External Scientific Report

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Identifying and collecting relevant literature related to the toxicity of polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and brominated phenols

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Abstract

An extensive literature search to identify and collect studies related to the toxicity of polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and brominated phenols (BPs) was performed in the three databases PubMed, Web of Science and SciFinder® for four Areas. After combination of the searches from the three databases and removal of the duplicates, the total number of references for Area 1 was 6,231, for Area 2 was 8,236, for Area 3 was 4,994 and for Area 4 was 6,363. The evaluation of all retrieved references for relevance by screening the title and abstract (if available) and applying eligibility criteria (inclusion/exclusion) resulted in a total number of relevant references for Area 1 of 378 (PBDEs), 46 (TBBPA) and 29 (BPs), for Area 2 of 188 (PBDEs), 37 (TBBPA) and 4 (BPs), for Area 3 of 518 (PBDEs), 180 (TBBPA) and 49 (BPs), and for Area 4 of 717 (PBDEs), 59 (TBBPA) and 18 (BPs).

Key words: Polybrominated diphenyl ethers, PBDE, tetrabromobisphenol A, TBBPA, brominated phenols, toxicity, extensive literature search

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Summary

The overall aim of this assignment was to identify and collect all relevant literature related to the toxicity of polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and brominated phenols (BP) to support the preparatory work for the hazard identification and characterisation steps in the human health risk assessment of these substances.

Initially, four tailored search strings were designed in collaboration with EFSA to retrieve all potentially relevant studies within the following four areas:

- Area 1: Data on toxicokinetics (absorption, distribution, metabolism, excretion) 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.
- Area 4: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure).

The search strings were tailored to the databases PubMed, Web of Science and SciFinder® and consisted of two major steps each designed to suit the respective databases.

Combinations of search terms were used, starting with a broad search for PBDEs, TBBPA and its derivatives and BPs and their derivatives, including synonyms and abbreviations (step 1) and followed by an Area specific step with the addition of search terms relevant to each Area (step 2).

Then the four tailored search strings were employed to retrieve all relevant studies from the three databases. Data published since the year 2010 were retrieved for PBDEs and TBBPA and its derivatives, and since 2011 for BPs and their derivatives. All retrieved references were exported as separate files into EndNoteTM (version X9). Duplicate studies were then removed after combining the three EndNoteTM files per Area into one single combined file per Area.

The total number of references from each database was 6,231 from Area 1, 8,236 from Area 2, 4,994 from Area 3 and 6,363 from Area 4.

All retrieved references were then evaluated for relevance by applying eligibility criteria (inclusion/exclusion). The selection for relevance was conducted by screening the title and abstract (if available) and all the retrieved studies were ultimately sorted into one of the following three categories:

- Relevant to the research objectives: References ultimately evaluated to be relevant were included in this category.
- Maybe relevant to the research objectives: In case the relevance could not be evaluated because, e.g. of missing or vague abstracts, or because the objective of the reference was borderline to be considered relevant according to the eligibility criteria, the references were included in this category, as a conservative approach.
- Not relevant to the research objectives: References ultimately evaluated not to be in-scope were included in this category.

The results of the reference selection process were reported in summary tables (Excel files), three tables per Area, i.e. one for each of the substance groups PBDEs, TBBPA and BPs. The summary tables include all pertinent information for each of the references in the 'Relevant' category as identified by the eligibility criteria and which could be retrieved from the title and abstract (when available). The summary tables also include references in the 'Maybe relevant'

and the 'Not relevant' categories, but without any study details except for including the reason for exclusion for the 'Not relevant' references, i.e. not target compound or not relevant for the specific Area is presented.

The evaluation for relevance resulted in a total number of relevant references for Area 1 of 378 (PBDEs), 46 (TBBPA) and 29 (BPs), for Area 2 of 188 (PBDEs), 37 (TBBPA) and 4 (BPs), for Area 3 of 518 (PBDEs), 180 (TBBPA) and 49 (BPs), and for Area 4 of 717 (PBDEs), 59 (TBBPA) and 18 (BPs).

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1 Introduction

1.1 Background and terms of reference as provided by the requestor

This contract was awarded by EFSA to:

Contractor: National Food Institute, Technical University of Denmark

Contract title: Identifying and collecting relevant literature related to the toxicity of polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and brominated phenols

Contract number: CT/EFSA/AMU/2014/01-LOT 2

1.2 Background as provided by EFSA

The Unit on Biological Hazard and Contaminants (BIOCONTAM Unit) supports the Panel on Contaminants in the Food Chain (CONTAM Panel), which provides scientific advice on contaminants in the food chain and undesirable substances such as natural toxicants, mycotoxins and residues of unauthorised substances.

In April 2018, EFSA received a mandate from the European Commission for a series of scientific opinions of the health risks related to the presence of Brominated Flame Retardants (BFRs) in food. The mandate was allocated to the CONTAM Panel. A Working Group will be established to develop the draft opinions.

To support the preparatory work for the hazard identification and characterisation steps in the human health risk assessment, EFSA wishes to outsource an Extensive Literature Search (ELS) as well as the selection of relevant studies by screening of title and abstract related to the toxicity of polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A (TBBPA) and its derivatives, and brominated phenols and their derivatives.

PBDEs are a class of brominated hydrocarbons with a basic structure consisting of two phenyl rings linked by an oxygen atom. There are 209 possible compounds, commonly referred to as PBDE congeners, which differ in the number and position of the bromine atoms in the two phenyl rings. Three commercial technical mixtures of PBDEs, PentaBDE, OctaBDE and DecaBDE, have been marketed under different trade names. They are composed of a mixture of congeners, and named according to their average bromine content (EFSA, 2011[1]).

TBBPA and its derivatives are a widely used group of flame retardants. There are several TBBPA derivatives, of which a number is commercially available as flame retardants: tetrabromobisphenol A bis(2-hydroxyethyl) ether (TBBPA-bOHEE), tetrabromobisphenol A bisallyl ether (TBBPA-bAE), tetrabromobisphenol A bis(2,3-dibromopropyl ether) (TBBPA-bDiBPrE), tetrabromobisphenol A bis(glycidyl ether) (TBBPA-bGE). For other TBBPA

[1] EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. EFSA Journal 2011;9(5):2156. [274 pp.] doi:10.2903/j.efsa.2011.2156.

derivatives there is some uncertainty about their commercial use as flame retardants: tetrabromobisphenol A bisacrylate (TBBPA-bAcr), 3,3',5,5'-tetrabromobisphenol A bis-acetate (TBBPA-bOAc) and tetrabromobisphenol A bis(2-hydroxyethyl)ether bisacrylate (TBBPA-bOHEE-bAcr). TBBPA derivatives that may potentially be used as BFRs are: tetrabromobisphenol A bismethyl ether (TBBPA-bME) and tetrabromobisphenol A bispropanoate (TBBPA-bOPr) (EFSA, 2011[2]).

Brominated phenols and their derivatives comprise a complex group of BFRs. Brominated phenols that have been identified as flame retardants include 2,4-dibromophenol (2,4-DBP), 2,4,6-tribromophenol (2,4,6-TBP), pentabromophenol (PBP), and tetrabrominated bisphenol S (TBBPS). 2,4,6-TBP, PBP and TBBPS are precursors of four non-phenolic derivatives also being applied as BFRs, i.e. TBP allyl ether (TBP-AE), PBP allyl ether (PBP-AE), TBP 2,3-dibromopropyl ether (TBP-DBPE) and TBBPS bis(2,3-dibromopropyl ether) (TBBPS-BDBPE) (EFSA, 2012[3]).

