exposure to **2,4,6-TBP** would not raise a health concern.

5 | RECOMMENDATIONS

The CONTAM Panel made the following recommendations to reduce the uncertainty in the risk assessment of **2,4,6-TBP** in food:

- To monitor occurrence in human milk and food for infants, with appropriate analytical methods, to enable an exposure assessment for infants.
- Despite the very large MOEs identified in the current Opinion, a refined risk assessment would benefit from the following data: toxicokinetic data in humans, longitudinal epidemiological studies of sufficient power and appropriate exposure and co-exposure assessment, as well as subchronic toxicity studies, reproductive/developmental studies, neurodevelopmental and immunotoxicity studies.

The CONTAM Panel made the following recommendations for obtaining additional data in order to perform a risk assessment of the other brominated phenols included in the TORs:

- Occurrence data in food, including human milk and food for infants, with appropriate analytical methods.
- Toxicokinetic data in rodents and humans.
- Genotoxicity and toxicological studies.

ABBREVIATIONS

2,3,4,6-TeBP	2,3,4,6-tetrabromophenol
2,4,5-TBP	2,4,5-tribromophenol
2,4,6-TBP	2,4,6-tribromophenol
2,4-DBP	2,4-dibromophenol
2,6-DBP	2,6-dibromophenol
4-BP	4-bromophenol
ALP	alkaline phosphatase
ALT	alanine transaminase
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
AST	aspartate aminotransferase
AUC	area under the curve
BCF	bioconcentration factors
BFRs	brominated flame retardants
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BUN	blood urea nitrogen
CA	competent authority

CAS	Chemical Abstract Service
CAT	catalase
CONTAM Panel	Panel on Contaminants in the Food Chain
DL	detection limit
DSB	double strand breaks
DTU	Denmark
ECHA	European Chemicals Agency
EQUASs	external quality assurance schemes
EURL	European Reference Laboratory
F	female
GC	gas chromatography
GD	gestation day
GLP	good laboratory practice
HBCDDs	hexabromocyclododecanes
HPVC	high production volume chemical
HRMS	high-resolution mass spectrometry
LB	lower bound
LC	liquid chromatography
LD50	lethal dose, 50%
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantification
LRTAP	long-range transboundary air pollution
M	male
MDA	malondialdehyde
mESC	embryonic stem cell
MOE	margin of exposure
MRL	maximum residue level
MS	mass spectrometry
MTD	maximum tolerance dose
ND	not detected
NOAEL	no-observed-adverse-effect level
NR	not reported
PBDD/Fs	polybrominated dibenzo-p-dioxins and dibenzofurans
PBDEs	polybrominated diphenyl ethers
PBDFs	polybrominated dibenzofurans
PBMCs	peripheral blood mononuclear cells
PBP	pentabromophenol
PBT	persistent, bioaccumulative and toxic
PCB	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-p-dioxins
PMT	persistent, mobile and toxic
PND	postnatal day
POPs	persistent organic pollutants
QSAR	quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	reference dose
ROS	reactive oxygen species
SOPs	standard operation procedures
SSB	single strand breaks
SVHCs	substance of very high concern
T3	triiodothyronine
TBBPA	tetrabromobisphenol A
TBBPS	tetrabrominated bisphenol S
TBBPS-BDBPE	tetrabromobisphenol-S bis(2,3-dibromopropyl ether)
TBBPS-BME	tetrabromobisphenol S bismethyl ether
TEBP-Anh	3,4,5,6-tetrabromophthalic anhydride
TORs	terms of reference
TRβ	thyroid hormone receptor β
TSH	thyroid-stimulating Hormone
TT3	total triiodothyronine
TT4	total thyroxine

UB	upper bound
UF	uncertainty factor
UGT	uridine diphosphate glucuronosyl transferases
UPLC	ultra-high performance liquid chromatography
vPvB	very persistent and very bioaccumulative
ww	wet weight
T4	thyroxine

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CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

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APPENDIX A

Levels in dust from non-European countries

The table below, which does not claim to be a comprehensive review of the literature, provides an overview of the occurrence of brominated phenols and derivatives in dust samples collected in non-European countries.

TABLE A.1 Occurrence of brominated phenols and derivatives in dust samples from non-European countries, and estimate of dust exposure when reported by the authors.

Country sampling year	Number of samples	Concentration	Exposure estimate	Reference
2,4,6-TBP				
China 2020	*n* = 113 e -waste recycling area *n* = 15 suburb residential homes	**e-waste recycling area** Mean, media (range): 352, 263 (< MLOQ–2000) ng/g **Suburb residential homes** Mean, media (range): 66.2, 63.9 (< MLOQ–181) ng/g	**e-waste dismantling workers**: median: 0.0298 ng/kg bw per day max: 0.836 ng/kg bw per day **Residents in suburb**: **Adults**: median: 0.0199 ng/kg bw per day max: 0.049 ng/kg bw per day **Children**: median: 0.033 ng/kg bw per day max: 0.0812 ng/kg bw per day	Lan et al. (2023)
Canada 2016	*n* = 7 e-waste recycling facility	Mean, media (SD): 174, 145 (157) ng/g	NR	Guo et al. (2018)
USA 2013	*n* = 30 residential dust	Mean, media (SD): 17.9, 6.69 (31.8) ng/g	NR	Guo et al. (2018)
USA 2014–2016	*n* = 186	Median: 46 ng/g Maximum: 1967 ng/g	NR	Levasseur et al. (2021)
Japan 2006	NR	**House A** (4.4 g of vacuum cleaner contents): 30 ng/g **House B** (3.7 g of vacuum cleaner contents): 15 ng/g	**Adults**: Using a mean dust ingestion rate of 4.16 mg per day: 62 pg per day Using a high dust ingestion rate of 50 mg per day: 1500 pg per day **Children**: Using a mean dust ingestion rate of 55 mg per day: 830 pg per day Using a high dust ingestion rate of 200 mg per day: 3000 pg per day	Takigami et al. (2009)[a]
Japan 2005	*n* = 19 house dust *n* = 14 office and laboratory dust	**House dust** Median (range): 34 (16–130) ng/g **Office dust** Median (range): 90 (27–620) ng/g	NR	Suzuki et al. (2008)[a]
TBBPS				
China July–Dec 2020	*n* = 113 e-waste recycling area *n* = 15 suburb residential homes	**e-waste recycling area**: Mean, median (range): 2.60, 1.31 (< MLOQ–15.5) ng/g **Ssuburb residential homes**: Mean, median (range): < MLOQ, < MLOQ (< MLOQ)	**e-waste dismantling workers** median: 0.000801 ng/kg bw per day max: 0.00646 ng/kg bw per day **Residents in suburb (adults and children)**: NR	Lan et al. (2023)

[a]The studies were not captured in the previous Opinion but they are reported in the current update for completeness.

APPENDIX B

Literature search

Information on physicochemical properties, production and industrial use, environmental fate and levels, analytical methods, previous assessments and legislation was gathered from the previous EFSA Opinion on brominated phenols and their derivatives (EFSA CONTAM Panel, 2012a), assessments by international bodies (by checking the original websites of the relevant organisations), and from current EU legislation. Literature searches were also conducted to identify new information in reviews and other peer-reviewed publications, also in the fields of previously reported occurrence data and exposure assessments, food processing and non-dietary exposure. The information was summarised in a narrative way based on expert knowledge and judgement.

Details of the literature search performed are shown in Table B.1 Search strings were run in the databases indicated. The literature searches were performed in August 2019. The outcome of the searches was saved in separate EndNote files and an automatic duplicate detection run. The references were then transferred to DistillerSR (a web-based systematic review software) where another automatic duplicate detection was again made. The selection for relevance based on title and abstract and full text was done by EFSA staff and WG members.

Since that date, the literature was monitored via WoS-Web of Science to identify studies relevant for the risk assessment until the time of endorsement (October 2023 and April 2024).

TABLE B.1 Details of the literature search.

2,4,6-tribromophenol OR 2,4,6-TBP OR 118-79-6 OR 2,4-dibromophenol OR 2,4-DBP OR 615-58-7 OR 4-bromophenol OR 106-41-2 OR 2,6-dibromophenol OR 608-33-3 OR "tetrabrominated bisphenol S" OR "tetrabromobisphenol S" OR TBBPS OR "tetrabromobisphenol S bismethyl ether" OR TBBPS-BME OR 39635-79-5 OR 70156-79-5 Sources: Web of Science (all databases) and PUBMED (excluding Chinese language) Period: 01.01.2011–05.10.2023	05.10.2023	Results: 1062 After removal of duplicates: 657 results
Period: 01.10.2023–03.04.2024	03.04.2023	Results: 55 After removal of duplicates: 36 results

APPENDIX C

Occurrence of TBBPA in human samples from non-European countries reported in the literature

The Table below, which does not claim to be a comprehensive review of the literature, provides an overview of the occurrence of brominated phenols in human samples collected in non-European countries.

TABLE C.1 Concentration of brominated phenols and their derivatives in **human milk, serum and adipose tissue samples** from non-European countries.

