1 Prioritised substance group: Flame retardants

<table>
<thead>
<tr>
<th>Responsible author</th>
<th>Lisa Melymuk</th>
<th>E-mail</th>
<th><a href="mailto:melymuk@recetox.muni.cz">melymuk@recetox.muni.cz</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Short name of institution</td>
<td>MU</td>
<td>Phone</td>
<td>+420 549 493 995</td>
</tr>
<tr>
<td>Co-authors</td>
<td>Jana Klánová, Lola Bajard, Garry Codling</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.1 Background information

Flame retardant (FR) is the term given to any compound or mixture added to a consumer product or building material to reduce the flammability and thus improve product safety. Flame retardants can be either chemically-bound to the material of the consumer product, or chemical additives (not bound to the product material). A range of both inorganic and organic FRs are in use; however of concern with respect to HBM4EU are in particular the synthetic organic flame retardants. There are three primary types of synthetic organic FRs categorised based on their elemental composition, these being bromine (Br), chlorine (Cl) and phosphate (P).

Since the 1970s, the primary FR compounds used were the polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD). However, due to concerns regarding their persistence, toxicity and bioaccumulative potential, these compounds have been added to the Stockholm Convention on Persistent Organic Pollutants (www.pops.int), including the most recent addition of deca-BDE (also called BDE-209, referring to the PBDE with 10 bromines) in 2017. Yet, although these compounds are regulated under the Stockholm Convention and through other regulatory mechanisms, the need for FRs has not decreased and this has led to a broadening of the market for FR compounds, with a wide range of replacement compounds used globally. These replacement compounds are typically brominated, chlorinated and organophosphate compounds, some of which are mentioned below. In the following document, OPE (organophosphate esters), refers to the organophosphate-based FRs, while NBFR (novel brominated flame retardant) refers to the brominated replacements for PBDEs and HBCDD.

1.1.1 Hazardous Properties

PBDEs and HBCDDs have been identified to have a range of adverse health effects, including potential neurotoxic, endocrine, and carcinogenic effects. The toxicity of tetrabromobisphenol A (TBBPA) is also well-studied and it has been identified to have a range of potential hazardous properties. Early evidence suggests that a number of the replacement FRs may have similar health concerns, and moreover, insufficient evidence exists to evaluate toxicity for many of these new FRs. The toxicity and human exposure of selected FRs has been investigated in individual studies, and aquatic toxicity has received significant attention, but there remain large gaps in toxicity studies of directly applicability to human populations.

Bis(2-ethylhexyl)tetabromophthalate (BEH-TEBP) and 2-ethylhexyl-2,3,4,5-tetabromobenzoate (EH-TBB) have been identified as potentially bioaccumulative. Decabromodiphenyl ethane (DBDPE) is structurally similar to BDE-209 and hypothesised to have similar toxicity. Triphenyl phosphate (TPHP) is identified by ECHA as very toxic to aquatic life, has been found to affect oestrogen receptor binding activities in zebrafish, and may be associated with altered hormone levels and decreased semen quality in men. Tris-2-chloroethyl phosphate (TCEP) was also found to be hazardous.

---

1 Actually, six isomers of HBCDD exist. Therefore, sometimes the plural HBCDDs is used as synonymous for HBCDD.
to affect oestrogen receptor binding activities in zebrafish,\textsuperscript{12} may affect neurodevelopment, with multiple mechanisms of toxicity,\textsuperscript{8} and is a possible reproductive toxin.\textsuperscript{14} TCIPP may also affect neurodevelopment\textsuperscript{8} and is potentially carcinogenic.\textsuperscript{14} Tris(1,3-dichloropropyl)phosphate (TDCIPP) may be associated with altered hormone levels and decreased semen quality in men,\textsuperscript{13} may affect neurodevelopment, with multiple mechanisms of toxicity,\textsuperscript{8} and also may be carcinogenic.\textsuperscript{14}

The OPEs in particular are seeing significant recent use as FRs, and the levels in consumer products, and in the environment are typically orders of magnitude higher than the brominated and chlorinated FRs.\textsuperscript{15,16} A number of OPEs have evidence of toxic effects in mammals, but generally toxicity data is insufficient, and is a crucial knowledge gap considering the high environmental levels of these compounds. Short-term and long-term toxicological data are needed, including additive or synergistic effects of FR mixtures. Many flame retardants exist in mixtures, e.g., the technical mixtures of the PBDEs, and Firemaster 550, which contains triphenyl phosphate (TPHP), isopropylated triphenyl phosphate isomers (ip-TPP), 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate (BEH-TEBP). In terms of toxicity, the PBDEs have received attention as mixtures and as individual compounds,\textsuperscript{17} and there is evidence of Firemaster 550 as an endocrine disrupting compound and obesogen.\textsuperscript{9} However, there is generally little attention given to the toxic effects of the typical mixtures of FRs occurring indoors and to which humans are exposed. Thus, the issue of mixture toxicity is highly relevant to FRs, and remains a large data gap within the toxicological knowledge on FRs.