The contractor should ensure that all the steps for conducting the ELS are properly documented and reported.

The present Call is based on EFSA's 2019 Work Programme for grants and operational procurements as presented in Annex IX of the EFSA Programming Document 2019 – 2021, available on the EFSA's website[4] .

1.3 Objectives as provided by EFSA

The objectives of the specific contract resulting from the present reopening competition are as follows:

Objective 1:

To develop tailored search strategies to retrieve studies pertinent to the hazard identification and characterisation of (i) PBDEs, (ii) TBBPA and its derivatives and (iii) brominated phenols and their derivatives in the following areas:

Area 1: Data on toxicokinetics (absorption, distribution, metabolism, excretion) 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.

[2] EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. EFSA Journal 2011;9(12):2477. [67 pp.] doi:10.2903/j.efsa.2011.2477.

[3] EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Brominated Flame Retardants (BFRs) in Food: Brominated Phenols and their Derivatives. EFSA Journal 2012;10(4):2634. [42 pp.] doi:10.2903/j.efsa.2012.2634.

[4] http://www.efsa.europa.eu/en/corporate/pub/amp1820

Area 4: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure).

The search strategies proposed by the contractor team will be discussed and agreed with EFSA before proceeding with the actual searches.

Objective 2:

To carry out the ELS using the tailored search strings developed by the contractor and agreed by EFSA for identifying studies published since 2010 for PBDEs and TBBPA and its derivatives, and since 2011 for brominated phenols and their derivatives.

Objective 3:

To screen the titles and abstracts for relevance to the risk assessment. To prepare a file compatible with EndNote (RIS file) with the relevant literature and a table summarising the relevant studies. The file compatible with EndNote (RIS file) and table should be organised by group of compounds and by area.

2 Data and Methodologies

The methodology for systematic reviews including guidance for development and optimisation of a search strategy and for selecting relevant studies has been described by EFSA (2010). This methodology was implemented as appropriate in the Tasks described below.

2.1 Objective 1

2.1.1 Task 1 Developing tailored search strategies and search strings for collecting relevant studies

A tailored search string for each of the four areas described above was developed for identifying all potentially relevant studies for the hazard identification and characterisation of PBDEs, TBBPA and its derivatives, and BPs and their derivatives.

The search strings were driven by the eligibility criteria for each Area (1-4) developed by the Contractor based on the eligibility criteria in Annex 3 of the technical specifications, and agreed upon by EFSA (see Appendix A of this external scientific report). The search strings were tailored to the databases PubMed, Web of Science and SciFinder®. The search consisted of two major steps each designed to suit the respective databases.

In PubMed, searches were made with the Text Words [tw] field tag thus including title, abstract, MesH headings and subheadings, keywords, chemical names of substances and secondary source identifiers . In Web of Science searches were made in Topic including title, abstract, author keywords and keywords plus. To limit the amount of irrelevant references restrictions were made in regard to science categories. In SciFinder® CAS registry numbers for specific substances were used in the search as substances are indexed with links to CAS

Registry, which makes search strings with CAS registry numbers preferable. In general, combinations of search terms by use of the Boolean operators (AND, OR) were used in the three databases. Use of the Boolean operator "NOT" is generally to be avoided as a relevant reference can contain discussions on both relevant and excluded search terms.

Step 1 consisted of a broad search for PBDEs, TBBPA and its derivatives and BPs and their derivatives.

Step 2 was Area specific with the addition of search terms relevant to each specific Area.

Search terms were identified in collaboration with the entire project team to identify as many relevant as possible. The search strings were developed in order to retrieve the largest number of potentially relevant studies on PBDEs, TBBPA and its derivatives and BPs and their derivatives within Area 1-4. The search strings were presented and discussed with EFSA at the kick-off meeting.

2.2 Objective 2

2.2.1 Task 2 Execution of the extensive literature searches using the tailored search strings developed in task 1

The tailored search strings developed in Task 1 and agreed upon by EFSA were employed to retrieve all relevant studies from the databases PubMed, Web of Science and SciFinder® on PBDEs, TBBPA and its derivatives and BPs and their derivatives.

Data published since year 2010 was retrieved for PBDEs and TBBPA and its derivatives and since year 2011 for BPs and their derivatives.

All references located in the extensive literature searches (ELSs) in PubMed, Web of Science and SciFinder® were exported as separate files into EndNoteTM. Title, author, journal, year of publication and abstract was included for each study imported to EndNoteTM and the number of references resulting from each of the tailored search strings in each of the three databases was recorded in a log file (example in Table 1). Duplicate studies were then removed after combining the three EndNoteTM files per Area into one single combined file per Area.

Table 1: Example of log files for the tailored search strings

	OBJECTIVE: Develop tailored search strategies to retrieve all relevant data on PBDEs, TBBPA and its derivatives, or BPs and their derivatives					
Date of search	**Substance group**	**Databases & Search Engines**	**Search terms**	**Limitations applied to search**	**No of references**	**Comments& follow up actions**
April 18, 2019	PBDEs	PubMed	(PBDE* OR	Year: 2010-	526	Add search terms to

BDE*) AND (tox*)	optimise search string

2.3 Objective 3

2.3.1 Task 3 Selection of all relevant studies retrieved by the extensive literature searches

All studies retrieved by the ELS and imported into the combined EndNoteTM files, one file per Area (Task 2), were evaluated for relevance by applying eligibility criteria (inclusion/exclusion) for each subject Area (1-4) developed by the Contractor based on the eligibility criteria in Annex 3 of the technical specifications, and agreed upon by EFSA (see Appendix A of this external scientific report). The selection for relevance was conducted by screening their title and abstract (if available) and all the retrieved studies was ultimately sorted into one of the following three categories:

- Relevant to the research objectives: References ultimately evaluated to be relevant were included in this category.
- Maybe relevant to the research objectives: In case the relevance could not be evaluated because, e.g. of missing or vague abstracts, or because the objective of the reference was borderline to be considered relevant according to the eligibility criteria, the references were included in this category, as a conservative approach.
- Not relevant to the research objectives: References ultimately evaluated not to be in-scope were included in this category.

To ensure a uniform understanding of the eligibility criteria in each Area, these were discussed in an internal meeting before all references were assessed for relevance.

According to the original protocol proposed by the Contractor, "Each study will be individually assessed by two reviewers in order to prevent the introduction of errors and personal bias. In the possible event of disagreements between reviewers a third member of the project team will assist in solving the specific issue as recommended by EFSA (2010)." However, as a result of the very broad search strings for each Area, a huge number of references were retrieved in the ELS for each Area. In addition, a great number of references appeared in more than one area. It was therefore decided that the principal team member for each Area performed an initial sorting of the references into one of the following four categories: 1) Relevant, 2) Maybe relevant, 3) Not relevant, and 4) To be further assessed. All the references in the fourth category ('to be further assessed') were then evaluated by the principal team member in collaboration with another team member and the references were then included either in the 'Relevant', the 'Maybe relevant' or in the 'Not relevant' category. If necessary, other relevant team members also assisted in this evaluation. In case relevance still remained uncertain, the references were included in the 'Maybe relevant' category, as a conservative approach. This deviation from the original protocol is not considered to invalidate the outcome of the selection for relevance of the studies retrieved from the ELSs because of the control measures and quality check taken in the execution of this task.

