Annex to: Update of the risk assessment on tetrabromobisphenol A and its derivatives in food. doi: 10.2903/j.efsa.2024.8859

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

The current protocol or strategy reports on the problem formulation and approach selected by the Panel on Contaminants in the Food Chain (CONTAM Panel) to update the previous risk assessments of brominated flame retardants (BFRs) in food. The protocol is in accordance with the draft framework for protocol development for the European Food Safety Authority's (EFSA) scientific assessments (EFSA, 2020). This framework foresees that the extent of planning in the protocol (i.e. the degree of detail provided in the protocol for the methods that will be applied in the assessment) can be tailored to accommodate the characteristics of the mandate. Considering the timelines and available resources, the CONTAM Panel applied a low level of planning.

1. Problem formulation

1.1. Objectives of the risk assessments

The objectives of the risk assessments are to assess the risk for adverse effects in humans associated with the dietary exposure to BFRs in food.

The BFRs to be considered are hexabromocyclododecanes (HBCDDs), polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, brominated phenols and their derivatives, and emerging and novel BFRs.[1] The CONTAM Panel published a series of Opinions on the risk assessments of these BFRs in food between 2011 and 2012 (EFSA CONTAM Panel, 2011a-c, 2012a,b), and these will be the starting point for the present updates of the risk assessments.

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 CONTAM Panel will evaluate the appropriateness of applying a mixture approach in an additional Opinion once the risk assessments for each BFR family have 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).

1.2. Target populations

The target population of the human risk assessment is the European population, including specific vulnerable groups (fetus and breastfed infants) and groups with high exposure due to dietary preferences, e.g. high and frequent fish consumers.

1.3. BFRs of concern and route of exposure

[1] As defined in EFSA (2012c).

The risk assessments will focus on the dietary exposure to BFRs, as shown in **Table 1**.

Table 1: BFRs to be considered

Family	Type of studies
HBCDDs	Studies with single stereoisomers (α-, β- and γ-HBCDD) Studies with mixtures of stereoisomers (α-, β- and γ-HBCDD) Studies with HBCDD technical mixture Studies with a mixture of different categories of BFRs, including HBCDDs
PBDEs	Studies with single congeners Studies with mixtures of single congeners Studies with PBDE technical mixtures Studies with a mixture of different categories of BFRs, including PBDEs
TBBPA and its derivatives	Studies with TBBPA or any of its derivatives Studies with mixtures of TBBPA and any of its derivatives Studies with TBBPA technical mixtures Studies with a mixture of different categories of BFRs, including TBBPA and/or any of its derivatives
Brominated phenols and their derivatives	Studies with single brominated phenols or any of their derivatives Studies with mixtures of brominated phenols and any of their derivatives Studies with technical mixtures of brominated phenols Studies with a mixture of different categories of BFRs, including one or more of the brominated phenols and their derivatives
Emerging and novel BFRs	Studies with any of the emerging and novel BFRs Studies with mixtures of any of the emerging and novel BFRs Studies with technical mixtures of any of the emerging and novel BFRs Studies with a mixture of different categories of BFRs, including one or more of the emerging and novel BFRs

BFR: brominated flame retardant; HBCDD: hexabromocyclododecane; PBDE: polybrominated diphenyl ether; TBBPA: tetrabromobisphenol A.

Potential influence of other flame retardants and associated contaminants and by-products (e.g. brominated dioxins and furans) on the outcome will be addressed in the uncertainty analysis.

It will be considered whether brominated organophosphate flame retardants evaluated in the previous Opinion on emerging and novel BFRs, i.e. tris(2,3-dibromopropyl) phosphate and tris(tribromoneopentyl) phosphate, are to be tackled within the current updates of the risk assessments or in a separate assessment together with e.g. other organophosphate halogenated flame retardants.

Consideration will be given to potential non-dietary sources of exposure, e.g. dust, to indicate the relative importance of the diet to the overall BFR exposure.

1.4. Adverse effects and end points

The human risk assessment will address the adverse effects associated with the dietary exposure to BFRs, as identified in the hazard identification step.

1.5. Identification of the risk assessment subquestions

A series of subquestions under each risk assessment pillar (i.e. hazard identification, hazard characterisation and exposure assessment) will be answered and combined for performing the risk assessment. The subquestions identified are reported in **Table 2**.