Further knowledge gaps exist in the area of carcinogenicity, especially for hormonal cancers; there is limited information on long-term and chronic health effects; reproductive health and endocrine disrupting effects also require further investigation. Finally, epidemiological studies that include mixtures of FRs are critical to assess links between exposure and health outcomes.

1.1.2 Exposure Characteristics
FRs are widely used in consumer products and building materials, in particular in electronics, textiles and furnishings, automobiles and other vehicles, building insulation, flooring, appliances and ducting, and studies have identified a range of FRs in all of these product groups.\textsuperscript{18–23} The amounts of and types of FRs vary widely even within product groupings, and can be found at up to percentage levels in consumer products, but typically are in the µg/g range.

There is extremely limited information on EU and/or global production of FRs. The provision of this information is challenging for the following reasons: (1) FR producers maintain proprietary control of the chemical composition of some commercial FR mixtures, and information may not be publicly available; (2) regulations and/or information on commercial production of FRs provided for the EU region may not reflect the use in the EU or the potential for human exposure, since many FRs enter the EU already incorporated into consumer products manufactured in other regions, and chemicals already incorporated into consumer products may not be included in some chemical inventories; and (3) the FR market is rapidly changing in response to regulations and shifts in product requirements, and usage information becomes quickly out of date. Further complexity of information of FRs in consumer products arises from variability in FR mass in the same products due to manufacturing variability or use and complex products such as cars contain a range of FRs with components from global sources.

Human exposure to FRs can occur through a variety exposure pathways, via inhalation, ingestion (either through food or ingestion of indoor dusts, as FRs migrate from products and materials into the indoor and outdoor environment) and dermal exposure, including through direct contact with flame-retarded consumer products.\textsuperscript{24} In addition to use as FRs, a number of these compounds (particularly the phosphorus-based FRs) also act as plasticizers,\textsuperscript{14} and thus are also added to
synthetic materials for this purpose. The exposure pathways differ based on the compound properties and FR use. For example, while adult exposure to some FRs is primarily through diet, for babies and toddlers, due to the hand-to-mouth behaviour and mouthing of toys, the primary exposure pathway is through ingestion of house dust.\textsuperscript{25}

In general, human exposure to PBDEs is lower in Europe than in North America,\textsuperscript{26} while evidence from indoor dust and chemical usage suggests higher human exposure to HBCDDs in Europe than in North America based on identified correlations between dust and serum concentrations.\textsuperscript{27,28} The strong interpretations of exposure trends from PBDEs suggest that sufficient biomarker data for other FRs, once obtained, will enable similar improvements in understanding of FR exposure and effects in the European population. Some evidence of regional differences in exposure pathways within Europe for the NBFRs and OPEs,\textsuperscript{29} however there is no systematic overview of regional differences.

1.1.3 Policy Relevance

A small number of FRs are restricted both within the EU as well as at the international level. PBDEs and HBCDD are restricted under the Stockholm Convention on Persistent Organic Pollutants, and now have limited use. Many replacement/alternative FRs are registered under REACH, however there are currently no regulations for a number of FR compounds. Given the existing regulations on flame retardants both at the international (e.g., Stockholm Convention) and European level (e.g., REACH), HBM4EU can contribute by providing information on the effect of legislative restrictions and bans on concentrations in the European human population, particularly with respect to establishing baseline exposure concentrations for current-use flame retardants.

Evaluating and comparing temporal trends for banned/restricted vs. current-use FRs will also allow us to determine if current regulations are effective across the EU, and if the emerging FRs are showing signs of accumulation in the environment or within the European population. For the majority of FRs there are no established safety limits, health-based reference values or guidance values, and limited knowledge of usage volumes due to manufacturer confidentiality.

Of the list of 62 FRs in HBM4EU, 1 is registered under REACH under the 10000-100000 t/y tonnage band, 7 FRs at 1000-10000 t/y and 9 at 100-1000 t/y; 3 FRs are not registered under REACH but listed under CoRAP based on (among others) high aggregated tonnage and wide dispersive use. 28 of the 62 FRs are not registered under REACH.

Of concern is the relative lack of information regarding the use, exposure pathways and toxicity of many of these compounds. The European Food Safety Authority (EFSA) identified 17 brominated FRs which are currently in use and with detectable levels in environmental and/or human matrices, and a further ten brominated FRs that have concentrations >0.1% in consumer products and materials, but lack any information on human and environmental levels or even occurrence at all.\textsuperscript{30} In conjunction with a lack of exposure data, there also is a lack of physicochemical and toxicological information for many of these compounds, and what information is available for some compounds is based on the chemical properties (e.g., quantitative structure–activity relationship models), and estimates rather than direct evidence. This makes it difficult for regulatory bodies and legislative agencies to make informed decisions. Furthermore, the broad suite of known FRs covers a wide range of structures and properties, meaning that in most cases each individual FR must be independently studied to understand emission, exposure and toxicity. Conclusively, it can be said that large data gaps exist for a wide number of FRs.