During the process of selection of relevance, the principal team member for a specific Area also identified references of potential relevance for other Areas. After the selection of

relevance was finalised for each Area, a cross-check was made between one specific Area and all other Areas to ensure that all relevant references have been captured for each Area. References that were identified in other Areas as being potential relevant for the specific Area, but not retrieved in the Area specific literature searches in PubMed, Web of Science and SciFinder® were included in both the Area specific summary table (in an additional sheet) and in the Area Specific EndNote file (in a separate folder).

To ensure a uniform reporting in the summary tables, representative references within each Area were assessed for relevance by all principal team members and discussed in an internal meeting before all references were assessed for relevance. These described measures were implemented to avoid the introduction of time-consuming mistakes.

The results of the reference selection process were reported in summary tables (Excel files), three tables per Area i.e. one for each of the substance groups PBDEs, TBBPA and BPs. The summary tables included all pertinent information from each of the relevant studies as identified by the eligibility criteria developed by the Contractor and agreed with EFSA. The information included in the summary tables ensures that all eligibility criteria of the studies were considered. Additional fields for substance group, potential relevance for other Areas, the person(s) responsible for the screening and comments were also included in the summary tables.

All references found relevant for the hazard identification and characterisation of PBDEs, TBBPA and its derivatives and BPs and their derivatives within Area 1-4 were collected in EndNoteTM files including all indexed fields per reference (i.e. title, author, publication year, journal and abstract). Three EndNoteTM files per Area, i.e. one for each of the substance groups PBDEs, TBBPA and BPs, were provided.

All relevant studies were collected in a reference list, one list per Area per substance group (see Appendix C).

3 Results

3.1 Objective 1

3.1.1 Task 1 Developing tailored search strategies and search strings for collecting relevant studies

The tailored search strings were developed in order to retrieve the largest number of potentially relevant studies for the human and animal risk assessment of PBDEs, TBBPA and its derivatives and BPs and their derivatives within Area 1-4.

The proposed search strings were submitted to EFSA on 29 April 2019 (email) as part of Deliverable 1, and were discussed, revised and agreed with EFSA at the kick-off meeting on 6 May. The agreed search strings for Step 1 and Step 2, for Area 1-4 are presented below.

The search string for step 1 was developed in order to capture all known and potentially unknown PBDEs, TBBPA and its derivatives and BPs and their derivatives by using search terms identified in the EFSA opinions on PBDEs (2011), TBBPA and its derivatives (2011) and BPs and their derivatives (2012) in food.

The search strings for step 2, Area 1-4 were developed based on the experiences obtained in two similar procurements recently carried out for EFSA, i.e. 'Identifying and collecting relevant literature related to the oral toxicity of furan and its methyl analogues, 2-methylfuran and 3-methylfuran', final report approved by EFSA on 1 July 2016, and 'Extensive literature search for studies related to fumonisins and their modified forms', final report approved by EFSA on 2 December 2016. In both procurements, the search terms were combined and tested in the databases PubMed and Web of Science to develop the most sensitive and appropriate search string. The search strings were also tested by assessing whether they retrieved relevant papers already known to the project team as recommended by EFSA (EFSA, 2010).

In the proposed search strings, "OR" is the Boolean operator that expands the amount of references returned when used in a search string as just one of the search terms need to be present in the returned references. "*" symbolises truncation and is used for finding singular and plural forms of words and various endings. Both PubMed and Web of Science use an asterisk as their truncation symbol.

Step 1:

The search string agreed for step 1 in PubMed and Web of Science is as follows:

PBDE*
OR BDE*
OR polybrominated*
OR DBDPE*
OR BTBPE*
OR TBBPA*
OR tetrabromobisphenol*
OR bromophenol*
OR monobromophenol*
OR dibromophenol*
OR tribromophenol*
OR tetrabromophenol*
OR pentabromophenol*
OR brominated*
OR bromophenyl*
OR tribromophenyl*
OR pentabromophenyl*
OR bromodiphenyl*
OR bromophenoxy*
OR tribromophenoxy*
OR pentabromophenoxy*
OR dibromopropyl*
OR TBBPS*
OR monoBDE*
OR mono-BDE*
OR diBDE*
OR di-BDE*
OR triBDE*
OR tri-BDE*
OR tetraBDE*

OR tetra-BDE*
OR pentaBDE*
OR penta-BDE*
OR hexaBDE*
OR hexa-BDE*
OR heptaBDE*
OR hepta-BDE*
OR octaBDE*
OR octa-BDE*
OR nonaBDE*
OR nona-BDE*
OR decaBDE*
OR deca-BDE*

The search string agreed for step 1 in SciFinder® is as follows:

79-94-7
OR 4162-45-2
OR 25327-89-3
OR 21850-44-2
OR 3072-84-2
OR 55205-38-4
OR 33798-02-6
OR 66710-97-2
OR 70156-79-5
OR 37419-42-4
OR 118-79-6
OR 615-58-7
OR 608-71-9
OR 168434-45-5
OR 3278-89-5
OR 3555-11-01
OR 35109-60-5
OR 39635-79-5
OR 70156-79-5
OR 42757-55-1
OR 41318-75-6
OR 5436-43-1
OR 60348-60-9
OR 189084-64-8
OR 68631-49-2
OR 207122-15-4
OR 207122-16-5
OR 1163-19-5
OR 37853-59-1
OR 84852-53-9

Step 2:

The Area specific search strings agreed for step 2 are as follows:

Area 1: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in experimental animals and humans and from *in vitro* studies.

(*in vitro* OR absor* OR tissue* OR metaboli* OR excret* OR kinetic* OR toxicokinetic* OR pharmacokinetic* OR degrad* OR biotrans* OR eliminat* OR PBPK OR PBTK OR PBK)

Area 2: Data on toxicity in experimental animals.

(*in vivo* OR acute OR chronic OR tox* OR cancer* OR carcino* OR tumor* OR tumour* OR organ* OR tissue* OR immun* OR neuro* OR developmental OR teratogen* OR repro* OR liver OR hepato* OR kidney* OR brain* OR lung OR lungs OR heart* OR thyroid* OR gene OR genes OR rat* OR mouse OR mice OR rabbit* OR guinea OR hamster* OR primate* OR monkey* OR pig* OR minipig* OR dog* OR cat* OR mink*)

Area 3: Data on *in vitro* and *in vivo* genotoxicity and mode of action (MoA).

(*in vitro* OR *in vivo* OR mode OR hormon* OR endocrin* OR estrogen* OR oestrogen* OR androgen* OR mechanism* OR apoptosis OR oxidative OR cytotox* OR genotox* OR muta* OR DNA OR clastogen* OR aneugen* OR chromosom* OR culture OR enzyme*)

Area 4: Data on observations in humans (including epidemiological studies, case reports, biomarkers of exposure).

(epidemio* OR intervention OR exposure* OR case* OR poison* OR cohort* OR cross-sectional OR random* OR work* OR occupation* OR biomark* OR human* OR meta-analys*)

3.2 Objective 2

3.2.1 Task 2 Execution of four extensive literature searches using the tailored search strings developed in task 1

The number of references resulting from each of the tailored search strings in each of the three databases PubMed, Web of Science and SciFinder® were recorded in a log file (see Appendix B).