Country year	Number of samples	Concentration (ng/g lipid)	Detection frequency	Reference
Human milk				
USA 2019	3-BP, **4-BP** 2,3-DBP, **2,4-DBP**, 2,5-DBP, **2,6-DBP** **2,4,6-TBP** *n* = 50 Primiparous women (24–42 years old)	Mean, Median (range): Sum 3-BP + **4-BP**: 0.0278, < 0.33 (< 0.33–1.11) Sum 2,3 + **2,4** + 2,5-DBP: 0.109, < 0.06 (< 0.06–2.51) **2,6-DBP**: 2.23, < 0.09 (< 0.09–25.0) **2,4,6-TBP**: 0.582, 0.326 (< 0.03–10.4) Total brominated phenols: 4.93, 0.996 (< 0.06–71.1)	Sum 3-BP + **4-BP**: 4% Sum 2,3 + **2,4** + 2,5-DBP: 16% **2,6-DBP**: 34% **2,4,6-TBP**: 84% Total brominated phenols: 88%	Schreder et al. (2023)
Japan 2005–2006	**2,4,6-TBP** *n* = 9 Women (26–39 years old)	Mean (SD), Median (range): 1.17 (0.75), 1.06 (0.13–2.73)	100%	Fujii, Nishimura, et al. (2014)
Japan 2008–2010	**2,4,6-TBP** *n* = 64 Women (average 31 years old)	Mean (SD), Median (range): 0.82 (0.57), 0.75 (< 0.0–3.4)	100%	Fujii et al. (2018)
Serum				
Japan 2006	**2,4,6-TBP** *n* = 10 women (40–47 years old)	Mean (SD), Median (range): 40.2 (30.1), 26 (18–100) pg/g ww	100%	Fujii, Nishimura, et al. (2014)
Japan 1989, 1999, 2010	**2,4,6-TBP** *n* = 60 males (20–69 years old)	Mean (range): 248 (46–960) pg/g ww 1989 (*n* = 20) 150 (46–370) pg/g ww 1999 (*n* = 20): 240 (110–380) pg/g ww 2010 (*n* = 20) 350 (62–960) pg/g ww 20s (*n* = 30) 250 (46–960) pg/g ww > 50s (*n* = 30) 250 (67–500) pg/g ww	100%	Fujii, Harada, et al. (2014)
China 2016	**TBBPS** *n* = 181 pregnant women	Median (range): 0.593 (< LOD–10.8) ng/mL	89.5%	Li et al. (2020)
China 2017–2018	**2,4,6-TBP** **2,4-DBP** *n* = 75 adults (*n* = 27 e-waste (EW) workers, *n* = 28 non-EW workers but engaged with other related activities, *n* = 20 adult residents living in the surrounding area)	Mean, Median (range): **2,4,6-TBP**: EW workers: 118, 101 (10.3–376) ng/g lipid Non-EW workers: 175, 178 (33.8–300) ng/g lipid Adults: 146, 126, (ND–381) ng/g lipid **2,4-DBP**: EW workers: 7.93, ND (ND–29.9) ng/g lipid Non-EW workers: 2.15, ND (ND–22.8) ng/g lipid Adults: 7.49, ND (ND–47.4) ng/g lipid	**2,4,6-TBP**: • EW workers: 100% • Non-EW workers: 100% • Adults: 96% **2,4-DBP**: • EW workers:50% • Non-EW workers: 21% • Adults: 48%	Lin et al. (2023)
USA 2008–2010	**2,4,6-TBP** *n* = 43 pregnant women	Geometric mean (95% CI): 19,200 (15,700–23,400) pg/g lipid Range: 5100–63,400 pg/g lipid	100%	Butt et al. (2016)
USA 2008–2010	**2,4,6-TBP** *n* = 55 pregnant women in their third trimester	P50, P95: < LOD, 101.67	38.13%	Miranda et al. (2015)

(Continues)

TABLE C.1 (Continued)

Country year	Number of samples	Concentration (ng/g lipid)	Detection frequency	Reference
Pakistan 2012	**2,4,6-TBP** *n* = 17 rural mothers *n* = 17 rural children *n* = 17 urban mothers *n* = 17 urban children *n* = 17 general population	Mean (SD), Median (range) Rural mothers: 4.7 (1.6), 5 (< 5–15) Rural children 11.5 (5.5), 11, (< 5–25) Urban mothers 3.2 (2.1), < 5 (< 5–15) Urban children 2.6 (2.1), < 5 (< 0.5–12) General population 3.5 (4.6), < 5 (< 5–15)	Rural mothers: 59% Rural children: 88% Urban mothers: 82% Urban children: 59% General population: 50%	Ali et al. (2013)
India 2007	**2,4,6-TBP** e-waste recycling workers *n* = 23 Residents near coastal area *n* = 20	Mean (SD), Median (range) Workers: 110 (70), 94 (21–292) pg/g ww Residents: 360 (270), 260 (72–1200) pg/g ww	100%	Eguchi et al. (2012)
Vietnam 2010–2011	**2,4,6-TBP** *n* = 77 adults Workers at an e-waste recycling site *n* = 34 adults residents rural area	Mean, Median (range): Workers: 270, 220 (68–1400) pg/g ww Residents: 220, 200 (100–400) pg/g ww	Residents: 99% Workers: 87%	Eguchi et al. (2015)
China 2011	Blood plasma **2,4,6-TBP** **2,4-DBP** *n* = 116 adults (54 women, 62 men)	Mean (range) **2,4,6-TBP**: Females: 13 (ND–46) pg/g lipid Males: 12 (ND–28) pg/g lipid **2,4-DBP**: Females: 5.2 (ND-17) pg/g lipid Males: 2.0 (ND–5.1) pg/g lipid	**2,4,6-TBP**: • Females: 37% > LOD • Males: 36% > LOD **2,4-DBP**: • Females: 44% > LOD • Males: 16% > LOD	Wang et al. (2012)
Adipose tissue				
USA 2003–2004	**2,4,6-TBP** *n* = 47 adults	Mean (SD), Median: 5.05 (9.74), 0.28 Mean (SD): ≤ 30 years old (*n* = 20): 3.13 (6.12) 30–40 years old (*n* = 18) 5.25 (12.9) > 40 years old (*n* = 9) 8.91 (8.87) Female (*n* = 28): 6.23 (11.6) Male (*n* = 19): 3.31 (6.04)	Detected in 20 out of 47 of the samples analysed (42.5%)	Gao et al. (2015)
Placental tissue				
USA 2010–2011	**2,4,6-TBP** *n* = 102 adults (18–40 years old)	Geometric mean (range): 15.4 (1.31–316)	Detected in 100% of the samples analysed	Leonetti, Butt, Hoffman, Miranda, et al. (2016)
USA 2010–2011	**2,4,6-TBP** *n* = 95 women at 37 or more weeks of gestation	Geometric mean (range): 15.8 (1.31–316.1)	Detected in 100% of the samples analysed	Leonetti, Butt, Hoffman, Hammel, et al. (2016)
Urine				
China 2010	**2,4,6-TBP** **2,4-DPB** *n* = 100 males and females (16–93 years old)	Geometric mean (confidence interval), Range: **2,4,6-TBP-glucoronide**: 0.87 (0.58–1.30), ND–102.21 µg/g creatinine **2,4,6-TBP-sulfate**: 0.10 (0.08–0.13), ND–2.93 µg/g creatinine **2,4-DBP glucuronide**: 0.32 (0.23–0.44), ND–23.81 µg/g creatinine **2,4-DBP-sulfate**: 0.11 (0.08–0.14), ND–2.08 µg/g creatinine	**2,4,6-TBP-glucoronide**: Detected in 68% of the samples analysed **2,4,6-TBP-sulfate**: Detected in 94% of the samples analysed **2,4-DBP glucuronide**: Detected in 71% of the samples analysed **2,4-DBP-sulfate**: Detected in 86% of the samples analysed	Ho et al. (2015)

TABLE C.1 (Continued)

Country year	Number of samples	Concentration (ng/g lipid)	Detection frequency	Reference
China 2017–2018	**2,4,6-TBP** **2,4-DBP** *n* = 94 (*n* = 27 e-waste (EW) workers, *n* = 28 non- EW workers but engaged with other related activities, *n* = 20 adult residents living in the surrounding area, *n* = 19 child (≤ 14 years old) residents living in the surrounding area	Mean (range) **2,4,6-TBP**: EW workers: 2.12 (0.35–7.44) µg/g Creatinine Non-EW workers: 1.69 (0.29–5.94) µg/g creatinine Adults: 1.99 (0.35–6.49) µg/g creatinine Children: 1.85 (0.47–5.26) µg/g creatinine **2,4-DBP**: EW workers: 0.48 (ND-2.20) µg/g creatinine Non-EW workers: 0.24 (ND–1.80) µg/g creatinine Adults: 0.02 (ND–0.22) µg/g creatinine Children: 1.36 (ND–17.0) µg/g creatinine	**2,4,6-TBP**: All groups: 100% **2,4-DBP**: EW workers: 56% Non-EW workers: 54% Adults: 10% Children: 16%	Lin et al. (2023)
China NR	**2,4,6-TBP** **2,4-DBP** **4-BP** *n* = 10	Mean (SD): **2,4,6-TBP**: 2.35 (0.91) µg/g creatinine **2,4-DBP**: 0.66 (0.27) µg/g creatinine **4-BP**: 3.46 (2.35) µg/g creatinine	NR	Feng et al. (2016)
China 2020	**TBBPS** *n* = 241 (121 from Wuxi City, 120 from Taishun County) 3–86 years old Males *n* = 127 Females *n* = 110	Geometric mean: 1.07 ng/mL	0% (concentrations < LOQ were replaced with a value equal to LOQ/√2)	Wei et al. (2022)
China	**TBBPS** *n* = 1157 samples from urban residents Males *n* = 624 Females *n* = 533	< LOD	0% LOD = 0.067 µg/L LOQ = 0.222 µg/L	Huang et al. (2023)
Chile	**2,4,6-TBP** *n* = 27 workers Chain conveyors system: *n* = 12 Packaging *n* = 3 Anti-stain solution preparation and packaging Hydraulic System: *n* = 6 Packaging *n* = 2 Anti-stain solution preparation and labelling of packs Manual system: *n* = 4 Dipping wood and packaging	Average (range): Chain conveyors – Packaging: 5.7 (1.9–12.3) mg/g creatinine Chain conveyors – Anti-stain solution preparation and packaging: 3.5 (2.0–6.3) mg/g creatinine Hydraulic system – packaging 0.2 (0.05–0.4) mg/g creatinine Hydraulic system – anti-stain solution preparation and labelling of packs: 4.4 (2.2–6.6) mg/g creatinine Manual system: 6.9 (4.2–9.9) mg/g creatinine	NR	Gutierrez et al. (2005)[a]
Hair				
China 2017–2018	**2,4,6-TBP** **2,4-DBP** *n* = 94 (27 e-waste (EW) workers, 28 non- EW workers but engaged with other related activities, 20 adult residents living in the surrounding area, 19 child (≤ 14 years old) residents living in the surrounding area)	Mean, Median (range) *Hair Internal* **2,4,6-TBP**: EW workers: 2124, 490 (46.2–41,139) ng/g dw Non-EW workers: 673, 410 (67.4–5906) ng/g dw Adults: 310, 206 (54.3–1493) ng/g dw Children: 165, 151 (38.0–395) ng/g dw **2,4-DBP**: EW workers: 80.6, 36.7 (9.87–870) ng/g dw Non-EW workers: 37.7, 26.7 (4.99–133) ng/g dw	*Hair Internal* **2,4,6-TBP**: All groups: 100% **2,4-DBP**: All groups: 100%, except Children: 89% *Hair external* **2,4,6-TBP**: All groups: 100% **2,4-DBP**: EW workers: 67% Non-EW workers: 75% Adults: 45% Children: 5%	Lin et al. (2023)