HBM4EU provides a platform to identify geographic patterns and time trends of exposure from existing data sets and to identify and rectify where major gaps exist through additional targeted investigation. This will allow regulatory agencies to identify any FRs that may be of concern and to make informed decisions.
1.1.4 Technical Aspects

Highly lipophilic FRs, particularly those with higher persistence, such as the PBDEs, can be detected in parent compound form in human matrices, most commonly in human serum and breast milk. In contrast, some NBFRs and many OPEs are metabolised in the body, and more commonly used biomarkers of exposure are metabolites detected in urine. However, many of the metabolites are uncertain, and metabolic pathways are only characterised for a limited number of FRs. Biomarkers for many FRs of emerging concern are unknown. Target matrices for biomonitoring for the emerging FRs can be inferred from physicochemical properties of the molecules, considering their structural similarity to better quantified compounds, and/or relying on chemical modelling techniques, but there is a lack of practical measurement data for many compounds. Many biomonitoring studies report high detection frequencies of FR biomarkers in human matrices, but there is little systematic assessment of temporal or spatial trends. PBDEs are one of the few compounds where generalisation of trends and distributions has been made from biomarkers. Quantification of a rapidly increasing temporal trend of PBDEs in maternal milk in Sweden lead to initial concerns regarding human exposure to PBDEs and first regulatory actions.

Analytical methods for PBDEs and HBCDD in serum and milk are relatively well-established, and have been applied around the world. Analysis for PBDEs is typically via GC-MS, and instrumental parameters vary in individual methods. Analysis of HBCDD can be via GC-MS or LC-MS, however the GC-MS method has limited accuracy and does not allow quantification of individual isomers. LC-MS is strongly recommended for HBCDD. The widespread use of C13-labelled internal standards for both PBDEs and HBCDD allows reliable quantification of these compounds.

Within the replacement NBFRs and OPEs, analytical methods are less established, and recent interlaboratory comparisons have identified large inconsistencies in laboratory performance. As the group of flame retardants is defined by its use, not by its chemical identity, it includes many structurally different chemicals. Thus, analytical methods will differ for certain sub-groups of flame retardants. While the phosphorous flame retardants are a relatively homogenous group, the NBFRs vary greatly. Consequently, methods will have to be optimised for each individual compound. The availability of standards often limits method developments. However, new standards become available each year, and specific interests can be communicated to the producers of analytical standards. Certified reference materials are usually not available, or are not applicable. Older reference materials (e.g., <2000) are not often useful as they do not contain the current complex mixture of FRs that are the replacements for the PBDEs and HBCDD.
1.2 Categorisation of Substances

Category A are substances for which HBM data are sufficient to provide an overall picture of exposure levels across Europe, and interpretation of biomonitoring results in terms of health risks is possible. These substances have identified toxicity to humans and/or environmental systems, and have been regulated/restricted in view of this. Category B substances have some existing HBM data, but it is insufficient to provide a clear picture of human exposure across Europe. Category C substances have scarce HBM data for the European population and require greater knowledge on toxicological characteristics; some biomonitoring data from outside Europe exists. Category D substances have no HBM data from Europe, but some limited HBM data from outside Europe, which can inform on appropriate methods and target matrices. Category E substances have no HBM data. Of the 62 FRs, 9 are in Category A, 12 in Cat. B, 14 in Cat. C, 12 in Cat. D, and 15 in Cat. E.

A detailed breakdown of the separate categorisation based on the availability of toxicological information and HBM data which was combined to determine the overall categorisation listed in Table 1 is available upon request, along with references to support the categorisation.
Table 1-1: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C, D, E substances

<table>
<thead>
<tr>
<th>Cat.</th>
<th>Abbrev./ Acronym</th>
<th>Systematic name</th>
<th>CAS No.</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>BDE-28&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2,4,4′-Tribromodiphenyl ether</td>
<td>41318-75-6</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-47</td>
<td>2,2′,4,4′-Tetrabromodiphenyl ether</td>
<td>5436-43-1</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-99</td>
<td>2,2′,4,4′,5-Pentabromodiphenyl ether</td>
<td>60348-60-9</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-100</td>
<td>2,2′,4,4′,6-Pentabromodiphenyl ether</td>
<td>189084-64-8</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-153</td>
<td>2,2′,4,4′,5,5′-Hexabromodiphenyl ether</td>
<td>68631-49-2</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-154</td>
<td>2,2′,4,4′,5,6′-Hexabromodiphenyl ether</td>
<td>207122-15-4</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-183</td>
<td>2,2′,3,4,4′,5,6-Heptabromodiphenyl ether</td>
<td>207122-16-5</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>BDE-209</td>
<td>2,2′,3,3′,4,4′,5,5′,6,6′-Decabromodiphenyl ether</td>
<td>1163-19-5</td>
<td>Restricted under REACH and listed on Stockholm Convention</td>
</tr>
<tr>
<td>A</td>
<td>HBCDD</td>
<td>Hexabromocyclododecane</td>
<td>3194-55-6, 25637-99-4, 1093632-34-8</td>
<td>On REACH Authorisation List and listed on the Stockholm Convention</td>
</tr>
<tr>
<td>B</td>
<td>TPHP</td>
<td>Triphenyl phosphate</td>
<td>115-86-6</td>
<td>Registered under REACH under the 1000-10000 T/y tonnage band and under CoRAP (suspected ED, consumer use High (aggregated) tonnage, Wide dispersive use)</td>
</tr>
<tr>
<td>B</td>
<td>TMPP</td>
<td>Tricresyl phosphate</td>
<td>1330-78-5</td>
<td>Registered under REACH, entered onto CoRAP for evaluation based on High (aggregated) tonnage, Suspected PBT/vPvB, Wide dispersive use.</td>
</tr>
<tr>
<td>B</td>
<td>TCEP</td>
<td>Tris-2-chloroethyl phosphate</td>
<td>115-96-8</td>
<td>SVHC (Toxic for reproduction (Article 57c)) all uses require an Authorisation under Annex XIV of REACH from 21/08/2015. Being considered for a restriction under Article 69(2)</td>
</tr>
<tr>
<td>B</td>
<td>TCIPP</td>
<td>Tris(1-chloro-2-propyl) phosphate</td>
<td>13674-84-5</td>
<td>Registered under REACH</td>
</tr>
<tr>
<td>B</td>
<td>TDCIPP</td>
<td>Tris(1,3-dichloropropyl)phosphate</td>
<td>13674-87-8</td>
<td>Registered under REACH, Entered onto CoRAP for evaluation in 2019 as potential endocrine disruptor</td>
</tr>
</tbody>
</table>