The total number of references from each database (combined total), as well as the total number of references after removal of the duplicates (combined) are summarised in the table below. The duplicates in the combined file for each Area 1-4 were removed by the EndNote tool; however, duplicates may still be present in the combined files as the EndNote tool for various reasons is not able to remove all duplicates. These duplicates were identified during the execution of Task 3 and then removed manually. The revised versions of the combined files were submitted as part of the draft final deliverable.

Area	PubMed	Web of Science	Scifinder®	Combined total	Combined
1	4,394	2,093	2,626	7,301	6,231
2	5,695	2,646	3,531	9,575	8,236

3	3,375	2,291	1,904	5,957	4,994
4	4,574	2,476	2,762	7,625	6,363

3.3 Objective 3

3.3.1 Task 3 Selection of all relevant studies retrieved by the extensive literature searches

The total number of relevant references for Area 1 was 378 (PBDEs), 46 (TBBPA) and 29 (BPs), for Area 2 it was 188 (PBDEs), 37 (TBBPA) and 4 (BPs), for Area 3 it was 518 (PBDEs), 180 (TBBPA) and 49 (BPs), and for Area 4 it was 717 (PBDEs), 59 (TBBPA) and 18 (BPs).

The final protocol and project plan implemented by the Contractor to carry out the project was submitted to EFSA on 20 September (by e-mail) as part of the draft final deliverable and the final version was submitted to EFSA on 4 October (by e-mail) as part of the final deliverable.

Summary tables

A proposal for the information (eligibility criteria) to be included in the summary tables for each Area was submitted to EFSA on 29 April, 2019, (e-mail) as part of Deliverable 1. The proposed summary tables were discussed with EFSA at the kick-off meeting on 6 May, 2019. EFSA had a few suggestions for revisions, which were agreed at the kick-off meeting, and reflected in the revised version of the summary tables submitted to EFSA on 7 May, 2019 (e-mail) and in the minutes accepted by EFSA May 13 (e-mail).

Summary tables (Excel files) with five motivated excluded papers per substance group and five motivated included papers per substance group for all four Areas were submitted to EFSA on 27 May, 2019, (email) as part of Deliverable 2. These summary tables were discussed with EFSA at the interim meeting on 3 June, 2019. EFSA had a few suggestions for revisions, which were agreed at the interim meeting and reflected in the minutes accepted by EFSA June 7 (e-mail).

Summary tables (Excel files) were prepared, one table for each Area. The summary tables include all pertinent information for each of the references in the 'Relevant' category as identified by the eligibility criteria suggested by the Contractor and agreed by EFSA, which could be retrieved from the title and abstract (when available). The summary tables also include 'Maybe relevant' and 'Not relevant' studies, but without any study details. For the 'Not relevant' studies, the reason for exclusion, i.e. not target compound or not relevant for the specific Area, is presented. In addition, there is also an indication if a specific reference is considered of potential relevance for other Area(s).

All references included in the 'Relevant' category appear on a green background; all references included in the 'Maybe relevant' category appear on a yellow background; and all references included in the 'Not relevant' category appear on a white background. An additional sheet has been added in the summary tables for all Areas. This additional sheet includes the references that were identified in other Areas as being potential relevant for the specific Area, but not retrieved in the Area specific literature searches in PubMed, Web of Science and SciFinder®.

The summary tables were submitted to EFSA on 20 September as part of the draft final deliverable. As a result of the final meeting, Area 2 and Area 4 summary tables were updated and also submitted to EFSA on 4 October (by e-mail) as part of the final deliverable. The summary tables are available in Annex A-L.

EndNote™ files

In the EndNote files (three files per Area, i.e. one file per substance group) all references were separated in up to six folders:

- 1. Relevant – green: Containing references evaluated to be of relevance for this procurement.
- 2. Relevant – from other Areas: Containing relevant or maybe relevant references for this procurement that were identified in another Area / other Areas than the specific Area, but not retrieved in the Area specific literature searches in PubMed, Web of Science and SciFinder®.
- 3. Maybe relevant – yellow: Containing references for which the relevance could not be evaluated because, e.g. of missing or vague abstracts, or because the objectives of the reference were borderline to be considered relevant according to the eligibility criteria.
- 4. Maybe relevant – unknown substance group: Containing references evaluated to be of relevance for this procurement, but where the substances were not specified.
- 5. Not relevant: Containing references evaluated not to be in-scope for this procurement.
- 6. Not relevant – substance groups: Containing references evaluated to be of relevance for the two other substance groups.

The EndNote files were submitted to EFSA on 20 September (by e-mail) as part of the draft final deliverable and are available in Annex M-X.

Reference lists

All relevant references were collected in a reference list (Word file), three files per Area, i.e. one file per substance group. The reference lists are included in Appendix C to this report.

4 Conclusion

An ELS to identify and collect all studies related to the toxicity of PBDEs, TBBPA and BPs was performed in the three databases PubMed, Web of Science and SciFinder® for four Areas.

The total number of references from each database was 6,231 from Area 1, 8,236 from Area 2, 4,994 from Area 3 and 6,363 from Area 4.

The evaluation of all retrieved references for relevance by screening the title and abstract (if available) and applying eligibility criteria (inclusion/exclusion) resulted in a total number of relevant references for Area 1 of 378 (PBDEs), 46 (TBBPA) and 29 (BPs), for Area 2 of 188

(PBDEs), 37 (TBBPA) and 4 (BPs), for Area 3 of 518 (PBDEs), 180 (TBBPA) and 49 (BPs), and for Area 4 of 717 (PBDEs), 59 (TBBPA) and 18 (BPs).

References

European Food Safety Authority; Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010; 8(6):1637. [90 pp.]. doi:10.2903/j.efsa.2010.1637. Available online: www.efsa.europa.eu

EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. EFSA Journal 2011;9(5):2156. [274 pp.] doi:10.2903/j.efsa.2011.2156. Available online: www.efsa.europa.eu/efsajournal

EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. EFSA Journal 2011;9(12):2477. [67 pp.] doi:10.2903/j.efsa.2011.2477. Available online: www.efsa.europa.eu/efsajournal

EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on Brominated Flame

Retardants (BFRs) in Food: Brominated Phenols and their Derivatives. EFSA Journal 2012;10(4):2634. [42 pp.] doi:10.2903/j.efsa.2012.2634. Available online: www.efsa.europa.eu/efsajournal

Abbreviations

BDE	Brominated diphenyl ethers
BFR	Brominated flame retardant
BP	Brominated phenol
BTBPE	1,2-Bis(2,4,6-tribromophenoxy)ethane
DBDPE	Decabromdiphenylethane
EFSA	European Food Safety Authority
ELS	Extensive literature search
MoA	Mode of Action
PBDE	Polybrominated diphenyl ether
TBBPA	Tetrabromobisphenol A
TBBPS	Tetrabromobisphenol S

Appendix A – Tables Regarding Eligibility Criteria for Area 1-4 (as in Annex 3 of the technical specifications

Table A1. Eligibility criteria for the selection of studies in **humans**

Study design	In	Cross-sectional studies Cohort studies Case-control studies (retrospective and nested) Case series/Case reports
	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, transplacental exposure) Studies in which levels of the following target compounds have been measured in human tissues (including by bioassays), OR Studies in which the total exposure to the following target compounds has been estimated: – PBDEs (including individual congeners), – TBBPA and its derivatives, – brominated phenols and their derivatives.
	Out	Studies on compounds other than PBDEs, TBBPA and its derivatives, and brominated phenols and their derivatives.
Specific outcome of interest	In	All endpoints
	Out	/
Language	In	English
Time	In	From 2010 onwards for PBDEs; From 2010 onwards for TBBPA and its derivatives; From 2011 onwards for brominated phenols and their derivatives.
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses [(a)]
	Out	Expert opinions, editorials, and letters to the editor PhD Theses Extended abstracts, conference proceedings

(a): Systematic reviews, reviews and meta-analysis will be included and used as background information for the hazard characterisation.

