Annex to:

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 20xx. Scientific Opinion - Update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food. EFSA Journal 20xx;xx(xx):xxxx.

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

To promote quality in its scientific processes and contribute to realising the strategic objectives related to evidence and methods for scientific assessments [1], EFSA has implemented the PROMETHEUS project (PROMoting METHods for Evidence Use in Science) [2]. The PROMETHEUS 4-step approach consists of: 1) planning upfront (i.e. before initiating any formal data collection, appraisal or synthesis) the strategy for the assessment and detailing it in a protocol. This includes tailoring the methodology for the assessment, to address the trade-off between applying extensive/complex approaches and responsiveness; 2) carrying out the assessment in line with the predefined strategy; 3) verifying compliance with the plan; and 4) thoroughly documenting and reporting the process, results and conclusions, and ensuring accessibility of methods and data. A key point is the recording of any deviations from the planned strategy.

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.

B.1. Problem formulation

Objectives of the risk assessments

The objectives of the risk assessments aim at assessing 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[3]. The CONTAM Panel published a series of Opinions on the risk assessments of these BFRs in food between 2011 and 2012 (EFSA, 2011a,b,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 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).

Target populations

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

BFRs of concern and route of exposure

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

[1] http://www.efsa.europa.eu/en/corporate/pub/strategy2020
[2] http://www.efsa.europa.eu/en/methodology/evidence
[3] As defined in EFSA (2012c).

Table B.1. BFRs to be considered.

HBCDDs	Studies with single stereoisomers (α-, β- and γ-HBCDD) Studies with mixtures of the stereoisomers (α-, β- and γ-HBCDD) Studies with HBCDD technical mixture Studies with 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 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 mixture of different categories of BFRs, including TBPPA 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 phenosl and any of its derivatives Studies with technical mixtures of brominated phenols Studies with 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 mixture of different categories of BFRs, including one or more of the emerging and novel BFRs

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 Organo Phosphate (OP) flame retardants evaluated in the previous Opinion on emerging and novel BFRs, i.e. tris(2,3-dibromopropyl) phosphate (TDBPP) and tris(tribromoneopentyl) phosphate (TTBNPP), are to be tackled within the current updates of the risk assessments or in a separated assessment together with, e.g. other OP 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.

Adverse effects and endpoints

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

Identification of the risk assessment sub-questions

A series of sub-questions 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 sub-question identified are reported in **Table B.2**.

Table B.2. Sub-questions to be answered for the risk assessment.

Risk assessment step	No	Sub-questions
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 absorption, distribution, metabolism and excretion (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 ADME of BFRs between humans and experimental animals?
Hazard characterisation	7	What is the dose-response relationship between BFRs and relevant endpoints in experimental animals?
Hazard characterisation	8	What is the dose-response relationship between BFRs and relevant endpoints 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 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, e.g. blood, breast milk, adipose tissue, 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 elimination.
(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, 2011a,b,c, 2012a,b).

Studies on both humans and experimental animals will be used for the hazard identification and characterisation. The potential association between the target compound(s) and the endpoints of interest for the human risk assessment will be evaluated. It will include an assessment of the dose-response relationship and an evaluation of possible uncertainties, for example those derived from consideration of the toxicokinetic and toxicodynamic properties of the target compounds and from considerations of inter-species 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 (HBGVs, e.g. a tolerable intake) or calculate the margin of exposure (MOE).

B.2. Method for answering the sub-questions

The sub-questions formulated in **Table B.1** will be answered by a comprehensive narrative approach. A literature search will be performed to identify primary research studies well as reviews and meta-analysis relevant to the sub-questions 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 will be used in deciding whether to pursue these further to complement the evidence collection.

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

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) endpoint, (iii) target compound(s) tested and (iii) study duration. The human epidemiological studies will be reported by: (i) endpoint, (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 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 statistical description of the results), irrespective of the results. Major limitations in the information used will be documented in the scientific Opinions.

Table B.3. Eligibility criteria related to report characteristics (all sub-questions).

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, PhD Theses
	Out	Editorials, letters to the editor

(a): Studies in languages other than English might also be cited if considered relevant by the experts from the CONTAM WG on BFRs or CONTAM Panel.