<sup>2</sup> Individual PBDE congeners are included rather than homologue groups (as in previous scoping document) in line with existing analytical methods and HBM data.
<table>
<thead>
<tr>
<th>Cat.</th>
<th>Abbrev./ Acronym</th>
<th>Systematic name</th>
<th>CAS No.</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>TNBP</td>
<td>Tri-n-butyl phosphate</td>
<td>126-73-8</td>
<td>Registered under REACH, Entered onto CORAP for evaluation in 2012 based on CMR, High (aggregated) tonnage, Wide dispersive use</td>
</tr>
<tr>
<td>B</td>
<td>TBBPA</td>
<td>Tetrabromobisphenol A</td>
<td>79-94-7</td>
<td>Registered under REACH under the 1000-10000 T/y tonnage band and under CoRAP (suspected PBT/vPvB, endocrine disruptor, consumer use, exposure of environment, etc.)</td>
</tr>
<tr>
<td>B</td>
<td>TBOEP</td>
<td>Tri(2-butoxyethyl) phosphate</td>
<td>78-51-3</td>
<td>Registered under REACH under 1000-10000 T/y tonnage band</td>
</tr>
<tr>
<td>B</td>
<td>BEH-TEBP</td>
<td>Bis(2-ethylhexyl)tetramethylphthalate</td>
<td>26040-51-7</td>
<td>Registered under REACH under the 100-1000 T/y tonnage band and under CoRAP (suspected PBT/vPvB and ED, Other hazard based concern, Exposure of environment, Wide dispersive use)</td>
</tr>
<tr>
<td>B</td>
<td>EH-TBB</td>
<td>2-ethylhexyl-2,3,4,5-tetrabromobenzoate</td>
<td>183658-27-7</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>BTBPE</td>
<td>1,2-bis(2,4,6-tribromophenoxy)ethane</td>
<td>37853-59-1</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>B</td>
<td>DDC-CO</td>
<td>Dechlorane Plus</td>
<td>13560-89-9</td>
<td>Registered under REACH under 100-1000 T/y tonnage band</td>
</tr>
<tr>
<td>C</td>
<td>TEHP</td>
<td>Tris(2-ethylhexyl) phosphate</td>
<td>78-42-2</td>
<td>Registered under REACH under 1000-10000 T/y tonnage band</td>
</tr>
<tr>
<td>C</td>
<td>EHDPP</td>
<td>2-ethylhexyl diphenyl phosphate</td>
<td>1241-94-7</td>
<td>Registered under REACH under 1000-10000 T/y tonnage band</td>
</tr>
<tr>
<td>C</td>
<td>DDC-DBF</td>
<td>Dechlorane 602 (1,2,3,4,6,7,8,9,10,11,11-Dodecachloro-1,4,4a,5a,6,9,9a,9b-octahydro-1,4:6,9 dimethanodibenzo[1,f]furan)</td>
<td>31107-44-5</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>C</td>
<td>DBDPE</td>
<td>Decabromodiphenylethane</td>
<td>84852-53-9</td>
<td>Registered under REACH under the 10000-100000 T/y tonnage band and under CoRAP (suspected PBT/vPvB, High (aggregated) tonnage and Wide dispersive use).</td>
</tr>
<tr>
<td>C</td>
<td>TEP</td>
<td>Triethyl phosphate</td>
<td>78-40-0</td>
<td>Registered under REACH</td>
</tr>
<tr>
<td>C</td>
<td>HBB</td>
<td>Hexabromobenzene</td>
<td>87-82-1</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>C</td>
<td>DBE-DBCH</td>
<td>Tetrabromoethylcyclohexane</td>
<td>3322-93-8</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>C</td>
<td>DBHCTD</td>
<td>Hexachlorocyclopentenyl dibromocyclooctane</td>
<td>51936-55-1</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>Cat.</td>
<td>Abbrev./Acronym</td>
<td>Systematic name</td>
<td>CAS No.</td>
<td>Regulation</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>-----------------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>C</td>
<td>PBEB</td>
<td>Pentabromoethylbenzene</td>
<td>85-22-3</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>C</td>
<td>DDC-Ant</td>
<td>Dechlorane 603 (1,2,3,4,5,6,7,8,12,12,13,13-Dodecachloro-1,4,4a,5,8,8a,9,9a,10,10a-decahydro-1,4:5:8:9:10-trimethanoanthracene)</td>
<td>13560-92-4</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>2,4,6-TBP</td>
<td>2,4,6-tribromophenol</td>
<td>118-79-6</td>
<td>Not registered under REACH but under CoRAP (suspected PBT/vPvB, CRM, High (aggregated) tonnage, High RCR, Wide dispersive use)</td>
</tr>
<tr>
<td>C</td>
<td>PBT</td>
<td>Pentabromotoluene</td>
<td>87-83-2</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>C</td>
<td>PBB-Acr</td>
<td>Pentabromobenzyl acrylate</td>
<td>59947-55-1</td>
<td>Registered under REACH under 100-1000 T/y tonnage band</td>
</tr>
<tr>
<td>C</td>
<td>V6</td>
<td>2,2-bis(chloromethyl)trimethylenebis[bis(2-chloroethyl)phosphate]</td>
<td>38051-10-4</td>
<td>Registered under REACH under the 100-1000 T/y tonnage band</td>
</tr>
<tr>
<td>D</td>
<td>ip-TPP</td>
<td>Isopropyl triphenyl phosphate</td>
<td>68937-41-7</td>
<td>Registered under REACH under the 1000-10000 T/y tonnage band</td>
</tr>
<tr>
<td>D</td>
<td>BPA-BDPP</td>
<td>Bisphenol A bis(diphenylphosphate)</td>
<td>5945-33-5</td>
<td>Registered under REACH</td>
</tr>
<tr>
<td>D</td>
<td>TBCO</td>
<td>1,2,5,6-tetabromocyclooctane</td>
<td>3194-57-8</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>PBP</td>
<td>Pentabromophenol</td>
<td>608-71-9</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>D</td>
<td>DBP</td>
<td>2,4-dibromophenol</td>
<td>615-58-7</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>D</td>
<td>TIBP</td>
<td>Tri-iso-butyl phosphate</td>
<td>126-71-6</td>
<td>Registered under REACH under the 1000-10000 T/y tonnage band</td>
</tr>
<tr>
<td>D</td>
<td>TnPP</td>
<td>Tri-n-propyl-phosphate</td>
<td>513-08-6</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>D</td>
<td>TDBPP</td>
<td>Tris(2,3-dibromopropyl) phosphate</td>
<td>126-72-7</td>
<td>Restricted under REACH</td>
</tr>
<tr>
<td>D</td>
<td>CDP</td>
<td>Cresyl diphenyl phosphate</td>
<td>26444-49-5</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>D</td>
<td>HCTBPH</td>
<td>Dechlorane 604 (1,2,3,4,7,7-hexachloro-5-(2,3,4,5-tetabromophenyl)-bicyclo[2.2.1]hept-2-ene)</td>
<td>34571-16-9</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>D</td>
<td>OBTMPI</td>
<td>Octabromotrimethylphenyl indane</td>
<td>1084889-51-9, 1025956-65-3, 893843-07-7, 155613-93-7</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>Cat.</td>
<td>Abbrev./Acronym</td>
<td>Systematic name</td>
<td>CAS No.</td>
<td>Regulation</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>D</td>
<td>TBX</td>
<td>2,3,5,6-tetrabromo-p-xylene</td>
<td>23488-38-2</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>E</td>
<td>DBNPG</td>
<td>Dibromoneopentylglycol</td>
<td>3296-90-0</td>
<td>Registered under REACH under the 100-1000 T/y tonnage band</td>
</tr>
<tr>
<td>E</td>
<td>TDBP-TAZTO</td>
<td>Tris(2,3-dibromopropyl)isocyanurate</td>
<td>52434-90-9</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>E</td>
<td>RBDPP</td>
<td>Resorcinol bis(diphenyl phosphate)</td>
<td>57583-54-7</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>E</td>
<td>TTBNPP</td>
<td>Tris(tribromoneopentyl)phosphate</td>
<td>19186-97-1</td>
<td>Registered under REACH under the 100-1000 T/y tonnage band</td>
</tr>
<tr>
<td>E</td>
<td>TDBP-TAZTO</td>
<td>1,3-bis(2,3-dibromopropyl)-5-(2-propen-1-yl)-1,3,5-triazine-2,4,5(1H,3H,5H)-trione</td>
<td>75795-16-3</td>
<td>None</td>
</tr>
<tr>
<td>E</td>
<td>4'-PeBPO-BDE208</td>
<td>Pentabromophenoxy-nonabromodiphenyl ether</td>
<td>58965-66-5</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>E</td>
<td>TBNPA</td>
<td>Tribromoneopentyl alcohol</td>
<td>1522-92-5</td>
<td>Registered under REACH under 100 – 1000 T/y</td>
</tr>
<tr>
<td>E</td>
<td>HBCYD</td>
<td>Hexabromocyclodecane</td>
<td>25495-98-1</td>
<td>None</td>
</tr>
<tr>
<td>E</td>
<td>DBS</td>
<td>Dibromostyrene</td>
<td>31780-26-4</td>
<td>Not registered under REACH</td>
</tr>
<tr>
<td>E</td>
<td>DBP-TAZTO</td>
<td>1-(2,3-dibromopropyl)-3,5-diallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione</td>
<td>57829-89-7</td>
<td>None</td>
</tr>
</tbody>
</table>