Table A2. Eligibility criteria for the **toxicity in experimental animals**

Study design	In	Experimental animal studies (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink, pigs)
	Out	Studies on transgenic animals Human studies *In vitro* studies
Study characteristics:	In	Any study duration Any number of animals
	Out	/
Population	In	Any experimental animal study, all ages, males and females
	Out	/
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), subcutaneous, intraperitoneal, intramuscular, intravenous Exposure regime: single or repeated administration Number of doses: any Compounds: – PBDEs (including individual congeners), – TBBPA and its derivatives, – brominated phenols and their derivatives.
	Out	Route of administration: dermal, inhalation, Studies on compounds other than PBDEs, TBBPA and its derivatives, and brominated phenols and their derivatives.
Specific outcome of interest	In	All endpoints, including: Studies on enzyme induction only (e.g. CYP modulation) Studies on gene expression only Studies on co-administration of pro-carcinogens (CON A, DMBA, NKK) only Studies on -omics profiles
	Out	Studies on the protective effects of certain substances against toxicity caused by PBDEs, TBBPA and its derivatives, and brominated phenols and their derivatives.
Language	In	English
Time	In	From 2010 onwards for PBDEs; From 2010 onwards for TBBPA and its derivatives; From 2011 onwards for brominated phenols and their derivatives.
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses [(a)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

(a): Systematic reviews, reviews and meta-analysis will be included and used as background information.

Table A3. Eligibility criteria for the **Toxicokinetics**

Study design	In	Experimental animal (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink, pigs), human and *in vitro* studies in relation to: • absorption • distribution • metabolism • excretion
	Out	/
Study characteristics:	In	Any study duration Any number of animals
	Out	/
Population	In	Any experimental animal (all ages, males and females), human or *in vitro* study
	Out	/
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), subcutaneous, intraperitoneal, intramuscular, intravenous Compounds: – PBDEs (including individual congeners), – TBBPA and its derivatives, – brominated phenols and their derivatives. Number of doses: any Exposure regime: single or repeated administration
	Out	Route of administration: dermal and inhalation. Studies on compounds other than PBDEs, TBBPA and its derivatives, and brominated phenols and their derivatives.
Specific outcome of interest	In	Any outcome in relation to absorption, distribution, metabolism, excretion, toxicokinetic modelling and levels in human tissues.
	Out	/
Language	In	English
Time	In	From 2010 onwards for PBDEs; From 2010 onwards for TBBPA and its derivatives; From 2011 onwards for brominated phenols and their derivatives.
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses [(a)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

(a): Systematic reviews, reviews and meta-analysis will be included and used as background information.

Table A4. Eligibility criteria for the **genotoxicity and mode of action**

Study design	In	Experimental animal studies (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink, pigs) and *in vitro* studies In relation to: • genotoxicity, • mode of action Including studies on transgenic animals [(a)]
	Out	/
Study characteristics:	In	Any study duration Any number of animals
	Out	/
Population	In	Any experimental animal (all ages, males and females) or *in vitro* study
	Out	/
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), subcutaneous, intraperitoneal, intramuscular, intravenous. Compounds: – PBDEs (including individual congeners), – TBBPA and its derivatives, – brominated phenols and their derivatives. Number of doses: any Exposure regime: single or repeated administration
	Out	Route of administration: dermal and inhalation Studies on compounds other than PBDEs, TBBPA and its derivatives, and brominated phenols and their derivatives.
Specific outcome of interest	In	Genotoxicity and mechanistic studies
	Out	/
Language	In	English
Time	In	From 2010 onwards for PBDEs; From 2010 onwards for TBBPA and its derivatives; From 2011 onwards for and brominated phenols.
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses [(b)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

(a): It is considered that studies on transgenic animals are helpful in terms of mechanism of action.
(b): Systematic reviews, reviews and meta-analysis will be included and used as background information.

Appendix B – Log file for the tailored search strings to retrieve all relevant data on the toxicity of PBDEs, TBBPA and BPs

Database: **PubMed**

Limitations applied to search: From 2010/01/01. Language = English

Date of search May 21, 2019

Search terms	No of references	Comments & follow-up actions
(PBDE*[Text Word] OR BDE*[Text Word] OR polybrominated*[Text Word] OR TBBPA*[Text Word] OR tetrabromobisphenol*[Text Word] OR bromophenol*[Text Word] OR monobromophenol*[Text Word] OR dibromophenol*[Text Word] OR tribromophenol*[Text Word] OR tetrabromophenol*[Text Word] OR pentabromophenol*[Text Word] OR brominated*[Text Word] OR bromophenyl*[Text Word] OR tribromophenyl*[Text Word] OR pentabromophenyl*[Text Word] OR bromodiphenyl*[Text Word] OR bromophenoxy*[Text Word] OR tribromophenoxy*[Text Word] OR pentabromophenoxy*[Text Word] OR dibromopropyl*[Text Word] OR TBBPS*[Text Word] OR monoBDE*[Text Word] OR mono-BDE*[Text Word] OR diBDE*[Text Word] OR di-BDE*[Text Word] OR triBDE*[Text Word] OR tri-BDE*[Text Word] OR tetraBDE*[Text Word] OR tetra-BDE*[Text Word] OR pentaBDE*[Text Word] OR penta-BDE*[Text Word] OR hexaBDE*[Text Word] OR hexa-BDE*[Text Word] OR heptaBDE*[Text Word] OR hepta-BDE*[Text Word] OR octaBDE*[Text Word] OR octa-BDE*[Text Word] OR nonaBDE*[Text Word] OR nona-BDE*[Text Word] OR decaBDE*[Text Word] OR deca-BDE*[Text Word] OR BTBPE*[Text Word] OR DBDPE*[Text Word]) AND (in vitro[Text Word] OR absor*[Text Word] OR tissue*[Text Word] OR metaboli*[Text Word] OR excret*[Text Word] OR kinetic*[Text Word] OR toxicokinetic*[Text Word] OR pharmacokinetic*[Text Word] OR degrad*[Text Word] OR biotrans*[Text Word] OR eliminat*[Text Word] OR PBPK[Text Word] OR PBK[Text Word] OR PBTK[Text Word])	4394	Area 1 Exported to EndNote™
(PBDE*[Text Word] OR BDE*[Text Word] OR polybrominated*[Text Word] OR TBBPA*[Text Word] OR tetrabromobisphenol*[Text Word] OR bromophenol*[Text Word] OR monobromophenol*[Text Word] OR dibromophenol*[Text Word] OR tribromophenol*[Text Word] OR tetrabromophenol*[Text Word] OR pentabromophenol*[Text Word] OR brominated*[Text Word] OR bromophenyl*[Text Word] OR tribromophenyl*[Text Word] OR pentabromophenyl*[Text Word] OR bromodiphenyl*[Text Word] OR bromophenoxy*[Text Word] OR tribromophenoxy*[Text Word] OR pentabromophenoxy*[Text Word] OR	5695	Area 2 Exported to EndNote™

