HBM4EU science and policy for a healthy future

HORIZON2020 Programme
Contract No. 733032 HBM4EU

SCOPING DOCUMENTS

(1st round of prioritization)

Prioritized substance group: Flame retardants

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Date: 20/11/2017 **Document version:**

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1. Introduction

HBM4EU has established Chemical Working Groups during the proposal phase for the nine prioritized substance groups that HBM4EU will work on in 2017 and 2018. Additional substance groups will be identified by late 2018 through the implementation of a refined prioritization strategy.

For each substance group, scoping documents are produced under Workpackage 4.4 of HBM4EU. The scoping document will contain a review of the available evidence, will list policy-related questions, identify knowledge gaps and propose research activities. Proposed activities will be fed into the framework of work packages and tasks of HBM4EU in a coordinated and harmonized manner, and will constitute the basis for the annual work plans. The scoping documents are the linkage between policy questions and the research to be undertaken (broken down for single substances) in order to answer those questions. This methodology will optimize work on the different substances, avoid redundancies, ensure coordination and facilitate the calculation of budgets for each WP. The scoping documents do not contain a comprehensive literature review per substance group but are intended to provide information for the WP leaders who will draft the Annual Work Plans.

For the selected substance groups the availability of (toxicology or human biomarker) data is variable. A scheme was therefore developed to classify the compounds within each substance group into categories A, B, C, D and E based on the availability of data to answer research questions (see further). In direct response to the key project goal of exploiting HBM data in policy making to positively impact on human health, the research activities for each substance group will generate knowledge on exposure trends and associated health effects. Throughout the course of the project, we will generate knowledge that will shift substances towards to a higher level of knowledge category.

For further information see www.hbm4eu.eu

Substance group: Flame retardants

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2. 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 categorized 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[1] (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.[inter alia ,1–3] The toxicity of tetrabromobisphenol A (TBBPA) is also well-studied and it has been identified to have a range of potential hazardous properties.[4–7] Early evidence suggests that a number of the replacement FRs may have similar health concerns,[8–10] 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)tetrabromophthalate (BEH-TEBP) and 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) have been identified as potentially bioaccumulative.[11] Decabromodiphenyl ethane (DBDPE) is structurally similar to BDE-209 and hypothesized to have similar toxicity. Triphenyl

[1] Actually, six isomers of HBCDD exist. Therefore, sometimes the plural HBCDDs is used as synonymous for HBCDD.

phosphate (TPHP) is identified by ECHA as very toxic to aquatic life, has been found to affect oestrogen receptor binding activities in zebrafish,[12] and may be associated with altered hormone levels and decreased semen quality in men.[13] Tris-2-chloroethyl phosphate (TCEP) was also found to affect oestrogen receptor binding activities in zebrafish,[12] may affect neurodevelopment, with multiple mechanisms of toxicity,[8] and is a possible reproductive toxin.[14] TCIPP may also affect neurodevelopment[8] and is potentially carcinogenic.[14] Tris(1,3-dichloropropyl)phosphate (TDCIPP) may be associated with altered hormone levels and decreased semen quality in men,[13] may affect neurodevelopment, with multiple mechanisms of toxicity,[8] and also may be carcinogenic.[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.[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,[17] and there is evidence of Firemaster 550 as an endocrine disrupting compound and obesogen.[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.[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.[24] In addition to use as FRs, a number of these compounds (particularly the phosphorus-based FRs) also act as plasticizers,[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.[25]

In general, human exposure to PBDEs is lower in Europe than in North America,[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.[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,[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.[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[31–33] and breast milk.[34,35] In contrast, some NBFRs and many OPEs are metabolized in the body, and more commonly used biomarkers of exposure are metabolites detected in urine.[36,37] However, many of the metabolites are uncertain, and metabolic pathways are only characterized for a limited number of FRs.[38–43] 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 generalization of trends and distributions has been made from biomarkers.[33] Quantification of a rapidly increasing temporal trend of PBDEs in maternal milk in Sweden[44,45] 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.[33,46–52] 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[53] 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.[53,54] 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.

3. Categorization 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 categorization based on the availability of toxicological information and HBM data which was combined to determine the overall categorization listed in Table 1 is available upon request, along with references to support the categorization.