**Table 1-2: Compounds recommended to remove from priority list**
<table>
<thead>
<tr>
<th>Cat.</th>
<th>Abbrev./ Acronym</th>
<th>Systematic name</th>
<th>CAS No.</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>Mirex/Dechlorane</td>
<td>Perchloropentacyclodecane</td>
<td>2385-85-5</td>
<td>Mirex was previously listed in FR target list, however it is banned under the Stockholm Convention, and has not been in use in EU for &gt;35 years. It is recommended to be excluded from further HBM activities.</td>
</tr>
<tr>
<td>Cat.</td>
<td>Abbrev./Acronym</td>
<td>Systematic name</td>
<td>CAS No.</td>
<td>Notes</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>----------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>benzene, ethenyl-, polymer with 1,3-butadiene, brominated</td>
<td>1195978-93-8</td>
<td>Suggested by ECHA; selected by a large part of the Expanded Polystyrene (EPS) and Extruded Polystyrene (XPS) Industry as replacement to HBCDD, suspected persistence (not registered under REACH because a polymer)</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]</td>
<td>21850-44-2</td>
<td>Suggested by ECHA; registered under REACH under the 1000-10000 T/y tonnage band and under CoRAP (suspected PBT/vPvB, endocrine disruptor, High (aggregated) tonnage)</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromo-2-methylpropoxy)benzene]</td>
<td>97416-84-7</td>
<td>Suggested by ECHA; registered under REACH under the 100-1000 T/y tonnage band and under CoRAP (suspected PBT/vPvB, endocrine disruptor, Exposure of environment)</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>bis(α,α-dimethylbenzyl) peroxide</td>
<td>80-43-3</td>
<td>Suggested by ECHA; used as a flame retardant synergist; registered under REACH under the 10000-100000 tonnage band and under CoRAP (suspected PBT/vPvB, Consumer use, Exposure of environment, High (aggregated) tonnage, High RCR, Wide dispersive use)</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>(pentabromophenyl)methyl acrylate</td>
<td>59447-55-1</td>
<td>Suggested by ECHA, registered under REACH under the 100-1000 T/y tonnage band</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>2-Butyne-1,4-diol, polymer with 2-(chloromethyl)oxirane, brominated, dehydrochlorinated, methoxylated</td>
<td>68441-62-3</td>
<td>Suggested by ECHA, registered under REACH under the 1,000-10,000 T/y tonnage band</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>2,2,6,6-tetrakis(bromomethyl)-4-oxaheptane-1,7-diol</td>
<td>109678-33-3</td>
<td>Suggested by ECHA, registered under REACH under a confidential tonnage band</td>
</tr>
</tbody>
</table>
1.3 Policy related questions