dibromopropyl*[Text Word] OR TBBPS*[Text Word] OR monoBDE*[Text Word] OR mono-BDE*[Text Word] OR diBDE*[Text Word] OR di-BDE*[Text Word] OR triBDE*[Text Word] OR tri-BDE*[Text Word] OR tetraBDE*[Text Word] OR tetra-BDE*[Text Word] OR pentaBDE*[Text Word] OR penta-BDE*[Text Word] OR hexaBDE*[Text Word] OR hexa-BDE*[Text Word] OR heptaBDE*[Text Word] OR hepta-BDE*[Text Word] OR octaBDE*[Text Word] OR octa-BDE*[Text Word] OR nonaBDE*[Text Word] OR nona-BDE*[Text Word] OR decaBDE*[Text Word] OR deca-BDE*[Text Word] OR BTBPE*[Text Word] OR DBDPE*[Text Word]) AND (in vivo[Text Word] OR acute[Text Word] OR chronic[Text Word] OR tox*[Text Word] OR cancer*[Text Word] OR carcino*[Text Word] OR tumor*[Text Word] OR tumour*[Text Word] OR organ*[Text Word] OR tissue*[Text Word] OR immun*[Text Word] OR neuro*[Text Word] OR developmental[Text Word] OR teratogen*[Text Word] OR repro*[Text Word] OR liver[Text Word] OR hepato*[Text Word] OR kidney*[Text Word] OR brain*[Text Word] OR lung[Text Word] OR lungs[Text Word] OR heart*[Text Word] OR thyroid*[Text Word] OR gene[Text Word] OR genes[Text Word] OR rat*[Text Word] OR mouse[Text Word] OR mice[Text Word] OR rabbit*[Text Word] OR guinea[Text Word] OR hamster*[Text Word] OR primate*[Text Word] OR monkey*[Text Word] OR pig*[Text Word] OR minipig*[Text Word] OR dog*[Text Word] OR cat*[Text Word] OR mink*[Text Word])		
(PBDE*[Text Word] OR BDE*[Text Word] OR polybrominated*[Text Word] OR TBBPA*[Text Word] OR tetrabromobisphenol*[Text Word] OR bromophenol*[Text Word] OR monobromophenol*[Text Word] OR dibromophenol*[Text Word] OR tribromophenol*[Text Word] OR tetrabromophenol*[Text Word] OR pentabromophenol*[Text Word] OR brominated*[Text Word] OR bromophenyl*[Text Word] OR tribromophenyl*[Text Word] OR pentabromophenyl*[Text Word] OR bromodiphenyl*[Text Word] OR bromophenoxy*[Text Word] OR tribromophenoxy*[Text Word] OR pentabromophenoxy*[Text Word] OR dibromopropyl*[Text Word] OR TBBPS*[Text Word] OR monoBDE*[Text Word] OR mono-BDE*[Text Word] OR diBDE*[Text Word] OR di-BDE*[Text Word] OR triBDE*[Text Word] OR tri-BDE*[Text Word] OR tetraBDE*[Text Word] OR tetra-BDE*[Text Word] OR pentaBDE*[Text Word] OR penta-BDE*[Text Word] OR hexaBDE*[Text Word] OR hexa-BDE*[Text Word] OR heptaBDE*[Text Word] OR hepta-BDE*[Text Word] OR octaBDE*[Text Word] OR octa-BDE*[Text Word] OR nonaBDE*[Text Word] OR nona-BDE*[Text Word] OR decaBDE*[Text Word] OR deca-BDE*[Text Word] OR BTBPE*[Text Word] OR DBDPE*[Text Word]) AND (in vitro[Text Word] OR in vivo[Text Word] OR mode[Text Word] OR hormon*[Text Word] OR endocrin*[Text Word] OR estrogen*[Text Word] OR oestrogen*[Text Word] OR androgen*[Text Word] OR mechanism*[Text Word] OR apoptosis[Text Word] OR oxidative[Text Word] OR cytotox*[Text Word] OR genotox*[Text Word] OR muta*[Text	3375	Area 3 Exported to EndNote™

Word] OR DNA[Text Word] OR clastogen*[Text Word] OR aneugen*[Text Word] OR chromosom*[Text Word] OR culture[Text Word] OR enzyme*[Text Word])		
(PBDE*[Text Word] OR BDE*[Text Word] OR polybrominated*[Text Word] OR TBBPA*[Text Word] OR tetrabromobisphenol*[Text Word] OR bromophenol*[Text Word] OR monobromophenol*[Text Word] OR dibromophenol*[Text Word] OR tribromophenol*[Text Word] OR tetrabromophenol*[Text Word] OR pentabromophenol*[Text Word] OR brominated*[Text Word] OR bromophenyl*[Text Word] OR tribromophenyl*[Text Word] OR pentabromophenyl*[Text Word] OR bromodiphenyl*[Text Word] OR bromophenoxy*[Text Word] OR tribromophenoxy*[Text Word] OR pentabromophenoxy*[Text Word] OR dibromopropyl*[Text Word] OR TBBPS*[Text Word] OR monoBDE*[Text Word] OR mono-BDE*[Text Word] OR diBDE*[Text Word] OR di-BDE*[Text Word] OR triBDE*[Text Word] OR tri-BDE*[Text Word] OR tetraBDE*[Text Word] OR tetra-BDE*[Text Word] OR pentaBDE*[Text Word] OR penta-BDE*[Text Word] OR hexaBDE*[Text Word] OR hexa-BDE*[Text Word] OR heptaBDE*[Text Word] OR hepta-BDE*[Text Word] OR octaBDE*[Text Word] OR octa-BDE*[Text Word] OR nonaBDE*[Text Word] OR nona-BDE*[Text Word] OR decaBDE*[Text Word] OR deca-BDE*[Text Word] OR BTBPE*[Text Word] OR DBDPE*[Text Word]) AND (epidemio*[Text Word] OR intervention[Text Word] OR exposure*[Text Word] OR case*[Text Word] OR poison*[Text Word] OR cohort*[Text Word] OR cross-sectional[Text Word] OR random*[Text Word] OR work*[Text Word] OR occupation*[Text Word] OR biomark*[Text Word] OR human*[Text Word] OR meta-analys*[Text Word])	4574	Area 4 Exported to EndNote™

Database: **Web of Science**

Limitations applied to search: From 2010/01/01. Language = English

Document types = Article OR Correction OR Correction, Addition OR Data Paper OR Discussion OR Early Access OR Note OR Retracted Publication OR Retraction OR Review.