Table 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

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
A	BDE-28[2]	2,4,4'-Tribromodiphenyl ether	41318-75-6	Restricted under REACH and listed on Stockholm Convention
	BDE-47	2,2'4,4'-Tetrabromodiphenyl ether	5436-43-1	Restricted under REACH and listed on Stockholm Convention
	BDE-99	2,2',4,4',5-Pentabromodiphenyl ether	60348-60-9	Restricted under REACH and listed on Stockholm Convention
	BDE-100	2,2',4,4',6-Pentabromodiphenyl ether	189084-64-8	Restricted under REACH and listed on Stockholm Convention
	BDE-153	2,2',4,4',5,5'-Hexabromodiphenyl ether	68631-49-2	Restricted under REACH and listed on Stockholm Convention
	BDE-154	2,2',4,4',5,6'-Hexabromodiphenyl ether	207122-15-4	Restricted under REACH and listed on Stockholm Convention
	BDE-183	2,2',3,4,4',5',6-Heptabromodiphenyl ether	207122-16-5	Restricted under REACH and listed on Stockholm Convention
	BDE-209	2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether	1163-19-5	Restricted under REACH and listed on Stockholm Convention
	HBCDD	Hexabromocyclododecane	3194-55-6, 25637-99-4, 1093632-34-8	On REACH Authorisation List and listed on the Stockholm Convention

[2] Individual PBDE congeners are included rather than homologue groups (as in previous scoping document) in line with existing analytical methods and HBM data.

B	TPHP	Triphenyl phosphate	115-86-6	Registered under REACH under the 1000-10000 T/y tonnage band and under CoRAP (suspected ED, consumer use High (aggregated) tonnage, Wide dispersive use)
	TMPP	Tricresyl phosphate	1330-78-5	Registered under REACH, entered onto CoRAP for evaluation based on High (aggregated) tonnage, Suspected PBT/vPvB, Wide dispersive use.
	TCEP	Tris-2-chloroethyl phosphate	115-96-8	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)
	TCIPP	Tris(1-chloro-2-propyl) phosphate	13674-84-5	Registered under REACH
	TDCIPP	Tris(1,3-dichloropropyl)phosphate	13674-87-8	Registered under REACH, Entered onto CoRAP for evaluation in 2019 as potential endocrine disruptor
	TNBP	Tri-n-butyl phosphate	126-73-8	Registered under REACH, Entered onto CORAP for evaluation in 2012 based on CMR, High (aggregated) tonnage, Wide dispersive use
	TBBPA	Tetrabromobisphenol A	79-94-7	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.)
	TBOEP	Tri(2-butoxyethyl) phosphate	78-51-3	Registered under REACH under 1000-10000 T/y tonnage band
	BEH-TEBP	Bis(2-ethylhexyl)tetrabromophthalate	26040-51-7	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)
	EH-TBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate	183658-27-7	None
	BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane	37853-59-1	Not registered under REACH
	DDC-CO	Dechlorane Plus	13560-89-9	Registered under REACH under 100-1000 T/y tonnage band
C	TEHP	Tris(2-ethylhexyl) phosphate	78-42-2	Registered under REACH under 1000-10000 T/y tonnage band
	EHDPP	2-ethylhexyl diphenyl phosphate	1241-94-7	Registered under REACH under 1000-10000 T/y tonnage band