Table 2: Subquestions to be answered for the risk assessment

Risk assessment step	No.	Subquestions
Hazard identification	1	What adverse outcomes are caused by exposure to BFRs[(a)] in experimental animals?
Hazard identification	2	What adverse outcomes are associated with exposure to BFRs in humans?
Hazard identification	3	Are the different classes of BFRs genotoxic?
Hazard characterisation	4	What is the ADME of BFRs in experimental animal species/strains?
Hazard characterisation	5	What is the ADME of BFRs in humans?
Hazard characterisation	6	What is the difference in the ADME of BFRs between humans and experimental animals?
Hazard characterisation	7	What is the dose–response relationship between BFRs and relevant end points in experimental animals?
Hazard characterisation	8	What is the dose–response relationship between BFRs and relevant end points in humans?
Hazard characterisation	9	What is the mode of action that can explain the observed adverse effects by BFRs?
Exposure assessment	10	What are the levels of BFRs in food in Europe?
Exposure assessment	11	What is the effect of processing on the levels of BFRs in food?
Exposure assessment	12	What are the consumption levels of foods contributing to BFR exposure among the European population?
Exposure assessment	13	What is the estimate of exposure to BFRs from the diet in the European population?
Exposure assessment	14	What are the concentrations of BFRs in human tissues, e.g. blood, breast milk, adipose tissue and placenta, in the European population?
Exposure assessment	15	What is the contribution of non-dietary exposure to the total exposure?

ADME: absorption, distribution, metabolism and excretion; BFR: brominated flame retardant; HBCDD: hexabromocyclododecane; PBDE: polybrominated diphenyl ethers; TBBPA: tetrabromobisphenol A.

(a): The BFRs to be considered are hexabromocyclododecanes (HBCDDs), polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, brominated phenols and their derivatives, and emerging and novel BFRs (EFSA CONTAM Panel, 2011a–c, 2012a,b).

Studies on both humans and experimental animals will be considered for hazard identification and characterisation. The potential association between the target compound(s) and the end points of interest for the human risk assessment will be evaluated. It will include an assessment of the dose–response relationship for the derivation of a chronic Reference Point and an evaluation of possible uncertainties, for example, those derived from the consideration of the toxicokinetic and toxicodynamic

properties of the target compounds and from considerations of the interspecies differences and intraspecies variability. As a next step, the human dietary exposure to the target compounds will be estimated. The final step will be the comparison of the exposure estimates to a health-based guidance value (HBGV, e.g. a tolerable intake) or the calculation of margins of exposure (MOEs).

2. Method for answering the subquestions

The subquestions formulated in **Table 2** will be answered through a comprehensive narrative approach. A literature search will be performed to identify primary research studies as well as reviews and meta-analyses relevant to the subquestions formulated. In addition, the bibliography of the key full-text papers will be checked for further potential relevant studies. This technique is known as snowballing. The expertise of the working group (WG) will be used in deciding whether to pursue these further to complement the evidence collection.

To inform the subquestions related to hazard identification and characterisation (**subquestions 1 to 9**), all studies reporting associations with effects in humans (e.g. epidemiological studies) and all *in vivo* studies in experimental animals that reported effects after exposure to BFRs will be considered. The eligibility criteria related to the report characteristic are listed in **Table 3** (and apply to all subquestions). The eligibility criteria related to study characteristics are listed in **Tables 4, 5 and 6** for studies in humans, studies in experimental animals and toxicokinetic studies, respectively.

The details of the studies will be reported in tables and discussed in the corresponding section of the Opinion. The experimental animal studies will be reported by (i) animal species, (ii) end point, (iii) target compound(s) tested and (iii) study duration. The human epidemiological studies will be reported by (i) end point, (ii) target compound(s) analysed and (iii) study design.

The selection of the scientific studies for inclusion or exclusion will be done by the relevant domain experts from the CONTAM WG on BFRs and CONTAM Panel. It will be based on the consideration of the extent to which the study is relevant to the assessment and 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 a statistical description of the results), irrespective of the results. Major limitations in the information used will be documented in the scientific Opinions.