(Continues)

TABLE C.1 (Continued)

Country year	Number of samples	Concentration (ng/g lipid)	Detection frequency	Reference
		Adults: 15.2, 9.22 (3.82–56.3) ng/g dw Children: 10.0, 8.02 (ND–27.1) ng/g dw *Hair external* **2,4,6-TBP**: EW workers: 220, 82.9 (2.94–3244) ng/g dw Non-EW workers: 80.4, 37.3 (7.31–543) ng/g dw Adults: 62.4, 32.6 (8.94–613) ng/g dw Children: 13.1, 9.41 (1.28–55.5) ng/g dw **2,4-DBP**: EW workers: 6.59, 2.11 (ND–36.5) ng/g dw Non-EW workers: 4.33, 2.60 (ND–24.3) ng/g dw Adults: 0.95, ND (ND–4.88) ng/g dw Children: 0.08, ND (ND–1.52) ng/g dw		

Abbreviations: LB, lower bound; LOD, limit of detection; LOQ, limit of quantification; ND, not detected; NR, not reported; UB, upper bound.

[a]The studies were not captured in the previous Opinion but they are reported in the current update for completeness.

APPENDIX D

Mode of action studies identified

TABLE D.1 Mode of action studies on **2,4,6-TBP**.

Brominated phenol	Comments	Reference
2,4,6, TBP	*Immunotoxicity* Treatment of the mouse macrophage cell line RAW264.7 with 50–800 μM 2,4,6-TBP for 24h decreased expression of the pro-inflammatory marker Ly6C and resistance to bacterial infection at sub-cytotoxic concentrations. RNA N6-methyladenosine (m6A) methyltransferases and total RNA m6A levels were increased in the cell line and also in freshly isolated mouse peritoneal macrophages and human PBMCs	Qin et al. (2023)
2,4,6, TBP	*Immunotoxicity* Administration to mice via drinking water for 12 weeks (0, 0.5, 10 and 200 μg/L). Some evidence of liver toxicity as described in the in vivo tox section, but not convincing at the doses tested. Changes of the hepatic transcriptome (0.5 μg/L) and serum metabolomic profiles (0.5 μg/L) indicated disturbed immune responses, and changes in glutathione metabolism. Gut microbiome changes (Disrupted Firmicutes/Bacteroidetes (F/B) ratio). Induction of M2-polarised status in macrophages = > immunosuppressive effects and tissue repair	Jiang et al. (2022)
2,4,6-TBP	*Oxidative stress* Cytotoxicity measured by MTS assay in Caco-2 and SH-SY5Y cells showed IC50 values of 215 and 155 μM, respectively. A concentration-related significant increase in ROS was reported in Caco-2 cells starting from 108uM. A significant increase in ROS was reported in SH-SY5Y cells at 15.5 and 38.8 μM, but not at higher concentrations. Study is primarily about combined effects with bromoacetic acid 3,5-dibromo-4-hydroxybenzoic acid and 3,5-dibromo-4-hydroxybenzaldehyde	Liu et al. (2022)
2,4,6-TBP	*Reproductive* A novel in vitro mouse embryo culture system was developed for study of development from pre-implantation to post-implantation. Studies with 2,4,6-TBP at 25, 50 and 100uM indicated concentration-related inhibition of development. Morphological changes in the embryos were associated with apoptosis. Since this is a novel model, and only 2,4,6-TBP was tested, the results cannot be interpreted without verification and testing with other compounds	Zhao et al. (2022)
2,4,6-TBP	*Other – apoptosis* 2,4,6-TBP (25 and 50 μM) was found to induce apoptosis in human peripheral blood mononuclear cells. At lower concentrations, elevation of the cytosolic calcium ion level, depleted the ΔΨm, activated caspase-8, −9, and −3 and PARP-1 cleavage, DNA fragmentation, and chromatin condensation indicated that the mitochondrial pathway was mainly involved, while the receptor pathway was of minor importance	Barańska, Sicińska, et al. (2022)
2,4,6-TBP	*Reproductive* Human extended pluripotent stem (EPS) cells were used to study the developmental toxicity of 2,4,6-TBP. Cytotoxicity was demonstrated at 200–800 μM using a cell counting kit. Morphological changes were observed at 10–200 μM. Also at 10–200 μM ectodermal differentiation of human EPS cells was promoted in an embryoid bodies (EBs) differentiation assay, while both endodermal and mesodermal differentiation were impaired	Liu et al. (2021)
2,4,6-TBP	*Reproductive* 20uM 2,4,6-TBP altered the composition of protein components of exosomes in human placental explants, with inhibition of pathways associated with cell survival, tissue repair and proliferation, as well as activation of cell death pathways	Sheller-Miller et al. (2020)
2,4,6-TBP	*Neurotoxicity, Other* Cytotoxicity measured by MTS assay in Caco-2 and SH-SY5Y cells showed IC50 values of 265 and 155 μM, respectively. Study is primarily about combined effects of various haloaromatic DBPs with lead	Liu et al. (2020)
2,4,6-TBP	*Thyroid function* TBP underwent bioconcentration in zebrafish larvae, but was not toxic up to concentrations of 100 μg/L. Whole-body T4 contents were significantly increased in the larvae at 10 and 100 μg/L. Gene transcription levels in the hypothalamic–pituitary-thyroid (HPT) axis indicated that transcription of corticotrophin-releasing hormone (1–100 μg/L), thyrotropin-releasing hormone (1–100 μg/L) and thyroid-stimulating hormone (0.3–100 μg/L) were down-regulated. The significance of the effects for mammalian systems is unclear	Fu et al. (2020)
2,4,6-TBP	*Immunotoxicity* Human placental explant cultures were treated with 0–40 μM 2,4,6-TBP in the presence and absence of heat-killed *E. coli* and concentrations of various cytokines were measured. No marked effects were observed	Ahmed (2019)
2,4,6-TBP	*Immunotoxicity* 2,4,6-TBP inhibited proliferation of mouse macrophage RAW264.7 cells and decreased the number of surviving cells at ≥ 200 μM. 2,4,6-TBP (200 μM) increased the mRNA level of Arg-1 (by > 5-fold), of IL-6 (by > 5-fold), of TGF-β1 and of IL-10. TBP (200 μM) decreased the transcriptional expression of iNOS (by more than half) and of TNF-α. At protein level, the production of TNF-α and IL-6 decreased, whereas the levels of TGF-β1 and IL-10 showed no significant changes. TBP (200 μM) also induced the expression of M2 marker CD206 (by 28-fold) and M1 marker CD16/32 (by 1.5-fold)	Xie et al. (2019)

(Continues)

TABLE D.1 (Continued)

Brominated phenol	Comments	Reference
2,4,6, TBP	*Other – apoptosis* TBP (0.06 and 6 μM) exhibited low toxicity to murine melanoma B16F1cells. The increase of ABCB5 gene expression positively modulates the cell chemoresistance, but decreased cell migration and proliferation	de De Souza Salgado et al. (2018)
2,4,6-TBP	*Thyroid function* The effect of 2,4,6-TBP on the activity of thyroid hormone (TH) sulfotransferases (SULTs) was investigated in a choriocarcinoma placenta cell line (BeWo). 2,4,6-TBP was a potent inhibitor of basal 3,3′-T2 SULT activity with Km = 1.46 ± 0.20 μM and Vmax = 2.29 ± 0.15 pmol T2S/mg protein/min in BeWo cells (Km for the 3,3′-T2 sulfation reaction in control BeWo cell homogenates was 0.61 ± 0.10 μM and Vmax was 2.29 ± 0.15 pM). Vmax for TBP was lower than for controls, while Km for TBP was higher than for controls, suggesting mixed-type inhibition (competitive & non-competitive). Basal 3,3′-T2 SULT activity decreased at all exposure durations reaching 86% reduction after 24 h of exposure. 2,4,6-TBP had no effect on the levels of T4, T3, rT3, or 3,3′-T2 (data not shown) or on expression of SULT1A1, TRα, TRβ (data not shown)	Leonetti et al. (2018)
2,4,6-TBP	*Thyroid function* The binding affinity of 2,4,6-TBP for the human and zebrafish thyroid receptor beta (TRβ) were compared with those for other brominated phenols. The binding affinity was similar in both human and zebrafish models (c. 31uM). Study aimed to be comparative and is not very informative for MOA of 2,4,6-TBP	Kollitz et al. (2018)
2,4,6-TBP	*Genotoxicity* Authors assert that 2,6-dibromohydroquinone (2,6-DBrHQ) is a metabolite of 2,4,6-TBP, although the evidence for this is unclear. Study reports synergistic effects of 2,6-DBrHQ and Cu(II) in inducing DNA damage. Relevance for 2,4,6-TBP is unclear	Shao et al. (2017)
2,4,6-TBP	*Thyroid function* In juvenile mice dosing sc with 0, 40, 250 mg/kg bw per day 2,4,6-TBP for 20 days (at which effects on thyroid hormones were demonstrated) resulted in decreased deiodinase 1 (*Dio1*) and thyroid hormone receptor isoform 2 (*Thrβ2*) mRNA in the pituitary gland. Deiodinase 2 (*Dio2*) and growth hormone (*Gh*) mRNA were increased. In the liver, 2,4,6-TBP had no effect on *Dio1* and *Thrβ1* expression	Lee et al. (2016)
2,4,6-TBP	*Reproductive* 2,4,6-TBP decreased the transcriptional activity of both human oestrogen and androgen receptors with IC50 values of 3.9–14.1 μM, depending on the assay (two reporter gene assays were used)	Ezechiáš et al. (2012)
2,4,6-TBP	*Thyroid function* 2,4,6-TBP inhibited deiodinase (DI) activity in human liver microsomes at μM concentrations	Butt et al. (2011)
2,4,6-TBP	*Reproductive* Plasma testosterone and oestradiol levels were increased and transcription of steroidogenic genes in brain and testes were upregulated by 0.3 μg/L 2,4,6-TBP in male zebrafish. In females, plasma testosterone and oestradiol levels were decreased and steroidogenic genes in brain and ovary were downregulated. Vitellogenic gene transcription in the liver was upregulated in males and downregulated in females. The male/female ratio of offspring was increased, together with increased malformation, reduced survival and retarded growth	Deng et al. (2010)
2,4,6-TBP	*Oxidative stress* Exposure of human peripheral blood mononuclear cells (PBMCs) for 24 h to 2,4,6-TBP (50–100 μg/mL) decreased ATP levels and cell viability. At lower concentrations lipid peroxidation (1–20 μg/mL) and protein damage (0.01–20 μg/ML were seen, however the latter was not concentration related	Włuka et al. (2020)
	The effect of 2,4,6-TBP was studied in vivo and *ex vivo* on two blood–brain barrier transporters, i.e. P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Exposure of brain capillaries isolated from male and female rats for 3 h decreased male P-gp transport activity at 1–100 pM and female P-gp transport activity at 1–100 nM. Similar effects were observed with mouse tissue to rat. Effects were also similar in tissue from wild type and ER-α knock-out mice, indicating against a role for ER-α signalling. In male tissue, transport decrease was maximal at 1h and recovered to basal level if the 2,4,6-TBP was removed. Studies on verapamil-induced ATPase activity indicated that the 2,4,6-TBP did not interact directly with P-gp, but might be due to dysregulation of signalling pathways. When male and female rats were dosed once with TBP at 0.132, 0.331 or 1.654 mg/kg bw followed 4h later by isolation of brain capillaries, P-gp transport in the capillaries was decreased at the lowest dose, but unchanged at the higher two doses. 2,4,6-TBP had no effect on MRP2 activity	Trexler et al. (2019)