Date of search: May 21, 2019

Search terms	**Limitations to search**	**No of references**	**Comments & follow-up actions**
(TS=(PBDE* OR BDE* OR polybrominated* OR TBBPA* OR tetrabromobisphenol* OR bromophenol* OR monobromophenol* OR dibromophenol* OR tribromophenol* OR tetrabromophenol* OR pentabromophenol* OR brominated* OR bromophenyl* OR	Science categories: TOXICOLOGY OR CHEMISTRY MULTIDISCIPLINARY OR CHEMISTRY MEDICINAL OR PHARMACOLOGY	2093	Area 1 Exported to EndNote™

Search terms	Limitations to search	No of references	Comments & follow-up actions
tribromophenyl* OR pentabromophenyl* OR bromodiphenyl* OR bromophenoxy* OR tribromophenoxy* OR pentabromophenoxy* OR dibromopropyl* OR TBBPS* OR monoBDE* OR mono-BDE* OR diBDE* OR di-BDE* OR triBDE* OR tri-BDE* OR tetraBDE* OR tetra-BDE* OR pentaBDE* OR penta-BDE* OR hexaBDE* OR hexa-BDE* OR heptaBDE* OR hepta-BDE* OR octaBDE* OR octa-BDE* OR nonaBDE* OR nona-BDE* OR decaBDE* OR deca-BDE* OR BTBPE* OR DBDPE*) AND (*in vitro* OR absor* OR tissue* OR metaboli* OR excret* OR kinetic* OR toxicokinetic* OR pharmacokinetic* OR degrad* OR biotrans* OR eliminat* OR PBPK OR PBK OR PBTK))	PHARMACY OR BIOCHEMISTRY MOLECULAR BIOLOGY OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR MULTIDISCIPLINARY SCIENCES OR FOOD SCIENCE TECHNOLOGY OR ENDOCRINOLOGY METABOLISM		
(TS=(PBDE* OR BDE* OR polybrominated* OR TBBPA* OR tetrabromobisphenol* OR bromophenol* OR monobromophenol* OR dibromophenol* OR tribromophenol* OR tetrabromophenol* OR pentabromophenol* OR brominated* OR bromophenyl* OR tribromophenyl* OR pentabromophenyl* OR bromodiphenyl* OR bromophenoxy* OR tribromophenoxy* OR pentabromophenoxy* OR dibromopropyl* OR TBBPS* OR monoBDE* OR mono-BDE* OR diBDE* OR di-BDE* OR triBDE* OR tri-BDE* OR tetraBDE* OR tetra-BDE* OR pentaBDE* OR penta-BDE* OR hexaBDE* OR hexa-BDE* OR heptaBDE* OR hepta-BDE* OR octaBDE* OR octa-BDE* OR nonaBDE* OR nona-BDE* OR decaBDE* OR deca-BDE* OR BTBPE* OR DBDPE*) AND (*in vivo* OR acute OR chronic OR tox* OR cancer* OR carcino* OR tumor* OR tumour* OR organ* OR tissue* OR immun* OR neuro* OR developmental OR teratogen* OR repro* OR liver OR hepato* OR kidney* OR brain* OR lung OR lungs OR heart* OR thyroid* OR gene OR genes OR rat* OR mouse OR mice OR rabbit* OR guinea OR hamster* OR primate* OR monkey* OR pig* OR minipig* OR dog* OR cat* OR mink*))	Science categories: TOXICOLOGY OR CHEMISTRY MULTIDISCIPLINARY OR PHARMACOLOGY PHARMACY OR MULTIDISCIPLINARY SCIENCES OR FOOD SCIENCE TECHNOLOGY OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR BIOCHEMISTRY MOLECULAR BIOLOGY OR NEUROSCIENCES OR REPRODUCTIVE BIOLOGY OR ONCOLOGY OR IMMUNOLOGY OR PATHOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS OR CLINICAL NEUROLOGY OR DEVELOPMENTAL BIOLOGY	2646	Area 2 Exported to EndNote™
(TS=(PBDE* OR BDE* OR polybrominated* OR TBBPA* OR tetrabromobisphenol* OR bromophenol* OR monobromophenol* OR dibromophenol* OR tribromophenol* OR tetrabromophenol* OR pentabromophenol* OR brominated* OR bromophenyl* OR tribromophenyl* OR pentabromophenyl* OR bromodiphenyl* OR bromophenoxy* OR tribromophenoxy* OR pentabromophenoxy* OR dibromopropyl* OR TBBPS* OR monoBDE* OR	Science categories TOXICOLOGY OR CHEMISTRY MULTIDISCIPLINARY OR BIOCHEMISTRY MOLECULAR BIOLOGY OR PHARMACOLOGY PHARMACY OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH	2291	Area 3 Exported to EndNote™

Search terms	Limitations to search	No of references	Comments & follow-up actions
mono-BDE* OR diBDE* OR di-BDE* OR triBDE* OR tri-BDE* OR tetraBDE* OR tetra-BDE* OR pentaBDE* OR penta-BDE* OR hexaBDE* OR hexa-BDE* OR heptaBDE* OR hepta-BDE* OR octaBDE* OR octa-BDE* OR nonaBDE* OR nona-BDE* OR decaBDE* OR deca-BDE* OR BTBPE* OR DBDPE*) AND (*in vitro* OR *in vivo* OR mode OR hormon* OR endocrin* OR estrogen* OR oestrogen* OR androgen* OR mechanism* OR apoptosis OR oxidative OR cytotox* OR genotox* OR muta* OR DNA OR clastogen* OR aneugen* OR chromosom* OR culture OR enzyme*))	OR MULTIDISCIPLINARY SCIENCES OR FOOD SCIENCE TECHNOLOGY OR ENDOCRINOLOGY METABOLISM OR GENETICS HEREDITY OR CELL BIOLOGY		
(TS=(PBDE* OR BDE* OR polybrominated* OR TBBPA* OR tetrabromobisphenol* OR bromophenol* OR monobromophenol* OR dibromophenol* OR tribromophenol* OR tetrabromophenol* OR pentabromophenol* OR brominated* OR bromophenyl* OR tribromophenyl* OR pentabromophenyl* OR bromodiphenyl* OR bromophenoxy* OR tribromophenoxy* OR pentabromophenoxy* OR dibromopropyl* OR TBBPS* OR monoBDE* OR mono-BDE* OR diBDE* OR di-BDE* OR triBDE* OR tri-BDE* OR tetraBDE* OR tetra-BDE* OR pentaBDE* OR penta-BDE* OR hexaBDE* OR hexa-BDE* OR heptaBDE* OR hepta-BDE* OR octaBDE* OR octa-BDE* OR nonaBDE* OR nona-BDE* OR decaBDE* OR deca-BDE* OR BTBPE* OR DBDPE*) AND (epidemio* OR intervention OR exposure* OR case* OR poison* OR cohort* OR cross-sectional OR random* OR work* OR occupation* OR biomark* OR human* OR meta-analys*))	Science categories TOXICOLOGY OR PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH OR CHEMISTRY MULTIDISCIPLINARY OR PHARMACOLOGY PHARMACY OR BIOCHEMISTRY MOLECULAR BIOLOGY OR FOOD SCIENCE TECHNOLOGY OR MULTIDISCIPLINARY SCIENCES OR NEUROSCIENCES OR REPRODUCTIVE BIOLOGY OR ONCOLOGY OR MEDICINE RESEARCH EXPERIMENTAL OR IMMUNOLOGY OR OBSTETRICS GYNECOLOGY OR PEDIATRICS OR MEDICINE GENERAL INTERNAL OR DEVELOPMENTAL BIOLOGY OR PATHOLOGY OR BEHAVIORAL SCIENCES OR PHYSIOLOGY OR CLINICAL NEUROLOGY OR OTORHINOLARYNGOLOGY OR GASTROENTEROLOGY HEPATOLOGY OR ANDROLOGY OR CARDIAC CARDIOVASCULAR	2476	Area 4 Exported to EndNote™

Search terms	Limitations to search	No of references	Comments & follow-up actions
	SYSTEMS OR WOMEN S STUDIES OR ANATOMY MORPHOLOGY OR HEMATOLOGY OR PSYCHOLOGY BIOLOGICAL OR UROLOGY NEPHROLOGY OR ALLERGY OR PERIPHERAL VASCULAR DISEASE		

Database: **SciFinder®**

Limitations applied to search:

From 2010/01/01 for PBDEs and TBBPA and its derivatives and from 2011/01/01 for BPs and their derivatives.