1. What are current HBM levels of legacy/regulated FRs (e.g., PBDEs and HBCDD)? How do these compare to any historical records? Is the current legislative framework and proposed actions leading to a significant decline in restricted compounds and is this uniform across the EU?

2. What is the exposure of the European population to current use FRs? In particular, what is the exposure of sensitive sub-groups (e.g., infants and children)?

3. How do the levels of legacy FRs compare to levels of new/emerging FRs? Is any temporal or spatial trend observed? Can we relate this to use patterns and/or production volume?

4. How does exposure to FRs differ between adults and children, males and females?

5. How does exposure differ by geographic area within Europe? Do countries/regions have different FR exposure levels?

6. Are there one or more occupationally exposed sub-groups? What occupations are associated with high exposure to FRs?

7. Is elevated exposure to FRs associated with particular consumption patterns or lifestyles?

8. What are the relevant exposure pathways for FRs, e.g., diet, air, water, indoor environmental exposure?

9. Do certain flame retardants co-occur in HBM matrices?

10. What current information is available regarding toxicity of FRs, both as individual compounds and as the mixtures of FRs typically occurring in indoor environments and diet?

11. Can exposure to FRs be linked with any adverse health effects?

12. What are the population groups most at risk?

13. As FR market shifts towards replacement/alternative FRs, does human exposure reflect that trend? E.g., DBDPE as replacement for BDE-209;

14. What additional FRs should be prioritised for further information regarding exposure and/or toxicity? How can use and risk information be combined to identify and prioritise knowledge gaps for further assessment?

15. Can reference values be established for any FRs?

1.4 Research activities to be undertaken

The list of FRs is extensive, and not fixed, as new FRs are identified in human and environmental matrices on a regular basis. Therefore, flexibility must be maintained in the list of relevant and priority compounds. However, of the current list of 62 FRs, we highlight 20 individual compounds to receive attention based on evidence of toxicity but a lack of HBM data.