TABLE D.2 Mode of action studies on **TBBPS**.

(Continues)

Brominated phenol	Comments	Reference
TBBPS	*Cardio-vascular* Exposure of human umbilical vein endothelial cells (HUVECs) to 0.01 or 1 μM (but not 0.1 μM) TBBPS attenuated T3-induced nitric oxide increase. Exposure of male mice for 28 days to TBBPS by oral gavage resulted in a dose-dependent decrease of serum nitric oxide levels, which was significant at the highest dose, 20 mg/kg BW per day (only lower doses tested in females). The same dose increased the endothelium thickness in males. There was a dose-dependent reduction in mRNA for eNOS in aorta endothelium, which was significant at the lowest dose (0.002 mg/kg BW per day). No dose-dependent effects on eNOS mRNA were observed in males. Treatment of HUVECs with 1 μM TBBPS decreased activating phosphorylation of nNOS (p-eNOS Ser^{1177}) both in the presence and absence of T3	Hu et al. (2024)
TBBPS	*Corticosteroid metabolism* The IC50 of TBBPS for 11β-hydroxysteroid dehydrogenase 1 was tested in rat liver microsomes and was found to be > 100 μM	Wang et al. (2024)
TBBPS	*Lipid metabolism, obesogenic effects* Exposure to 0.1 μM of TBBPS for 8 days promoted adipogenesis of mouse 3T3-L1 preadipocytes. Multivariate analysis of non-targeted metabolomics data revealed increases in glycerophospholipids, sphingolipids and steroids relative levels in 3T3-L1 cells exposed to TBBPS at the final stage of preadipocyte differentiation	Yu et al. (2024)
TBBPS	*Sex steroid metabolism* TBBPS did not inhibit CYP19A1 in rat placental microsomes up to a concentration of 100 μM.	Zheng et al. (2024)
TBBPS	*Angiogenic potential* The angiogenic potential of TBBPS and the underlying mechanism were investigated using human umbilical vein endothelial cells (HUVECs). Tube length and microvessel sprouting were significantly inhibited by 37.2% after exposure to 1 μM TBBPS. TBBPS inhibited the interaction between phosphatidylinositol 3-kinase (PI3K) and thyroid receptor (TR). Exposure of HUVECs dose-dependently decreased mRNA for ESR1 and VEGFR with significant reduction observed at 0.02 μM and higher concentrations	Lu et al. (2023)
TBBPS	*Thyroid function* Downregulation of protein expression (TSHR, NIS, TPO) at 0.02 mg/kg bw per day and at 20 mg/kg bw per day in mouse. Downregulation of protein expression of TG at 20 mg/kg bw per day in mouse	Hu et al. (2023)
TBBPS	*Circadian rhythm* Embryo-larval exposure of zebrafish to TBBPS at 0, 0.4, 0.6 or 1.2 mg/L (0, 0.68, 1.02, and 2.04 μM) resulting in internal concentrations of 0, 2, 4.9, and 12.3 μg/g tissue, respectively. Heart rate and body length were dose-dependently reduced 48-120hpf with significance at all concentration. All concentrations resulted in aberrations in circadian rhythm activity 120 hpf and this was associated with changed expression of genes and proteins (Cry2 and Per3) involved in the circadian rhythm network	Ding et al. (2022)
TBBPS	*Metabolism – phospholipids, energy metabolism, fatty acid metabolism* Untargeted metabolomics was carried out to study the metabolic perturbations in HepG2 cells exposed to TBBPS and other halogenated bisphenols. There were perturbations in glycerophospholipid and fatty acyl levels in HepG2 cells upon exposure to 0.1 or 1 μM TBBPS. Expression of genes involved in glycerophospholipid metabolism were measured and the results suggest that the increases in glucose-1P and fructose-6P levels by TBBPS were caused by the promotion of upstream gene expression and the inhibition of downstream gene expression	Yu et al. (2022)
TBBPS	*Neural effects; immune response; wnt signalling* Human embryonic stem cells were differentiated into retinal organoids and used to assess effects of TBA, TBBPA and TBBPS. The retinal organoids were exposed to 10 nM TBBPS or 0.1% DMSO (vehicle control) from day 18 (first time point where neural retina structures can be identified) until day 81 of the induction process. After 3-week exposure, the area of retinal organoids was decreased in the TBBPS-exposed group compared to the DMSO control. After 3 weeks of exposure, the organoids were analysed for transcriptomics changes by RNA-seq. 1696 differentially expressed genes were identified in the TBBPS-treated group. Differentially expressed genes following TBBPS exposure were highly enriched for Gene Ontology annotations associated to Cytokine-cytokine receptor interaction, TNF signalling, IL- 17 signalling, Wnt signalling	Li et al. (2022)
TBBPS	*Apoptosis* Human peripheral mononuclear cells (PBMCs) were exposed in vitro to TBBPS concentrations ranging from 0.01 to 50 mg/L. Apoptosis in TBBPS exposed PBMCs was assessed by measuring phosphatidylserine externalisation at the plasma membrane, cytosolic calcium ion concentration, transmembrane mitochondrial potentials, caspase-8, –9 and –3 activation, PARP-1 cleavage, DNA fragmentation and chromatin condensation. The number of apoptotic PBMCs increased dose-dependently and was significantly increased after exposure to 5 mg/L and above. The most sensitive marker of apoptosis was cytosolic [Ca^{2+}] which was elevated at TBBPS concentrations of 0.1 mg/L and above. TBBPA triggers apoptosis primarily through the mitochondrial pathway	Barańska, Bukowska, et al. (2022)

(Continues)

TABLE D.2 (Continued)