Table 3: Eligibility criteria related to report characteristics (all subquestions)

Language	In	English[(a)]
Time	In	HBDDDs: from 2010 onwards PBDEs: from 2010 onwards TBBPA and its derivatives: from 2010 onwards Brominated phenols and their derivatives: from 2011 onwards Emerging and novel BFRs: from 2011 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data), systematic reviews, reviews, meta-analyses, extended abstracts, conference proceedings and PhD theses

	Out	Editorials and letters to the editor

HBCDD: hexabromocyclododecane; PBDE: polybrominated diphenyl ether; TBBPA: tetrabromobisphenol A; BFR: brominated flame retardant.

(a): Studies in languages other than English might also be cited if considered relevant by the experts from the Contaminants in the Food Chain (CONTAM) Panel working group (WG) on brominated flame retardants (BFRs) or the CONTAM Panel.

Table 4: Eligibility criteria for the selection of human epidemiological studies (subquestions 1 and 7)

Study design	In	Cross-sectional studies Cohort studies Case-control studies (retrospective and nested) Case series/case reports Clinical trials
	Out	Animal studies *In vitro* studies
Study characteristics	In	Any study duration Any number of subjects
	Out	–
Population	In	All populations groups, all ages, males and females Study location: all countries
	Out	–
Exposure/ intervention	In	All routes of exposure (dietary, dermal, inhalation and transplacental exposure) Exposure: – Studies in which the levels of BFRs have been measured in human tissues – Studies in which the dietary exposure to BFRs has been estimated
	Out	–
Specific outcome of interest	In	All endpoints, including hormone levels
	Out	–

–: not applicable; BFR: brominated flame retardant.

Table 5: Eligibility criteria for the selection of toxicological studies in experimental animals and *in vitro* studies (subquestions 2, 3, 8 and 9)

Study design	In	Experimental animal studies in mammals (e.g. rats, mice, monkeys, guinea pigs, mini pigs, rabbits, hamsters, dogs, cats and mink) *In vitro* studies in relevant systems (mammalian (including human) primary cells and cell lines, subcellular interaction studies and bacterial cell lines used in genotoxicity studies, as described in the OECD guidelines for the testing of chemicals)
	Out	Human studies and studies in non-relevant species
Study characteristics	In	Any study duration Any number of animals Any human culture cells/models
	Out	–
Population	In	Any age, males and females
	Out	–

Exposure/intervention	In	Route of administration: oral (feeding and gavage studies), *s.c.*, *i.p.* and *i.m.* Compounds: as specified in Section 1 under 'BFRs of concern and route of exposure' OR Estimated exposure validated Number of doses: single or repeated administration Dose groups: ≥ 1 dose groups + control group
	Out	Inhalation and dermal application Studies on other BFRs
Specific outcome of interest	In	All end points
	Out	–

–: not applicable; OCED: Organisation for Economic Co-operation and Development; *s.c.*: subcutaneous; *i.p.*: intraperitoneal; *i.m.*: intramuscular; BFR: brominated flame retardant.

Table 6: Eligibility criteria for toxicokinetic studies (subquestions 4, 5 and 6)

Study design/test system	In	*In vivo* studies in humans *In vivo* studies in experimental animals *In vitro* studies in human culture cells/models
	Out	–
Exposure/intervention	In	Route of administration: Oral (feeding and gavage studies), *s.c.*, *i.p.* and *i.m.* Any of the classes of BFRs under evaluation, individually or as mixtures
	Out	–
Specific outcome of interest	In	Any outcome related to the absorption, distribution, metabolism and excretion of the target compounds

–: not applicable; *s.c.*: subcutaneous; *i.p.*: intraperitoneal; *i.m.*: intramuscular; BFR: brominated flame retardant.

Information about previous risk assessments by international bodies, chemistry, analytical methods, current European Union (EU) legislation and previously reported occurrence data in food and exposure assessments (including time trends), as reported in the literature, will be gathered and summarised in a narrative way (supported by tables, if relevant) based on expert knowledge and judgement.

The general principles of the risk assessment process for chemicals in food as described by WHO-IPCS (2009) will be applied, which include hazard identification and characterisation, exposure assessment and risk characterisation. In addition, the following EFSA guidance documents pertaining to risk assessment will be followed for the development of the risk assessment:

- Guidance of the Scientific Committee on a request from EFSA related to uncertainties in dietary exposure assessment (EFSA Scientific Committee, 2007).
- Scientific Committee guidance of the Scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles (EFSA Scientific Committee, 2009).