	DDC-DBF	Dechlorane 602 (1,2,3,4,6,7,8,9,10,10,11,11-Dodecachloro-1,4,4a,5a,6,9,9a,9b-octahydro-1,4:6,9 dimethanodibenzofuran)	31107-44-5	Not registered under REACH
	DBDPE	Decabromodiphenylethane	84852-53-9	Registered under REACH under the 10000-100000 T/y tonnage band and under CoRAP (suspected PBT/vPvB, High (aggregated) tonnage and Wide dispersive use).
	TEP	Triethyl phosphate	78-40-0	Registered under REACH
	HBB	Hexabromobenzene	87-82-1	Not registered under REACH
	DBE-DBCH	Tetrabromoethylcyclohexane	3322-93-8	Not registered under REACH
	DBHCTD	Hexachlorocyclopentenyldibromocyclooctane	51936-55-1	Not registered under REACH
	PBEB	Pentabromoethylbenzene	85-22-3	Not registered under REACH
	DDC-Ant	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)	13560-92-4	None
	2,4,6-TBP	2,4,6-tribromophenol	118-79-6	Not registered under REACH but under CoRAP (suspected PBT/vPvB, CRM, High (aggregated) tonnage, High RCR, Wide dispersive use)
	PBT	Pentabromotoluene	87-83-2	Not registered under REACH
	PBB-Acr	Pentabromobenzyl acrylate	59947-55-1	Registered under REACH under 100-1000 T/y tonnage band
	V6	2,2-bis(chloromethyl)trimethylenebis[bis(2-chloroethyl) phosphate]	38051-10-4	Registered under REACH under the 100-1000 T/y tonnage band
D	ip-TPP	Isopropyl triphenyl phosphate	68937-41-7	Registered under REACH under the 1000-10000 T/y tonnage band
	BPA-BDPP	Bisphenol A bis(diphenylphosphate)	5945-33-5	Registered under REACH
	TBCO	1,2,5,6-tetrabromocyclooctane	3194-57-8	None
	PBP	Pentabromophenol	608-71-9	Not registered under REACH
	DBP	2,4-dibromophenol	615-58-7	Not registered under REACH
	TIBP	Tri-iso-butyl phosphate	126-71-6	Registered under REACH under the 1000-10000 T/y tonnage band
	TnPP	Tri-n-propyl-phosphate	513-08-6	Not registered under REACH
	TDBPP	Tris(2,3-dibromopropyl) phosphate	126-72-7	Restricted under REACH
	CDP	Cresyl diphenyl phosphate	26444-49-5	Not registered under REACH
	HCTBPH	Dechlorane 604 (1,2,3,4,7,7-hexachloro-5-(2,3,4,5-tetrabromophenyl)-bicyclo[2.2.1]hept-2-ene)	34571-16-9	Not registered under REACH

	OBTMPI	Octabromotrimethyphenyl indane	1084889-51-9, 1025956-65-3,893843-07-7, 155613-93-7	Not registered under REACH
	TBX	2,3,5,6-tetrabromo-p-xylene	23488-38-2	Not registered under REACH
E	DBNPG	Dibromoneopentylglycol	3296-90-0	Registered under REACH under the 100-1000 T/y tonnage band
	TDBP-TAZTO	Tris(2,3-dibromopropyl)isocyanurate	52434-90-9	Not registered under REACH
	RBDPP	Resorcinol bis(diphenyl phosphate)	57583-54-7	Not registered under REACH
	TTBNPP	Tris(tribromoneopentyl)phosphate	19186-97-1	Registered under REACH under the 100-1000 T/y tonnage band
	EBTEBPI	N,N'-ethylenebis(tetrabromophthalimide)	32588-76-4	Registered under REACH under the 100-1000 T/y tonnage band and under CoRAP (suspected PBT/vPvB, consumer use, Exposure of environment, Exposure of workers, Wide dispersive use)
	HEEHP-TEBP	2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate	20566-35-2	Registered under REACH under 100 – 1000 T/y
	TTBP-TAZ	2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine	25713-60-4	Not registered under REACH
		Melamine polyphosphate	20208-95-1, 218768-84-4	Not registered under REACH
		Diethylphosphinic acid	813-76-3	Not registered under REACH
	BDBP-TAZTO	1,3-bis(2,3-dibromopropyl)-5-(2-propen-1-yl)-1,3,5-triazine-2,4,5(1H,3H,5H)-trione	75795-16-3	None
	4'-PeBPO-BDE208	Pentabromophenoxy-nonabromodiphenyl ether	58965-66-5	Not registered under REACH
	TBNPA	Tribromoneopentyl alcohol	1522-92-5	Registered under REACH under 100 – 1000 T/y
	HBCYD	Hexabromocyclodecane	25495-98-1	None
	DBS	Dibromostyrene	31780-26-4	Not registered under REACH
	DBP-TAZTO	1-(2,3-dibromopropyl)-3,5-diallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	57829-89-7	None

Table 2: Compounds recommended to remove from priority list.

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Notes
NA	Mirex/Dechlorane	Perchloropentacyclodecane	2385-85-5	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 >35 years. It is recommended to be excluded from further HBM activities.

Table 3: Compounds to be considered for addition to priority list.