Brominated phenol	Comments	Reference
TBBPS	*Liver, development* A human embryonic stem cell hepatic differentiation-based system was used together with transcriptomics analysis to investigate the effects of TBBPS on hepatic differentiation. Cells were exposed to 10 nM TBBPS during the 12-day differentiation process and analysed for transcriptomics profiles on days 0, 4 and 12. Gene Set Enrichment Analysis (GSEA) showed that TBBPS promoted the expression of neural-related genes at day 4, possibly via inhibiting apelin signalling, and proliferative genes at day 12 possibly by up-regulating the Fibroblast growth factor 10 (FGF10) pathway. GSEA also showed enrichment of 'lung-related' genes potentially also as a result of the up-regulation of FGF10 signalling	Yang et al. (2021)
TBBPS	*Red blood cells* TBBPS caused increases in the fluidity of the erythrocyte membrane in their hydrophilic layer, and conformational changes to membrane proteins. TBBPS also caused thiol group elevation, an increase in lipid peroxidation and reduced in the level of ATP in cells. The most sensitive endpoint related to membrane fluidity which was increased after 48-h exposure to 10 mg/L TBBPS	Jarosiewicz et al. (2021)
TBBPS	*Cytotoxicity* Cytotoxicity of 27 compounds, including four mono-substituted TBBPS derivates synthesised in-house, were screened using three different mammalian cell lines (HepG2, mouse primary astrocytes and Chang liver cells). The 24-h IC50 for one of the TBBPS-derivatives, using the formazan dye method, ranged from 333 to 1593 μM with HepG2 cells being the most sensitive	Guo et al. (2020)
TBBPS	*Nervous system* A human neural stem cell (hNSC)-based system to assess the developmental neurotoxic effects of TBBPS and other brominated flame retardants. TBBPS decreased expression of mRNA for hNSC identity markers SOX2, SOX3 and NES, at concentrations ranging from 1 to 100 nM, without effects on cell viability or proliferation. Further experiment indicated that the effects were mediated in part by modulating glycogen synthase kinase 3 beta (GSK3β) signalling and the NOTCH pathway. hNSC differentiation may also be mediated by altering triiodothyronine (T3) cellular signalling as indicated by dose-dependent (10–100 nM TBBPS; no effect at 1 nM) increased *SOX3* expression in the presence of 3 nM T3	Liang, Liang, Zhou, et al. (2019)
TBBPS	*Nervous system; development* Potentially toxic effects of TBBPA and other halogenated flame retardants on the developing central nervous system were investigated in vitro using induced human embryonic stem cells (ESC). The ESC were differentiated into neural ectoderm in the presence of 1 or 5 μM TBBPS and five other halogenated flame retardants (BDE-47, BDE-209, TBBPA, and TCBPA), individually or in combination. Transcriptome analysis (RNAseq with follow-up qRT-PCR) was used to identify biological processes that were affected by these chemicals. The most significantly enriched Gene Ontology terms in the set of differentially regulated genes related to 'neural system development', 'neuron differentiation', 'neuron migration' Wnt signalling, and positive regulation of transcripts from genes with 'RNA-polymerase II promoter'. Transcripts for transcription factors of importance for neural development, such as ZIC1, ZIC3, HES3, IGFBP3 and DLX5, were evaluated in follow-up experiments and found to be dysregulated by TBBPS with significance apparent at 10 nM. In addition, TBBOS might influence axon growth/guidance and neuron transmission-related processes, as evidenced by dysregulating genes for CNTN2, SLIT1, LRRC4C, RELN, CBLN1, CHRNB4 and GDF7	Liang, Liang, Yin, et al. (2019)
TBBPS	*Thyroid function* Interactions between TBBPS and six other structurally related compounds and the Thyroid hormone Receptor β (TRβ) was investigated. TBBPS showed dose-dependent binding to the ligand binding domain of TRβ (1.5 μM; through fluorescence quenching) in the TBBPS concentration range of 1 to 20 μM. Molecular Docking and Molecular Dynamics simulations were implemented to model binding of TBBPS to the ligand binding domain of TRβ and the decomposition of Binding Free Energy, ΔG_{calc}, was determined to −42.28 kcal/mol. A two-hybrid yeast assay for TRβ showed that under the experimental conditions TBBPS has antagonistic activity toward TRβ, with an IC10 of 10.1 nM in the presence of 100 μM T3. The *TRβ* gene was upregulated in zebrafish larvae at TBBPS concentrations of 0.01 and 1 μM but the effect did not show monotonic dose–response as no effect was observed at 0.1 μM TBBPS	Lu et al. (2018)
TBBPS	*Neurodevelopment* A mouse embryonic stem cell (mESC) system was used as an in vitro model to evaluate developmental neurotoxicity of TBBPS, TBBPA and TCBPA. The 72-h IC50 of cell viability (formazan dye method) for TBBPS was 172 μM. TBBPS concentrations of 100 μM and higher stimulated formation of reactive oxygen species. Influence of expression of genes of importance for neurodifferentiation (*Pax6*, *Sox1, Sox3, Map2,* and *NeuroD*) was measured and these were upregulated by non-cytotoxic concentrations of TBBPS (1–100 nM) but the dose–response was unclear. TBBPS inhibited Wnt signalling which is a negative regulator of cell differentiation. Overall, the data suggest that in the mESC system TBBPS has the potential to stimulate neural differentiation	Yin et al. (2018)

TABLE D.2 (Continued)

Brominated phenol	Comments	Reference
TBBPS	*Oestrogenicity* The oestrogenic potency of 14 selected bisphenol analogues were investigated with in vitro and in silico methods. TBBPS showed very low cell proliferation stimulation in human adenocarcinoma-derived MCF-1 cells (E-screen) with a proliferation effect relative to oestrogen of 15% at the highest concentrations of TBBPS tested (10 μM). TBBPS did not activate the oestrogen receptor on a reporter gene assay	Cao et al. (2017)
TBBPS	*Binding to trypsin* An integrated approach to study interactions between contaminant chemicals and proteins was developed using physicochemical and computations tools. Binding of TBBPS (and TBBPA) to bovine trypsin was investigated using fluorescence spectroscopy, circular dichroism and Molecular Dynamics computer simulations. TBBPS bind at the 8-anilinonaphthalene-1-sulfonate (ANS) binding site with an association constant of 2.41×10^4 M^{-1} at 298 K. The binding of TBBPS was dominated by electrostatic interactions	Ding et al. (2015)
TBBPS	*Oxidative stress* Exposure of human peripheral blood mononuclear cells (PBMCs) for 24 h to TBBPS (100 μg/mL) decreased ATP levels and cell viability. At lower concentrations, lipid peroxidation (0.1–20 μg/mL) and protein damage (0.01–20 μg/ML were seen; however, the latter was not concentration related	Włuka et al. (2020)
TBBPS	*Liver, inflammation, oxidative stress* Exposure to TBBPS resulted in a significant dose-dependent attenuation of the proliferative capacity of THLE-2 and AML12 cells derived from liver of human and mouse, respectively, with significant reduction at concentrations of 10 μg/mL and higher. TBBPS (10–60 μg/mL) increased expression of inflammatory mediators, such as TNFα, IL-1β and IL-6. TBBPS induced necroptosis through reactive oxygen species formation, and expression of RIP3 and pMLKL. It also suppressed mitochondrial autophagy at all concentrations tested (10–60 μg/mL) mediated by the PINK1-PARKIN signalling pathway	Yin et al. (2024)

TABLE D.3 Mode of action study on other brominated phenols included in the TORs.

Brominated phenol	Comments	Reference
4-BP	*Oxidative stress* Female ICR mice were exposed by gavage for 28 days to 0, 1, 10 or 100 mg 4-BP/kg bw per day. The oxidant/antioxidant responses in liver were measured. There was a decrease in SOD activity at 10 mg/kg bw per day, CAT activity at 100 mg/kg bw per day and MDA level was lower at all doses	Shi et al. (2013)
4-BP	*Other* Dehaloperoxidase-haemoglobin A (DHP A) is a haemoglobin that oxidises a variety of substituted phenols in the presence of H_2O_2. Despite this, 4-BP inhibits DHP A. K_i decreased from 2.56 to 0.15 mM at temperatures from 283 to 298 K, allowing calculations of the enthalpy and entropy for inhibitor binding as -135.5 ± 20.9 kJ/mol and 526.1 ± 71.9 J/(mol·K), respectively	Zhao and Franzen (2013)
4-BP	*Liver* ^{14}C-4-BP was found to bind to liver proteins following ip injection of the substance in Sprague–Dawley rats. Four animals were injected with [14C]-4BP (8.05 mCi/mmol, 1 mmol/kg, ip) in corn oil (2.4 mL/kg). Five hours after injection, the animals were killed. The liver proteins were involved in maturation or stabilisation, enzymes of intermediary metabolism, proteins involved in electrophile or peroxide defence mechanisms and albumin. Cultured rat hepatocytes metabolised 4-BP to sulfate and glucuronide conjugates as well as a quinone-derived glutathione conjugate	Koen et al. (2012)
2,4-DBP	*Other* 2,4,-DBP was found to bind spontaneously to purified human Hb and to inhibit its esterase activity in cell-free systems. The authors considered this may have implications for human health, but it is unknown whether such reactions could occur with HB or other proteins in vivo	Sharma et al. (2023)
2,4,6-TBP **2,6-DBP**	*Reproductive effects and oxidative stress* EC50 values for cytotoxicity to 2,4,6-TBP and 2,6-DBP in HepG2 cells were approximately 0.25 mM and 1.2 mM, respectively. 2,4,6-TBP and 2,6-DBP exhibited weak oestrogenic and antiandrogenic activity in MDA-kb2 cells or a MCE-7-derived cell line (MVLN) and induced ROS in HepG2 cells. Transcriptome analysis showed that the most significantly differentially expressed genes at the EC20 were involved in antioxidant, immune and endocrine associated systems. A weighted gene correlation network analysis (WGCNA) indicated that the MAPK signalling pathway played a role in the cytotoxicity and anti-androgenic effects	Li, Song, et al. (2023)

(Continues)

TABLE D.3 (Continued)

Brominated phenol	Comments	Reference
2,4,6-TBP **2,4-DBP** **TBBPS**	*Oxidative stress* TBBPS, 2,4-DBP and 2,4,6-TBP induced ROS formation in human erythrocytes at µg/mL concentrations but with no clear concentration-dependency. Apoptosis was demonstrated by increased phosphatidyl choline externailsation and caspase-3 activation. Calcium ions and calpain did not play a significant role	Jarosiewicz, Michałowicz, et al. (2019)
2,4,6-TBP **2,4-DBP** **TBBPS**	*Oxidative stress* TBBPS, 2,4-DBP and 2,4,6-TBP decreased antioxidant enzymes (SOD, CAT and GSH-Px) and GSH in human erythrocytes at µg/mL concentrations	Jarosiewicz, Krokosz, et al. (2019)
2,4,6-TBP **2,4-DBP** **TBBPS**	*Other* TBBPS, 2,4-DBP and 2,4,6-TBP induced haemolysis and methemoglobin formation in human erythrocytes at µg/mL concentrations	Jarosiewicz et al. (2017)

APPENDIX E

Occurrence of brominated phenols in food and dietary exposure assessment reported in the literature since the previous Opinion

TABLE E.1 Literature data on occurrence of Brominated phenols and their derivatives included in the current assessment in food samples from European countries.