- Management of left-censored data in the dietary exposure assessment of chemical substances (EFSA, 2010a).
- Guidance of EFSA on the use of the EFSA Comprehensive European Food Consumption Database in exposure assessment (EFSA, 2011a).
- Overview of the procedures currently used at EFSA for the assessment of dietary exposure to different chemical substances (EFSA, 2011b).
- Scientific Committee Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011).
- Scientific Committee guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data (EFSA Scientific Committee, 2012a).
- Scientific Committee Opinion on risk assessment terminology (EFSA Scientific Committee, 2012b).
- Scientific Committee guidance on the use of the weight of evidence approach in scientific assessments (EFSA Scientific Committee, 2017a).
- Scientific Committee guidance on the assessment of the biological relevance of data in scientific assessments (EFSA Scientific Committee, 2017b).
- Scientific Committee guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (EFSA Scientific Committee, 2017c).
- Scientific Committee guidance on uncertainty analysis in scientific assessments (EFSA Scientific Committee, 2018).
- Scientific Committee guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2019).
- Guidance on communication of uncertainty in scientific assessments (EFSA, 2019).
- Scientific Committee Update: Guidance on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2022).

2.1. Literature searches

The literature searches to inform the risk assessments on BFRs will be performed by searching the following bibliographic databases or scientific citation research platforms:

1 PubMed
2 Web of Science™, encompassing the following databases:
   - Web of Science™ Core Collection
   - BIOSIS Citation Index℠
   - CABI: CAB Abstracts®
   - Current Contents Connect®
   - Data Citation Index℠
   - FSTA® – the food science resource
   - MEDLINE®
   - SciELO Citation Index
   - Zoological Record®

The literature searches for studies relevant to HBCDDs and emerging and novel BFRs will be performed by EFSA staff, while those on the oral toxicity and mode of action of PBDEs, TBBPA and brominated phenols and their derivatives will be outsourced to an external contractor.

The output from the searched databases, i.e. the bibliographic references including relevant information, e.g. title, authors and abstract, will be exported into separate EndNote files, allowing a count of the individual hits per database. Files will then be combined, and duplicate records will be removed. The selection process will be performed either in a web-based systematic review software, e.g. with DistillerSR® (Evidence Partners, Ottawa, Canada), or using XLS or Word files.

In addition, grey literature was identified by a dedicated search in the Organohalogen Compounds database (extended abstracts from DIOXIN conferences) and in the BFR conference abstracts available from its website.

2.2. Integration of the lines of evidence for hazard identification and method to perform hazard characterisation

The final critical end points will be identified by integrating evidence from both human and experimental animal lines of evidence, considering the respective level of confidence. A dose–response assessment will be performed on relevant adverse effects for the identification of chronic Reference Points, e.g. no-observed-adverse-effect levels or benchmark doses and its lower confidence limits for a particular incidence of effect. The relevant Reference Points will be considered for the possible derivation of an HBGV or to calculate the MOE.

Data on the toxicokinetics (absorption, distribution, metabolism, and excretion and toxicokinetic modelling) will support the extrapolation of results from experimental animal studies and human studies to the general population. This information is also important to determine which uncertainty factors related to interspecies difference and interindividual variability need to be taken into account when establishing an HBGV or an MOE.

Information on the mode of action will also support this step, as the mode of action can describe the key events and the relationships required for the various adverse outcomes as a result of BFR exposure, and inform the human relevance of effects observed in *in vivo* and *in vitro* experimental models.

3. Method to address the exposure assessment subquestions

To address **subquestion 10** on the levels of BFRs in food in European countries, a structured approach will be followed to collect and evaluate the evidence. The available occurrence data on BFRs in food will be extracted from the EFSA database by the EFSA Evidence Management Unit. Occurrence data are collected through the continuous annual call for data issued by EFSA requesting data on a list of prioritised chemical contaminants.[2] National food authorities and research institutions, academia, food business operators and other stakeholders are invited to submit data occurrence by the 1st of October of each year. The data submission to EFSA must follow the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010b); occurrence data will be managed following the EFSA standard operational procedures on 'data collection and validation' and 'data analysis and reporting'.

For these risk assessments, all occurrence data on the different BFRs under study received since the previous Opinions and by a certain deadline will be considered.