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Notes
E		benzene, ethenyl-, polymer with 1,3-butadiene, brominated	1195978-93-8	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)
E		1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]	21850-44-2	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)
E		1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromo-2-methylpropoxy)benzene]	97416-84-7	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)
E		bis(α,α-dimethylbenzyl) peroxide	80-43-3	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, Exposure of workers, High (aggregated) tonnage, High RCR, Wide dispersive use)

E		(pentabromophenyl)methyl acrylate	59447-55-1	Suggested by ECHA, registered under REACH under the 100-1000 T/y tonnage band
E		2-Butyne-1,4-diol, polymer with 2-(chloromethyl)oxirane, brominated, dehydrochlorinated, methoxylated	68441-62-3	Suggested by ECHA, registered under REACH under the 1,000-10,000 T/y tonnage band
E		2,2,6,6-tetrakis(bromomethyl)-4-oxaheptane-1,7-diol	109678-33-3	Suggested by ECHA, registered under REACH under a confidential tonnage band

4. 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 prioritized for further information regarding exposure and/or toxicity? How can use and risk information be combined to identify and prioritize knowledge gaps for further assessment?
15. Can reference values be established for any FRs?

5. 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, EHDPP, 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.
- **DBNPG, TDBP-TAZTO, 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 4: Listing of research activities to be carried out to answer the policy questions summed up in 1.3

Policy question	Substance	Available knowledge[3]	Knowledge gaps and activities needed
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[33,35,44,46,49,56–72] o Norway[51,73–80] o Germany[81–83] o France[31,84–87] o Denmark[86,88,89] o Finland[86,90,91] o Belgium[92–96] o Netherlands[97–101] o Spain[102–107] o Poland[108] o Austria[109] o Czech Republic[110–113] o Italy[114] o UK[47] o Greece[32,115]	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).
1, 3, 4, 5, 6, 7, 8, 11, 13, 15	**HBCDD**	• **Established analytical methods, widely available analytical standards, reference materials**	Gaps: ▸ Biomonitoring data for Southern and Central/Eastern Europe ▸ Coherence and synthesis in data

[3] Complete database of evaluated HBM knowledge is available upon request from flame retardants CGL

		• **Biomonitoring data for HBCDDs in many studies in a range of human matrices (primarily serum, maternal milk):** o Belgium[28,92–94,96] o Norway[28,51,77–80,116] o Netherlands[98–100] o France[84,86] o UK[47] o Denmark[86] o Finland[86] o Sweden[35,46,49,56,60] o Germany[83] o Czech Republic[111,112] o Spain[52] o Greece[32]	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[125] • UK[47] • Ireland[126] • Czech Rep.[112] • Slovakia[127] • France[31,84,128] Many studies report only TBBPA or a sub-set of Cat. B FRs	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

		Biomonitoring data for OPEs, usually OPE metabolites in urine. Studies usually report a sub-set of the OPEs; methods vary widely between studies • Norway[36,118,129,130] • Germany[37,131,132] • Finland[124] • Sweden[133–136] • Belgium[137]	
	Cat. C substances	HBM data for individual locations, or based on small method development studies; variability in matrices and analytical methods; many values below detection limits: • TEHP[118,124,129] • EHDPP[129,130,136] • DDC-DBF[31,76,117,119,122] • DBDPE[46,47,59,76,119,122,126,138] • HBB[46,76,119,122,126,127,138] • DBE-DBCH[46,47,59,127] • DBHCTD[76,119,127,139] • PBEB[46,59,127,138] • DDC-Ant[31,76,117,119,122] • 2,4,6-TBP[73,75,140] • PBT[59,127] • PBB-Acr[127] • V6[141]	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.
2, 9, 10, 14	**Cat. D substances**	Limited HBM data, often none from Europe: • OBTMPI[139,142] • TIBP[129,143] • TBX[46,59,139,144] • TBCO[127] • HCTBPH[139,145] • BPA-BDPP[146] • ip-TPP[147] • PBP[140] • TnPP[148,149]	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
2, 14	**Cat. E substances**	No available HBM or toxicity information for diethylphosphinic acid, BDBP-TAZTO, 4'-PeBPO-BDE208, HBCYD, DBS and DBP-TAZTO Toxicity information but no HBM data for DBNPG, TDBP-TAZTO, RBDPP, TTBNPP, EBTEBPI, HEHP-TEBP, TTBP-TAZ, and melamine polyphosphate	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

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HORIZON2020 Programme
Contract No. 733032 HBM4EU

This document contains additional details regarding TCEP, TCIPP and TDCIPP as a supplement to the HBM4EU scoping document on flame retardants.