Country	Year	Food matrices analysed	Food matrices BPs detected (detection frequency)	Mean (range)	Exposure estimates	Reference
General food categories						
Belgium	2015–2016	**Food samples** *N* = 183 'Fish and fish products' (*n* = 61 including fish, crustaceans and molluscs), 'Meat and meat products' (*n* = 35), 'Milk and dairy products' (*n* = 38, including liquid milk, desserts and cheese), 'Food for infants and small children' (*n* = 18), 'Animal and vegetable fat' (*n* = 9), 'Grains and grain-based products' (*n* = 7), 'Eggs and egg products' (*n* = 4), 'Potatoes and derived products' (*n* = 4), 'Other food' (stock: *n* = 4, food supplements: *n* = 1; vegetables: *n* = 2)	**2,6-DBP**: ND **TBBPS**: ND **2,4,6-TBP** Cheese and other dairy products (6/25) Baby food (1/18) Oils (4/4) Fish (25/51) Molluscs and crustaceans (8/10) Grains (1/7) Potatoes (1/4) Meat stock (2/4) Spinach (1/1) Meat (4/69) **2,4-DBP** Cheese and other dairy products (1/25) Fish (13/51) Molluscs and crustaceans (6/10) **4-BP** Fish (17/51) Molluscs and crustaceans (6/10) Meat (4/69)	LOQ: 500–10,000 pg/g ww LOQ: 150–1800 pg/g ww < 10 (LOQ)–289 pg/g ww < 5 (LOQ)–27 pg/g ww 227–318 pg/g ww < 5 (LOQ)–946 pg/g ww < 4 (LOQ)–4216 pg/g ww < 10 (LOQ)–175 pg/g ww < 10 (LOQ)–156 pg/g ww < 50 (LOQ)–98 pg/g ww 24 pg/g ww < 50 (LOQ)–83 pg/g ww < 65 (LOQ)–373 pg/g ww < 15 (LOQ)–4637 pg/g ww < 45 (LOQ)–8259 pg/g ww < 75 (LOQ)–21,042 pg/g ww < 75 (LOQ)–22,915 pg/g ww < 215 (LOQ)–710 pg/g ww	No exposure assessment	Poma et al. (2018)
Belgium	NR	*N* = 24 Fish (6), meat (7), chicken eggs (2), cow milk (2), baby food (3), oils (2), cheese (1), vegetables (1)	**2,4-DBP**: ND **2,6-DBP**: ND **TBBPS**: ND **2,4,6-TBP**: ND **4-BP** Chicken egg (2/2) Salmon (2/2)	LOQ: 15–600 pg/g ww LOQ: 320–10,000 pg/g ww LOQ: 150–1800 pg/g ww LOQ: 10–200 pg/g ww 194–243 pg/g ww 260–305 pg/g ww	No exposure assessment	Malysheva et al. (2018)

(Continues)

TABLE E.1 (Continued)

Country	Year	Food matrices analysed	Food matrices BPs detected (detection frequency)	Mean (range)	Exposure estimates	Reference
Ireland	2015	**Food samples** Milk (12 samples), eggs (yolk only, 12 samples), fish (10 samples), carcass fat taken from cattle, pigs, lambs and chickens (12 samples in total), and liver (bovine, porcine, ovine, equine and avian, 7 samples in total) *N* = 53	**4-BP** Egg(12/12) Milk (0/12) Carcass fat (0/12) Offal (0/7) Fish oily (0/6) Fish white (2/4) **2,4-DBP** Egg (0/12) Milk (0/12) Carcass fat (0/12) Offal (0/7) Fish oily (0/6) Fish white (2/4) **2,6-DBP** Egg (0/12) Milk (0/12) Carcass fat (0/12) Offal (0/6) Fish (0/10) **2,4,6-TBP** Egg (0/12) Milk (0/12) Carcass fat (0/12) Offal (0/7) Fish (0/10) **TBBPS** Milk (0/7) Carcass fat (0/11) Fish white (0/1)	0.28–0.63 µg/kg ww LOQ: 0.02 µg/kg ww LOQ: 0.06–0.44 µg/kg ww LOQ: 0.03–0.21 µg/kg ww LOQ: 0.34–1.05 µg/kg ww < 0.1 (LOQ)-0.91 µg/kg ww LOQ: 0.24–0.98 µg/kg ww LOQ: 0.01–0.04 µg/kg ww LOQ: 0.22–2.4 µg/kg ww LOQ: 0.08–0.27 µg/kg ww LOQ: 0.88–1.7 µg/kg ww < 0.09 (LOQ)–0.98 µg/kg ww LOQ: 0.83–4 µg/kg ww LOQ: 0.1–0.29 µg/kg ww LOQ: 1.2–6.9 µg/kg ww LOQ: 0.39–1.3 µg/kg ww LOQ: 0.8–1.9 µg/kg ww LOQ: 0.45–2.6 µg/kg ww LOQ: 0.01–0.03 µg/kg ww LOQ: 0.05–0.21 µg/kg ww LOQ: 0.05–0.21 µg/kg ww LOQ: 0.03–0.44 µg/kg ww LOQ: 0.03–0.24 µg/kg ww LOQ: 0.09–0.71 µg/kg ww LOQ: 0.42 µg/kg ww	No exposure assessment	Garcia Lopez et al. (2018)
UK, Ireland, Germany, USA	NR	*N* = 20 Whiskies	**2,4-DBP** (3/20) **2,6-DBP** (12/20) **2,4,6-TBP** (2/20)	< 0.010 (LOQ)–44 ng/L < 0.010 (LOQ)–398 ng/L < 0.010 (LOQ)–112 ng/L	No exposure assessment	Bendig et al. (2014)

TABLE E.1 (Continued)

Country	Year	Food matrices analysed	Food matrices BPs detected (detection frequency)	Mean (range)	Exposure estimates	Reference
Fish and seafood						
Europe Italy, Spain, Portugal, Greece, Denmark, the Netherlands, France, Ireland, India 10 species from the Mediterranean Sea, the North Sea and the north-east Atlantic Ocean, including 3 samples imported from the Pacific Ocean (cod and tuna) and one from India (shrimp)	2014–2015	**Fish and seafood (mainly marine)** *N* = 42 Cod (3), Mackerel (11), Monkfish (4), Mussel (10), Nile perch (1), Plaice (1), Salmon (3), Seabream (2), Shrimp (1), Tuna (6)	**2,4,6-TBP** Mussels (10/10) Plaice (1/1)	99.1 (38.9–176) ng/g lipid; fat 0.03%–2.89% 23.6 ng/g lipid; fat 2.35%	No exposure assessment	Aznar-Alemany et al. (2017)
Sweden two sites (Askö and Ängskärsklubb) in the Baltic Sea	2012	Baltic herring *N* = 24 (12 per site)	**Sum 2,4-DBP and 2,4,6-TBP**	Southern Bothnian Sea, Ängskärsklubb: GM 9.6 ng/g lipid (0.71 ng/g ww) Northern Baltic Proper, Askö: GM 4.3 ng/g lipid (0.23 ng/g ww)	No exposure assessment	Dahlberg et al. (2016)
Czech Republic	NR	*N* = 5 bivalve (from Spain and Denmark) *N* = 32 fish (from European and non-European countries, wild and from aquaculture)	**2,4-DBP** Blue mussels (3/4) **2,4,6-TBP** Blue mussels (3/4)	19.6–43.5 µg/kg ww 2.3–7.5 µg/kg ww	No exposure assessment	Lankova et al. (2013)

Abbreviations: 2,4,6-TBP, 2,4,6-tribromophenol; 2,4-DBP, 2,4-dibromophenol; 2,6-DBP, 2,6-dibromophenol; 4-BP, 4-bromophenol; ND, not detected; NR, not reported; TBBPS, tetrabromobisphenol S.

TABLE E.2 Literature data on occurrence of brominated phenol and their derivatives included in the current assessment in food samples from non-European countries.

Country	Year	Food matrices analysed	Food matrices BPs detected (detection frequency)	Mean (range)	Exposure estimates	Reference
General food categories						
Japan	2017	**Infant food** Whole-day meals of infants (rice, cereals, potatoes, beans, nuts and seeds, vegetables, vegetable juices, fruits, fruit juices, mushrooms, seaweed, seafood, meat, eggs, milk, confectioneries, beverages, liquids) (7–24-months old) *N* = 46	**2,4,6-TBP** Edible seaweed (4/4)	5.5 ± 6.6 ng/g ww	46 duplicate-diet from 46 families (one duplicate-diet per family) Median 2,4,6-TBP intake 3.5 ng per day (0.33–109 ng/day) **For seaweed** *Consumption*: average intake of seaweed was 1.2 ± 1.9 g per day in this study *Exposure scenarios*: seaweed consumption constant throughout the year and 2,4,6-TBP concentration varied day-by-day P95 estimate: 30 ng per day Seaweed consumption and 2,4,6-TBP concentration constant throughout the year P95 estimate: 45 ng per day	Fujii et al. (2021)
Fish and seafood						
South Korea	2022	**Fish and seafood (freshwater)** Crucian carp *N* = 40	**2,4,6-TBP** Crucian carp muscle tissue (0/40) **2,4-DBP** Crucian carp muscle tissue (0/40)	ND LOD: 1.34 ng/g ww ND LOD 1.43 ng/g ww	No exposure assessment	Kim et al. (2023)
Tunisia (Bizerte lagoon)	2018	Fish and seafood [8 species (3 fish, 5 shellfish (1 crustacean and 4 molluscs))] *N* = 24 [each species, three pools of 3 to 60 individual samples]	**Fish** European eel (*Anguilla anguilla*) Seabass (*Dicentrarchus labrax*) Common sole (*Solea solea*) **Crustacean** Shrimp (*Penaeus notialis*) **Mollusc** Marine mussel (*Mytilus galloprovincialis*) Clam (*Ruditapes decussatus*) Banded murex (*Hexaplex trunculus*) Common cuttlefish (*Sepia officinalis*)	**4-BP**: < LOQ **2,4-DBP**: 0.02 (< LOQ-0.07) ng/g ww **2,6-DBP**: < LOQ **2,4,6-TBP**: 0.01 (< LOQ-0.04) ng/g ww **4-BP**: < LOQ **2,4-DBP**: < LOQ **2,6-DBP**: < LOQ **2,4,6-TBP**: < LOQ **4-BP**: < LOQ **2,4-DBP**: < LOQ **2,6-DBP**: < LOQ **2,4,6-TBP**: < LOQ **4-BP**: < LOQ **2,4-DBP**: 0.11 (< LOQ-0.24) ng/g ww	No exposure assessment	Mahfoudhi et al. (2023)

TABLE E.2 (Continued)