Language = English.

Document types = Clinical Trial OR Journal OR Preprint OR Review.

Specific compounds and their CAS RN:

Compound	CAS RN
Tetrabromobisphenol A (TBBPA)	79-94-7
TBBPA-bOHEE	4162-45-2
TBBPA-bAE	25327-89-3
TBBPA-bDiBPrE	21850-44-2
TBBPA-bGE	3072-84-2
TBBPA-bAcr	55205-38-4
TBBPA-bOAc	33798-02-6
TBBPA-bOHEE-bAcr	66710-97-2
TBBPA-bME	70156-79-5
TBBPA-bOPr	37419-42-4
2,4,6-tribromophenol (2,4,6-TBP)	118-79-6
2,4-dibromophenol (2,4-DBP)	615-58-7
Pentabromophenol (PBP)	608-71-9
Tribromophenol-2,3-dibromopropyl ether (TBP-DBPE)	168434-45-5
2,4,6-TBP allyl ether (TBP-AE)	3278-89-5
PBP allyl ether (PBP-AE)	3555-11-1
TBP 2,3-dibromopropyl ether (TBP-DBPE)	35109-60-5
Tetrabromobisphenol S (TBBPS)	39635-79-5
TBBPS bismethyl ether (TBBPS-BME)	70156-79-5
TBBPS bis(2,3-dibromopropyl ether)	42757-55-1
BDE-28	41318-75-6
BDE-47	5436-43-1

BDE-99	60348-60-9
BDE-100	189084-64-8
BDE-153	68631-49-2
BDE-154	207122-15-4
BDE-183	207122-16-5
BDE-209	1163-19-5
BTBPE (1,2-Bis(2,4,6-tribromphenoxy)ethane)	37853-59-1
DBDPE (BDPE-209, Decabromdiphenylethane)	84852-53-9

Date of search	**Search terms**	**No of references**	**Comments & follow-up actions**
10-05-2019	((79-94-7 OR 4162-45-2 OR 25327-89-3 OR 21850-44-2 OR 3072-84-2 OR 55205-38-4 OR 33798-02-6 OR 66710-97-2 OR 70156-79-5 OR 37419-42-4 OR 118-79-6 OR 615-58-7 OR 608-71-9 OR 168434-45-5 OR 3278-89-5 OR 3555-11-1 OR 35109-60-5 OR 39635-79-5 OR 70156-79-5 OR 42757-55-1 OR 41318-75-6 OR 5436-43-1 OR 60348-60-9 OR 189084-64-8 OR 68631-49-2 OR 207122-15-4 OR 207122-16-5 OR 1163-19-5 OR 37853-59-1 OR 84852-53-9) AND (*in vitro* OR absorption OR tissue OR metabolite OR excretion OR kinetic OR toxicokinetic OR pharmacokinetic OR degradation OR biotransformation OR elimination OR PBPK OR PBK OR PBTK))	2626	Area 1 Exported to EndNote™
13-05-2019	((79-94-7 OR 4162-45-2 OR 25327-89-3 OR 21850-44-2 OR 3072-84-2 OR 55205-38-4 OR 33798-02-6 OR 66710-97-2 OR 70156-79-5 OR 37419-42-4 OR 118-79-6 OR 615-58-7 OR 608-71-9 OR 168434-45-5 OR 3278-89-5 OR 3555-11-1 OR 35109-60-5 OR 39635-79-5 OR 70156-79-5 OR 42757-55-1 OR 41318-75-6 OR 5436-43-1 OR 60348-60-9 OR 189084-64-8 OR 68631-49-2 OR 207122-15-4 OR 207122-16-5 OR 1163-19-5 OR 37853-59-1 OR 84852-53-9) AND (*in vivo* OR acute OR chronic OR toxic OR cancer OR tumor OR organ OR tissue OR immune OR neuro OR developmental OR teratogen OR repro OR liver OR hepato OR kidney OR brain OR lung OR heart OR thyroid OR gene OR rat OR mouse OR rabbit OR guinea OR hamster OR primate OR monkey OR pig OR minipig OR dog OR cat OR mink))	3531	Area 2 Exported to EndNote™
10-05-2019	((79-94-7 OR 4162-45-2 OR 25327-89-3 OR 21850-44-2 OR 3072-84-2 OR 55205-38-4 OR 33798-02-6 OR 66710-97-2 OR 70156-79-5 OR 37419-42-4 OR 118-79-6 OR 615-58-7 OR 608-71-9 OR 168434-45-5 OR 3278-89-5 OR 3555-11-1 OR 35109-60-5 OR 39635-79-5 OR 70156-79-5 OR 42757-55-1 OR 41318-75-6 OR 5436-43-1 OR 60348-60-9 OR 189084-64-8 OR 68631-49-2 OR 207122-15-4 OR 207122-16-5 OR 1163-19-5 OR 37853-59-1 OR 84852-53-9) AND (*in vitro* OR *in vivo* OR mode OR hormone OR endocrine OR estrogen OR androgen OR mechanism OR apoptosis OR	1904	Area 3 Exported to EndNote™

	oxidative OR cytotoxic OR genotoxic OR mutagenic OR DNA OR clastogen OR aneugen OR chromosome OR culture OR enzyme))		
13-05-2019	((79-94-7 OR 4162-45-2 OR 25327-89-3 OR 21850-44-2 OR 3072-84-2 OR 55205-38-4 OR 33798-02-6 OR 66710-97-2 OR 70156-79-5 OR 37419-42-4 OR 118-79-6 OR 615-58-7 OR 608-71-9 OR 168434-45-5 OR 3278-89-5 OR 3555-11-1 OR 35109-60-5 OR 39635-79-5 OR 70156-79-5 OR 42757-55-1 OR 41318-75-6 OR 5436-43-1 OR 60348-60-9 OR 189084-64-8 OR 68631-49-2 OR 207122-15-4 OR 207122-16-5 OR 1163-19-5 OR 37853-59-1 OR 84852-53-9) AND (epidemio OR intervention OR exposure OR case OR poison OR cohort OR cross-sectional OR random OR work OR occupation OR biomar OR human OR meta-analysis))	2762	Area 4 Exported to EndNote™

Appendix C – Log file for the tailored search strings to retrieve all relevant data on the toxicity of PBDEs, TBBPA and BPs

AREA 1 PBDEs

Reference list with all relevant references identified for Area 1: Data on toxicokinetics (absorption, distribution, metabolism, excretion) in experimental animals and humans and from in vitro studies, published in English since year 2010 for PBDEs.

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AREA 3

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AREA 3

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AREA 4

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