- **TPHP, TMPP, TCEP, TCIPP, TDCIPP, TNBP, TBBPA**, and **TBOEP** are Cat. B compounds for which available HBM data suggests significant human exposure, and there is sufficient evidence of toxicity to warrant concern

- **TEHP, EHDP, DDC-DBF, ip-TPP, V6, 2,4,6-TBP** and **TDBPP** are Cat. C and D compounds with very limited HBM data, and in some cases none at all within Europe, but suggestion of toxicological concern.

- **DBNP, TDBP-TAHTO, RBDPP, melamine polyphosphate** and **EBTEBPI** are Cat. E compounds for which no HBM data exists but toxicological evidence suggests concern.
Additionally, we highlight the 6 compounds which entirely lack toxicological and HBM data: diethylphosphinic acid, BDBP-TAZTO, 4'-PeBPO-BDE208, HBCYD, DBS and DBP-TAZTO. These compounds should receive attention in the form of suspect screening to determine if they are present in any human matrices and warrant further attention.

### Table 1-4: Listing of research activities to be carried out to answer the policy questions summed up in 1.3

<table>
<thead>
<tr>
<th>Policy question</th>
<th>Substance</th>
<th>Available knowledge&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Knowledge gaps and activities needed</th>
</tr>
</thead>
</table>
| 1, 3, 4, 5, 6, 7, 8, 11, 13, 15 | PBDEs (BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-209) | • Established analytical methods, widely available analytical standards, reference materials  
• Existing information on temporal trends and geographic differences in human matrices and exposure pathways (e.g., 26,33,55,56)  
• Biomonitoring data for PBDEs in a range of human matrices (primarily serum, maternal milk) in a large number of studies:  
  o Sweden<sup>33,35,44,46,49,56–72</sup>  
  o Norway<sup>51,73–80</sup>  
  o Germany<sup>81–83</sup>  
  o France<sup>31,84–87</sup>  
  o Denmark<sup>86,88,89</sup>  
  o Finland<sup>86,90,91</sup>  
  o Belgium<sup>92–96</sup>  
  o Netherlands<sup>97–101</sup>  
  o Spain<sup>102–107</sup>  
  o Poland<sup>108</sup>  
  o Austria<sup>109</sup>  
  o Czech Republic<sup>110–113</sup>  
  o Italy<sup>114</sup>  
  o UK<sup>47</sup>  
  o Greece<sup>32,115</sup> | Gaps:  
• Biomonitoring data for Southern and Central/Eastern Europe  
• Coherence and synthesis in data  
Activities:  
• Synthesis and/or meta-analysis of existing HBM data to identify time trends in exposure and possible regional differences. Inform on whether current regulatory structure can effectively lead to decreases in human exposure  
Statistical evaluation of average concentrations, time trends and potential variance between population subgroups both regional and at risk (meta-analysis). |

<sup>3</sup> Complete database of evaluated HBM knowledge is available upon request from flame retardants CGL
<table>
<thead>
<tr>
<th>Policy question</th>
<th>Substance</th>
<th>Available knowledge</th>
<th>Knowledge gaps and activities needed</th>
</tr>
</thead>
</table>
| 1, 3, 4, 5, 6, 7, 8, 11, 13, 15 | HBCDD | • Established analytical methods, widely available analytical standards, reference materials  
• Biomonitoring data for HBCDDs in many studies in a range of human matrices (primarily serum, maternal milk):  
  - Belgium\(^{28,92–94,96}\)  
  - Norway\(^{28,51,77–80,116}\)  
  - Netherlands\(^{98–100}\)  
  - France\(^{84,86}\)  
  - UK\(^{47}\)  
  - Denmark\(^{86}\)  
  - Finland\(^{96}\)  
  - Sweden\(^{35,46,49,56,60}\)  
  - Germany\(^{83}\)  
  - Czech Republic\(^{111,112}\)  
  - Spain\(^{52}\)  
  - Greece\(^{32}\) | Gaps:  
• Biomonitoring data for Southern and Central/Eastern Europe  
• Coherence and synthesis in data  
Activities:  
• Synthesis and/or meta-analysis of existing HBM data needed to identify time trends in exposure and possible regional differences. Inform on whether current regulatory structure can effectively lead to decreases in human exposure  
Statistical evaluation of average concentrations, time trends and potential variance between population subgroups both regional and at risk (meta-analysis). |
| 2, 3, 4, 5, 8, 9, 10, 11, 13 | Cat. B | Biomonitoring data for NBFRs and CFRs in milk, serum for selected countries, small study sizes:  
  - France\(^{31}\)  
  - Germany\(^{117}\)  
  - Norway\(^{118,119}\)  
  - Netherlands\(^{97}\)  
  - Sweden\(^{46,72,120}\)  
  - UK\(^{47,121}\)  
  - Belgium\(^{96,121–123}\)  
  - Finland\(^{124}\)  
  - Greece\(^{125}\)  
  - Romania\(^{126}\)  
  - UK\(^{47}\)  
  - Ireland\(^{126}\)  
  - Czech Rep\(^{112}\)  
  - Slovakia\(^{127}\)  
  - France\(^{31,84,128}\) | Interlaboratory validation exercises  
Development of SOPs for determination of compounds in target human matrices  
Synthesis of existing data regarding biomonitoring and exposure – evaluation of data gaps for regions and compounds.  
Screening of existing HBM projects or biobank archives for Cat. B substances with lack of HBM data. Particular data gap for Southern and Eastern Europe |