Country	Year	Food matrices analysed	Food matrices BPs detected (detection frequency)	Mean (range)	Exposure estimates	Reference
Tunisia (Bizerte lagoon)	2018	Fish and seafood [8 species (3 fish, 5 shellfish (1 crustacean and 4 molluscs))] *N* = 24 [each species, three pools of 3 to 60 individual samples]	**Fish** European eel (*Anguilla anguilla*) Seabass (*Dicentrarchus labrax*) Common sole (*Solea solea*) **Crustacean** Shrimp (*Penaeus notialis*) **Mollusc** Marine mussel (*Mytilus galloprovincialis*) Clam (*Ruditapes decussatus*) Banded murex (*Hexaplex trunculus*) Common cuttlefish (*Sepia officinalis*)	**2,6-DBP**: < LOQ **2,4,6-TBP**: 0.01 (< LOQ-0.03) ng/g ww **4-BP**: 8.40 (< LOQ-14.1) ng/g ww **2,4-DBP**: 2.71 (1.28–4.05) ng/g ww **2,6-DBP**: < LOQ **2,4,6-TBP**: < LOQ **4-BP**: 1.78 (< LOQ-5.35) ng/g ww **2,4-DBP**: 6.91 (5.35–8.3) ng/g ww **2,6-DBP**: < LOQ **2,4,6-TBP**: 2.51 (0.54–5.98) ng/g ww **4-BP**: 7.57 (< LOQ-22.7) ng/g ww **2,4-DBP**: 176 (12.1–422) ng/g ww **2,6-DBP**: < LOQ **2,4,6-TBP**: 18.67 (1.42–31.3) ng/g ww **4-BP**: 0.10 (< LOQ-0.29) ng/g ww **2,4-DBP**: < LOQ **2,6-DBP**: < LOQ **2,4,6-TBP**: < LOQ LOQs **4-BP**: 0.25 ng/g ww **2,4-DBP**: 0.07 ng/g ww **2,6-DBP**: 1 ng/g ww **2,4,6-TBP**: 0.03 ng/g ww	No exposure assessment	Mahfoudhi et al. (2023)
South Africa	2017	Chokka squids (*Loligo reynaudii*) *N* = 21 Seven (site A), nine (site B) and five (site C) squid samples	**2,4,6-TBP** Chokka squids Site A Chokka squids Site B Chokka squids Site C **2,4-DBP** Chokka squids Site A Chokka squids Site B Chokka squids Site C **2,6-DBP** Chokka squids Site A Chokka squids Site B Chokka squids Site C	13 (1.7–30) ng/g lw 18 (2.0–29) ng/g lw 28 (13–47) ng/g lw 0.7 (< LOD–1.8) ng/g lw 4.0 (1.6–6.2) ng/g lw 1.8 (1.1–2.6) ng/g lw LOQ: 0.13 ng/g lw ND ND 0.16 (< LOD–0.73) ng/g lw LOQ: 0.08 ng/g lw	No exposure assessment	Wu et al. (2019)

(Continues)

TABLE E.2 (Continued)

Country	Year	Food matrices analysed	Food matrices BPs detected (detection frequency)	Mean (range)	Exposure estimates	Reference
Brasil	2015–2016	37 *Micropogonias furnieri* (whitemouth croaker) 39 *Sardinella brasiliensis* (sardines) 25 *Mugil liza* (mullet) from 2 sites *N* = 101	**Guanabara Bay** Sardines (1/20) Whitemouth croaker (0/19) Mullet (1/16) Sardines (8/20) Whitemouth croaker (10/19) Mullet (11/16) **Ilha Grande Bay** Sardines (0/19) Whitemouth croaker (0/18) Mullet (0/9) Sardines (3/19) Whitemouth croaker (10/18) Mullet (7/9)	**2,4-DBP**: 2.8 (ND–2.8) ng/g lw ND 11 (ND–11) ng/g lw **2,4,6-TBP**: 1 (ND–4) ng/g lw 3 (ND–7) ng/g lw 2 (ND–6) ng/g lw **2,4-DBP**: ND ND ND **2,4,6-TBP**: 2 (ND–4) ng/g lw 6 (ND–23) ng/g lw 1 (ND–2) ng/g lw	No exposure assessment	Estrella et al. (2018)

Abbreviations: 2,4,6-TBP, 2,4,6-tribromophenol; 2,4-DBP, 2,4-dibromophenol; 2,6-DBP, 2,6-dibromophenol; 4-BP, 4-bromophenol; ND, not detected.

APPENDIX F

Identification of sources of uncertainty

A systematic approach was used to identify sources of uncertainty affecting the assessment of **2,4,6-TBP**. This was restricted to the risk assessment for the general population. Due to the limited occurrence data for human milk and infant formula, no exposure or risk assessment and hence no uncertainty analysis was performed for exposure of breastfed and formula-fed infants (see Sections 3.1.1.3 and 3.3.1.3).

A previously prepared list of sources of uncertainty commonly encountered in risk assessments of the CONTAM Panel was reviewed to identify and describe those sources that applied to the present assessment. In addition, the Panel considered each part of the present assessment in turn to identify any additional sources of uncertainty, beyond those in the existing list. Subsequently, the Panel considered which of those sources of uncertainty would have most impact on the outcome of the exposure assessment, and of the hazard identification and characterisation.

A complete list of the sources of uncertainty identified is presented in Tables F.1–F.3. The most important uncertainties are listed together with a qualitative evaluation of their potential impact on the assessment in four categories: negligible, low, medium and high. These qualitative ratings were used later in the analysis to prioritise consideration of the main sources of uncertainty and to facilitate the assessment of overall uncertainty.

TABLE F.1 Uncertainties identified and their impact on the outcome of the exposure assessment.

Description of the uncertainty		Impact on the exposure assessment[a]
Occurrence data		
Analytical measurements	Performance (e.g. specificity for the target compounds) of the analytical method (GC-ECD, GC–MS, etc.)	**1 – Low impact**. Methods for **2,4,6-TBP** are well established. Most of the data were analysed by GC–MS using isotope labelled standards. MS methods are available for brominated phenols and are considered to be reliable. The availability of more analytical reference standards, proficiency testing and interlaboratory studies would improve quality
	Lack of information on the analytical methods	**1 – Low impact**. Lack of information on the analytical methods used for around 12% of the analytical results
	Proportion of left-censored data and magnitude of difference between risk estimates for LB and UB exposures	**3 – High impact**. Although the proportion of left-censored data is high and the LOQs reported for some of the food categories, the uncertainty is addressed by using the substitution method. The estimation of the UB, which is in this case likely a great overestimation of the exposure, represented worst-case scenarios for the purpose of risk assessment. The impact of this uncertainty was considered to be high for the exposure assessment, but medium for the risk characterisation
	Consideration of recovery (e.g. correction carried out or not)	**0 – Negligible impact**. No reported results that needed to be corrected
Data reporting	Potential errors in reporting the occurrence data (e.g. in the classification of the food category, unit of measurement, parameter, fat vs. whole weight, etc.) – unidentified errors (not apparent from the data provided)	**1** – **Low impact**. Data cleaning procedures that identify outliers and clarifications received by data providers aim to solve most of the possible reporting errors. Although some errors might remain unidentified their overall impact on the results should be low
	Missing information in reporting the occurrence data (e.g. analytical method)	**1** – **Low impact**. Clarifications received by data providers
	Missing or unclear information about the treatment/processing applied prior to the analysis of the sample that is submitted to EFSA	**0** – **Negligible impact**. No information available on the impact of food processing on the concentration of **2,4,6-TBP**
	Use of food categories at high (often not enough specified) FoodEx/FoodEx2 level	**1** – **Low impact**. 98.6% of the analytical results were reported at Foodex2 Level 3 or more detailed
	Uncertainty in the reporting of fat content by data providers and need for conversion to whole weight	**0 – Negligible impact**. No results were reported on a fat weight basis

(Continues)

TABLE F.1 (Continued)

Description of the uncertainty		Impact on the exposure assessment[a]
Representativeness of the data	Limited number of analytical results per food categories expected to contribute to the exposure	**1 – Low impact**. Sufficient number of analytical results were available for each of the 21 Level 1 food categories of the Foodex2 classification system
	Extrapolation of data from one food category to others, and other assumptions	**1** – **Low impact**. Occurrence data have been extended to all similar foods when there was no reason to assume **2,4,6-TBP** was not present in the concerned similar foods. This allows to include in the exposure assessment also foods for which no specific occurrence data are available. This could lead to an under or over estimation of the true exposure but the impact is considered to be low on the risk assessment
	Sampling strategy not fully random	**0** – **Negligible impact**. Analytical results reported as 'Suspect sampling' were excluded from the assessment
	Uneven distribution of the data per year (e.g. recent years not sufficiently represented)	**0** – **Negligible impact**. Analytical results were distributed evenly among the different years and the most recent years were used (2011 onwards)
	Uneven distribution of the data per country (e.g. large number of MSs not sufficiently represented)	**1 – Low impact**. Data on **2,4,6-TBP** were submitted by 9 Member States. Most results were provided by France (60%), Sweden (19%) and Finland (13%). Considering a common market, these data were considered sufficiently representative for the exposure assessment
	Limited number of analytical results per variables that could explain higher/lower levels, such as production method (e.g. wild vs. farmed), processing (e.g. peeled vs. raw), etc.	**0 – Negligible impact**. The additional information provided is limited but no specific aspects have been identified to have a major impact
Consumption data		
Data reporting	Unidentified errors in reporting consumption data, e.g. in the classification of the food, portion size, body weight estimation, memory errors, capacity to report details in dietary surveys Different dietary survey methodologies (e.g. dietary record vs. 24-h re-call), dietary software, interview options, use of portion-size measurement 1. Use of national standard recipes and ingredients factors for composite dishes (potentially leading to, e.g. underestimation of minor ingredients, overestimation of standard ingredients) 2. Different sample size and response rate of the dietary surveys Long-term (chronic) exposure assessed based on few days of consumption per individual. Information about processing/cooking method not consistently reported in consumption records	**1 – Low impact**. Uncertainties and limitations related to the use of the EFSA Comprehensive Food Consumption Database have been described by EFSA (EFSA, 2011a). These uncertainties are common to dietary exposure assessments performed using the Comprehensive Database, and have the potential to cause either an over- or under-estimation of the exposure No specific uncertainties affecting the food consumption data used for the **2,4,6-TBP** exposure assessment were identified
Representativeness of the data	Availability of food consumption data for special population groups, including consumers only of specific foods of special interest, or following special diets	**1 – Low impact**. Consumers of mostly contaminated foods are covered by 95th percentile exposure estimates. Pregnant, lactating women and vegetarians surveys provided similar exposure results as adults from the general population. No other specific population groups that might have a particular exposure to **2,4,6-TBP** were identified
Exposure estimates		
Non-dietary exposure	Sources of exposure other than dietary – how much important is dietary exposure to the total	**1** – **Low impact**. Exposure from dust can vary greatly between individuals and age classes,, although not as great as exposure from diet. It can be particularly relevant for young children. Limited data on dermal and inhalation and other potential non-dietary routes of exposure
Exposure assessment scenario	Consumers' loyalty to specific brands or from specific local areas not considered	**0** – **Negligible impact**. Exposure assessment was made for the general population. Brand loyalty and consumer's only scenarios were considered not relevant for the **2,4,6-TBP** exposure assessment. High exposures due to variability across individuals are covered by the 95th percentile of the exposure estimates

Abbreviations: ECD, electron capture detector; FR, France; GC, gas chromatography; LB, lower bound; LC, liquid chromatography; MS, mass spectrometry; MSs, Member States; NO, Norway; POPs, persistent organic pollutants; UB, upper bound; UK, United Kingdom.