[2] http://www.efsa.europa.eu/en/data/call/datex101217

To guarantee an appropriate quality of the analytical data used in the exposure assessment, the initial dataset will be evaluated before being used to estimate dietary exposure. Regarding the consumption levels of foods among the European population (**subquestion 12**), the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) will be the source of the food consumption information. This database provides a compilation of existing national information on food consumption at the individual level. It was first built in 2010 (EFSA, 2011a; Huybrechts et al., 2011; Merten et al., 2011) and updated frequently.[3] Details on how the Comprehensive Database is used were published in the Guidance of EFSA (EFSA, 2011a).

As indicated by the EFSA WG on Food Consumption and Exposure (EFSA, 2011b), dietary surveys with only 1 day per subject will be considered only for acute exposure, as they are not adequate to assess repeated exposure. Similarly, subjects who participated only 1 day in the dietary studies, when the protocol prescribed more reporting days per individual, will also be excluded from the chronic exposure assessment.

To estimate the human dietary exposure and identify the main food contributors to the exposure (**subquestion 13**), both occurrence and consumption data will be codified and classified according to the FoodEx classification system (EFSA, 2011c). FoodEx is a food classification system developed with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances.

The CONTAM Panel considered that only chronic dietary exposure to BFRs is to be assessed for the general population. For this, food consumption and body weight data at the individual level will be accessed in the Comprehensive Database. Food occurrence data and consumption data will be linked at the least possible aggregated FoodEx level. In addition, the different food commodities will be grouped within each food category to better explain their contribution to the total dietary exposure to BFRs. Exposure estimates will be calculated per dietary survey and age class. The mean and the high (95th percentile) chronic dietary exposures will be calculated by combining mean BFR 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. When occurrence data on BFRs are reported on fat content basis, consumption levels will be converted into the amount of fat before dietary exposure is estimated. When the fat content of consumed foods is not available for specific eating occasions, an average value will be derived according to the different levels of hierarchy in the FoodEx1 catalogue from the available consumption data.

The estimates will be performed by the EFSA Evidence Management Unit. All analyses will be run using the SAS Statistical Software.

Subquestions 11, 14 and 15 will be addressed narratively by carrying out a literature search to identify reviews as well as other peer-reviewed single studies published in the open literature that will be screened and evaluated by relevant domain experts from the WG.

4. Method to address the uncertainties in the risk assessment

The evaluation of the inherent uncertainties in the risk assessments on BFRs will be performed based on the guidance of the Opinion of the Scientific Committee Related to Uncertainties in Dietary Exposure

[3] http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb

Assessment (EFSA, 2007), the report on 'Characterizing and Communicating Uncertainty in Exposure Assessment' (WHO/IPCS, 2008), the new guidance on uncertainties of the EFSA Scientific Committee (EFSA Scientific Committee, 2018) and the guidance on the communication of uncertainty in scientific assessments (EFSA, 2019).

Recommendations will be included in the Scientific Opinion for the generation of additional data that could decrease the impact of the identified uncertainties on the conclusions of the risk assessment.

5. Approach for reaching risk characterisation conclusions

The general principles of risk characterisation for chemicals in food as described by WHO/IPCS (2009) as well as the different EFSA guidance documents relevant to this step of the risk assessment (see Section 2 above) will be applied.

6. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed will be repeated approximately 7 and 4 months before the planned date of endorsement for public consultation and adoption of the Opinions. The scientific papers retrieved by these additional searches will be screened for relevance by the members of the WG and EFSA staff and included in the draft Opinions as appropriate by the WG experts.

7. Public consultation

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft Opinions on BFRs that will be developed will be subject to public consultation before their final adoption by the CONTAM Panel.

The comments received will be evaluated by the WG on BFRs in food and by the CONTAM Panel and, wherever appropriate, taken into account for the finalisation of the draft Opinion.

8. History of the amendments to the protocol

The following amendments to the protocol were introduced before the final adoption of the draft Opinion on the update of the risk assessment of TBBPA and its derivatives in food.

2. Method for answering the subquestions: an EFSA guidance pertaining to risk assessment was added: (i) Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age.

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Abbreviations

BFR	brominated flame retardant
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
HBCDD	hexabromocyclododecane

PBDE	polybrominated diphenyl ether
TBBPA	tetrabromobisphenol A
HBGV	health-based guidance value
MOE	margin of exposure
WG	working group