Table B.4. Eligibility criteria for the selection of human epidemiological studies.

Sub-questions 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
	In	Any study duration

Study characteristics:		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, transplacental exposure). Exposure: - Studies in which levels of the BFRs have been measured in human tissues - Studies in which the dietary exposure to the BFRs has been estimated
	Out	/
Specific outcome of interest	In	All endpoints, including hormone levels
	Out	/

98 **Table B.5.** Eligibility criteria for the selection of studies in experimental animals and *in vitro* studies.

Sub-question 2, 3, 8 and 9		
Study design	In	Experimental animal studies (rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink) *In vitro* studies
	Out	Human studies
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, gavage studies), *s.c.*, *i.p.*, *i.m.* Compounds: as specified in Section A.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, dermal application Studies on other BFR
Specific outcome of interest	In	All endpoints
	Out	/

99 **Table B.6.** Eligibility criteria for the studies on toxicokinetics.

Sub-questions 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	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 elimination of the target compounds

100

Information about previous risk assessments by international bodies, chemistry, analytical methods, current EU legislation, 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),
- 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 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 Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011)
- 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 SC, 2012a),
- Scientific Opinion on Risk Assessment terminology (EFSA SC, 2012b).
- Update: use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2017)
- Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019).

Literature searches

The literature searches to inform the risk assessments on BFRs will be performed 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, 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 also 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.

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

The final critical endpoints will be identified by integrating evidence from both human and experimental animal lines of evidence considering the respective level of confidence. For each endpoint, dose-response assessment will be performed on relevant adverse effects for the identification of reference points, e.g. a no-observed-adverse-effect level (NOAEL) or a benchmark dose (BMD) and its lower confidence limit (BMDL) for a particular incidence of effect. The lowest reference point will be considered for the possible derivation of an HBGV or to calculate the MOE.

Data on the toxicokinetics (ADME 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 inter-species difference and inter-individual variability need to be taken into account when establishing an HBGV or an MOE.

Information on mode of action will also support this step, as mode of action studies can establish the key events and their relationships required for the various adverse outcomes as a result of BFR exposure.

B.3. Method to address the exposure assessment sub-questions

To address **sub-question 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[4]. National food authorities and also 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 (SOPs) on 'Data collection and validation' and on '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.

To guarantee an appropriate quality of the food data used in the exposure assessment, the initial dataset will be evaluated before being used to estimate dietary exposure. Among others, re-codification of samples under FoodEx classification will be carried out, as well as the application of the substitution method to left-censored data, the exclusion of suspect samples or those samples with incomplete information (e.g. absence of particular congeners). These steps will be carried out by the EFSA DATA Unit in collaboration with the members of the Working Group and/or Panel members.

Regarding the consumption levels of foods among the European population (**sub-question 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 individual level. It was first built in 2010 (EFSA, 2011a; Huybrechts et al., 2011; Merten et al., 2011) and then updated in 2015[5]. Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011a).

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

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

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

To estimate the human dietary exposure (**sub-question 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 by the former EFSA DCM Unit in 2009 with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. It contains 20 main food groups (first level), which are further divided into subgroups having 140 items at the second level, 1 261 items at the third level and reaching about 1 800 end-points (food names or generic food names) at the fourth level. The EFSA Evidence Management Unit will verify the correct application of FoodEx classification to the data before dietary exposure is estimated.

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 BFRs mean occurrence values for food samples collected in different countries (pooled European occurrence data) with the average daily consumption for each food at individual level in each dietary survey. When occurrence data on BFRs are reported on fat content basis, consumption levels will be converted into 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 of 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.

Sub-questions 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 Working Group.

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

B.5. Approach for reaching risks characterisation conclusions

The general principles of the risk characterisation for chemicals in food as described by WHO/IPCS (2009) will be applied as well as the different EFSA guidance documents relevant to this step of the risk assessment (see **Section A.1** above).

B.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 adoption of the Opinions. The scientific papers retrieved by these additional searches will be screened for relevance by the members of the Working Group and EFSA staff and included in the draft Opinions as appropriate by the Working Group experts.

B.7. History of the amendments

N/A

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