[a]0 – Uncertainty with negligible impact; 1 – Uncertainty with low impact; 2 – Uncertainty with medium impact; 3 – Uncertainty with high impact.

TABLE F.2 Uncertainties identified and their impact on the outcome of the hazard identification and characterisation.

Description of the uncertainty		Impact on the hazard identification and characterisation[a]
Chemical composition and analytical methods		
Dosing and chemical composition	Uncertainty associated with the dose in the critical studies used in the risk assessment	**1 – Low impact**. Most of the studies are conducted using gavage dosing, but for two studies administration was via drinking water
Hazard identification and characterisation		
ADME	ADME in relation to the critical studies	**0 – Negligible impact**.TK data on rat are available by gavage or iv route
	Relevance in humans, genetic background/susceptibility/ sensitive populations	**0 – Negligible impact**. Immature metabolism for young children could lead to underestimation of the risk. This would be covered by the default UF for intraindividual variability
	Accumulation potential	**0 – Negligible impact**. Studies in rats and mice (cited by ECHA, US-EPA) with single and repeated exposure show rapid clearance. Data on bioaccumulation indicates that **2,4,6-TBP** is not bioaccumulative compared to HBCDDs or PBDEs
	Little information on transfer rate to animal products	**0 – Negligible impact**. No studies are available but no impact on the risk assessment.
	Transfer via mother's milk	**0 – Negligible impact**. Based on studies in rats, low levels of **2,4,6-TBP** in the pups have been detected
Toxicity studies in experimental animals: **endpoints and study design**	Limitations in the study design of the studies that can result in uncertainties	**3 – High impact**. Only sub-acute toxicity studies (including a screening of reproductive effects) and one developmental toxicity study have been conducted in rats exposed by gavage. One sc study indicated dose-related effects on the thyroid, but cannot be used to identify a Reference Point because of the route of administration. Effects on thyroid were not investigated in gavage studies. No studies on sub-chronic and chronic toxicity, reproductive toxicity, carcinogenicity, neurotoxicity, developmental neurotoxicity and immunotoxicity were available. No studies with exposure during a critical period (gestation and lactation), as was the case for other BFRs evaluated, were identified The Panel noted some limitations in the critical study Tanaka et al. (1999, as reported by WHO, 2005; US-EPA, 2009): urinalysis was not performed, haematological and blood chemistry analyses were not performed in females, and lack of a number of standard parameters to be examined (according to the test guideline OECD TG 422 reported to have been applied in this study)
	Relevance for humans of the adverse effect	**0 – Negligible impact**: The only effects reported were on liver, kidney and thyroid, and these are relevant for humans
	Biomarkers of effect	**1 – Low impact**: Serum creatinine is a marker of renal function. Although there is some uncertainty about not considering this as the critical effects for the risk assessment, the impact is low due to the small difference it would make to the Reference Point (reduced by a factor of 3)
Genotoxicity	Uncertainty in the assessment of genotoxicity	**1 – Low impact**. **2,4,6-TBP** did not induce mutations in bacteria but induced chromosomal aberrations in mammalian cells in vitro. In in vitro Comet assays, **2,4,6-TBP** induced SSB and DSB as well as oxidised DNA bases in human peripheral blood mononuclear cells. These changes may be indicative for ROS involvement in vitro as shown in Section 1.3.4. It did not induce micronuclei in bone marrow of mice in vivo after ip injection up to the maximum tolerated dose of 300 mg/kg bw per day. Although no toxicity in the bone marrow was demonstrated, systemic exposure is expected after ip injection and clinical signs of toxicity were reported (e.g. lethargy, ataxia and tremors, see Table 5). Based on the overall evidence, the CONTAM Panel considered in vivo genotoxicity of **2,4,6-TBP** to be unlikely
MOA	Uncertainties associated with the data on mode of action	**2 – Medium impact**. The mode of action studies provide indication of toxic effects (e.g. neurotoxicity, immunotoxicity, thyroid toxicity) not investigated in the identified experimental animal studies. Except for oxidative stress no investigation of mechanisms for genotoxicity, liver or kidney toxicity have been identified

(Continues)

TABLE F.2 (Continued)

Description of the uncertainty		Impact on the hazard identification and characterisation[a]
Selection of Reference Point	Selection of BMDL and BMR	**0 – Negligible impact**. BMR of 10% for quantal data as recommended in the EFSA 2022 Guidance. BMD criteria satisfied. For increased serum creatinine, the CONTAM Panel considered that 1 standard deviation of the control group (10%) would be regarded as the practically lowest BMR
	Weaknesses in non-critical studies and uncertainty about whether the endpoints they tested might have been critical if the weaknesses were not present	**0 – Negligible impact**. Two studies involved dosing **2,4,6-TBP** to mice via drinking water (Jiang et al., 2022; Miao et al., 2022). Concentrations in water were not measured. The CONTAM Panel considered that the results of these studies were not convincing due to limitations in the study design and absence of clear renal or liver lesions. No NOAELs/LOAELs were identified

Abbreviations: ADME, absorption, distribution, metabolism, excretion; BMD, benchmark dose; BMDL, benchmark dose lower confidence limit; BMR, benchmark response; DSB, double strand breaks; MOA, mode of action; NTP, National Toxicology Program; OECD, Organisation for Economic Co-operation and Development; SSB, single strand breaks; TDI, tolerable daily intake; TK, toxicokinetic; UF, uncertainty factor.

[a]0 – Uncertainty with negligible impact; 1 – Uncertainty with low impact; 2 – Uncertainty with medium impact; 3 – Uncertainty with high impact.

TABLE F.3 Uncertainties identified and their impact on the outcome of the risk characterisation.

Description of the uncertainty		Impact on the hazard identification and characterisation [a]
Margin of exposure (MOE)	Inter-species differences not correctly covered by standard UFs	The default UFs for inter-species differences in kinetics and dynamics are considered sufficient. This is therefore considered a standard uncertainty
	Intra-species differences not correctly covered by standard UFs	The default UFs for intra-species differences in kinetics and dynamics are considered sufficient. This is therefore considered a standard uncertainty
	Uncertainty factor to account for the short exposure duration of the critical study	**1 – Low impact**. The EFSA SC guidance (2012) does not recommend a default value for extrapolating from sub-acute to chronic studies, even though it noted the default value of 6 applied by ECHA. Therefore, there is uncertainty about the appropriateness of this value. The impact is considered low due to the large MOEs
	Additional factors due to limitations in the toxicological database	**1 – Low impact**. The EFSA guidance specifies that this factor should be dependent on the data set available. WHO/IPCS (1994, 1999) has recommended a factor of 3 or 5 if there are minor deficiencies in the database and a factor of 10 if there are major deficiencies in the database. The factor of 10 is applied because of the major data gaps. There is uncertainty about the appropriateness of this value. The impact is considered low due to the large MOEs
Risk characterisation for infants under 16 weeks of age	Not possible to perform a risk characterisation due to lack of occurrence data	

Abbreviations: HBGV, health-based guidance value; TDI, tolerable daily intake; UF, uncertainty factor.

[a]0 – Uncertainty with negligible impact; 1 – Uncertainty with low impact; 2 – Uncertainty with medium impact; 3 – Uncertainty with high impact.

ANNEX A

Protocol for the risk assessments for human health related to the presence of brominated flame retardants (BFRs) in food

The Annex is provided as a separate pdf file containing the risk assessment protocol applied by the CONTAM Panel to update the previous risk assessments of brominated flame retardants (BFRs) in food, and is available under the Supporting Information section on the online version of the Scientific output.

ANNEX B

Occurrence data on brominated phenols and their derivatives in food submitted to EFSA, dietary surveys per country and age group available in the EFSA Comprehensive Database considered in the exposure assessment, and chronic dietary exposure to 2,4,6-TBP and the contribution of different food groups to the dietary exposure

The Annex is provided as a separate excel file, containing the occurrence data submitted to EFSA, the dietary surveys per country and age group, and the chronic dietary exposure to 2,4,6-TBP, and is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.13850431.

ANNEX C

Benchmark dose analysis

The Annex is provided as a separate pdf file containing the results of the benchmark dose (BMD) analysis, and is available under the Supporting Information section on the online version of the Scientific output.

ANNEX D

Uncertainty analysis – protocol and results of the EKE

The Annex is provided as a separate pdf file containing the details and outcome of the EKE performed for the uncertainty analysis, and is available under the Supporting Information section on the online version of the Scientific output.

ANNEX E

Outcome of the public consultation

The Annex is provided as a separate pdf file containing the comments received during the public consultation and the replies by the CONTAM Panel, and is available under the Supporting Information section on the online version of the Scientific output.