Many studies report only TBBPA or a sub-set of Cat. B FRs  
Biomonitoring data for OPEs, usually OPE metabolites in urine. Studies usually report a sub-set of the OPEs; methods vary widely between studies  
  - Norway\(^{96,118,129,130}\)  
  - Germany\(^{37,131,132}\)  
  - Finland\(^{124}\)  
  - Sweden\(^{133–136}\)  
  - Belgium\(^{137}\)
<table>
<thead>
<tr>
<th>Policy question</th>
<th>Substance</th>
<th>Available knowledge</th>
<th>Knowledge gaps and activities needed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cat. C substances</strong></td>
<td>HBM data for individual locations, or based on small method development studies; variability in matrices and analytical methods; many values below detection limits:</td>
<td></td>
<td>Evaluation of published methods to determine validity and applicability. Assessment of HBM data quality – appropriateness of monitored matrices for target compounds Screening of existing data regarding biomonitoring and exposure for all target FR – evaluation of data gaps for regions and compounds. Screening of existing HBM projects or biobank archives for Cat. C substances.</td>
</tr>
<tr>
<td></td>
<td>o TEHP&lt;sup&gt;118,124,129&lt;/sup&gt;</td>
<td>o PEBE&lt;sup&gt;46,59,127,138&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o EHDPP&lt;sup&gt;129,130,136&lt;/sup&gt;</td>
<td>o DDC-An&lt;sup&gt;31,76,117,119,122&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o DDC-DBF&lt;sup&gt;31,76,117,119,122&lt;/sup&gt;</td>
<td>o 2,4,6-TBP&lt;sup&gt;73,75,140&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o DBDPE&lt;sup&gt;46,47,59,76,119,126,138&lt;/sup&gt;</td>
<td>o PBT&lt;sup&gt;59,127&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o DBB&lt;sup&gt;46,76,119,122,127,138&lt;/sup&gt;</td>
<td>o PBB-Acr&lt;sup&gt;127&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o DBE-DBCH&lt;sup&gt;46,47,59,127&lt;/sup&gt;</td>
<td>o V6&lt;sup&gt;141&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o DBHCTD&lt;sup&gt;76,119,127,139&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cat. D substances</strong></td>
<td>Limited HBM data, often none from Europe:</td>
<td></td>
<td>Evaluation of existing methods, matrices to provide recommendations for future screening or method development. Screen (semi-quantitative) for presence of compounds in human and/or environmental matrices, using existing biobank archives where possible Develop validated methods to improve quantification for compounds that are consistently identified or listed as high concern based on gathered toxicity information</td>
</tr>
<tr>
<td></td>
<td>o OBTMP&lt;sup&gt;139,142&lt;/sup&gt;</td>
<td>o BPA-BDPP&lt;sup&gt;146&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o TIBP&lt;sup&gt;129,143&lt;/sup&gt;</td>
<td>o Ip-TPP&lt;sup&gt;147&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o TBX&lt;sup&gt;46,59,139,144&lt;/sup&gt;</td>
<td>o PBP&lt;sup&gt;140&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o TBCO&lt;sup&gt;127&lt;/sup&gt;</td>
<td>o TnPP&lt;sup&gt;148,149&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o HCTBPH&lt;sup&gt;139,145&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cat. E substances</strong></td>
<td>No available HBM or toxicity information for diethylphosphinic acid, BDPP-TAZTO, 4'-PeBPO-BDE208, HBCYD, DBS and DBP-TAZTO Toxicity information but no HBM data for DBNPG, TDBP-TAZTO, RBDPP, TTNPP, EBTEBPI, HEHP-TEBP, TTBP-TAZ, and melamine polyphosphate</td>
<td></td>
<td>Screen (semi-quantitative) for presence of compounds in human and/or environmental matrices, using existing biobank archives where possible Develop validated methods to improve quantification for compounds that are consistently identified or listed as high concern based on gathered toxicity information</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.5 References


20. ARCADIS. *Identification and evaluation of data on flame retardants in consumer products*; Brussels, 2011.


49. Lignell, S.; Aune, M.; Glynn, A.; Cantillana, T.; Isaksson, M.; Aune, M.; Glynn, A.; Cantillana, T. Polybrominated diphenylethers (PBDE) and hexabromocyclododecane (HBCD) in paired samples of blood serum and breast milk – a correlation study; Uppsala, 2013.


62. Lignell, S.; Aune, M.; Darnerud, P. O.; Hanberg, A.; Larsson, S. C.; Glynn, A. Prenatal exposure to polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) may influence birth weight among infants in a Swedish cohort with background exposure: a cross-sectional study. Environ. Health 2013, 12, 44.


120. Larsson, K.; Wit, C. De: Berglund, M. Tidstrender av kemiska ämnen i barns urin och utvärdering av förskoledamm som exponeringskälla; Stockholm, 2017.