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tris(2-chloroethyl) phosphate **CAS: 115-96-8**

TCEP

Recent scientific studies described below emphasize (1) TCEP is consistently detected in areas that directly lead to human exposure (e.g., indoor air, dust), (2) high levels in these areas are associated with higher human exposure based on biomonitoring data, and (3) TCEP is concluded to be a reproductive toxicant, thus the evidence of widespread human exposure suggests concern.

TCEP is consistently detected in indoor dust in Europe and North America (Fang et al., 2013; Stapleton et al., 2014; Vykoukalová et al., 2017), including in 100% of 125 samples from homes of pregnant women in California (Castorina et al., 2017), and 100% of dust from school classrooms in Norway (Cequier et al., 2014). It was found in 14% of polyurethane foam samples collected from baby products on the North American market, at levels of up to 5.94 mg/g (Stapleton et al., 2011). This stems from its independent use as a flame retardant, but also, TCEP is also an impurity in other OPEs, such as V6, where it was found 14% by weight in the V6 commercial mixture (Fang et al., 2013).

Relationships between OPE levels in house dust and dermal wipes of children suggest that exposure pathways for OPEs will be similar to the known exposure pathways for PBDEs (e.g., hand to mouth behavior, dust ingestion) (Stapleton et al., 2014). TCEP was detected in 97% of human placenta samples in a study in China, suggesting a pathway for prenatal exposure to TCEP (Ding et al., 2016).

In the ECHA draft screening report (European Chemicals Agency, 2017)**, it is concluded that TCEP is "a reproductive toxicant with a significant toxic potential adverse to fertility".** A recent study using the male mouse model also supports this conclusion (Chen et al., 2015). Consistently, it is included in the list of substances of very high concern as "toxic for reproduction".

The ECHA report also concluded that TCEP is a carcinogen, with an unidentified, most likely non genotoxic, mode of action. Consistently US Environmental Protection Agency classifies TCEP with High hazard for carcinogenicity (Baker et al., 2015) and a recent cohort study concludes on statistically significant links between exposure to TCEP and risk of developing thyroid cancer (Hoffman et al., 2017a). It is also included in the proposition 65 list of chemicals known to cause cancer (Kammerer, 2017). To our knowledge, no clear mode of action has been identified.

Finally, the ECHA report raises a concern for neurotoxicity. In agreement, two recent cohort studies establish a link between exposure to TCEP (alone, or as part of a sum of 4 OPFRs) and cognitive performances in school children or social neurobehavior in pre-school children (Hutter et al., 2013; Lipscomb et al., 2017).

tris(2-chloro-1-methylethyl) phosphate **CAS: 13674-84-5**

TCIPP

Recent scientific studies described below emphasize (1) TCIPP is consistently detected in areas that directly lead to human exposure (e.g., indoor air, dust), and (2) TCIPP is identified as having negative developmental and reproductive effects. Thus the evidence of widespread contamination of indoor environments combined with identified hazard suggests concern.

TCIPP is frequently detected in indoor dust in Europe and North America (Vykoukalova et al. 2017, Stapleton et al. 2014), including in 97.6% of 125 samples from homes of pregnant women in California (Castorina et al. 2017), and 100% of dust from school classrooms in Norway (Cequier et al. 2014). TCIPP is also detected on hand wipes (Liu et al. 2017) and was detected at highest concentrations of OPEs in indoor air in Czech homes (Vykoukalova et al. 2017), and the highest levels out of the OPEs in dust from homes in Norway (Cequier et al. 2014).

Levels of OPEs in indoor dust differ between countries, suggesting differences in product use and indoor environments, but universally, TDCIPP is one of the major contributors to the signal of OPEs in indoor dust, and in particular for European countries (Brandsma et al., 2014; Cequier et al., 2014; Dirtu et al., 2012). TCIPP is found at percent levels by weight in consumer products with direct use in residential indoor environments (Stapleton et al., 2009). TCIPP was detected at levels up to 14.4 mg/g in foam baby products from the North American market (Stapleton et al., 2011).

In the ECHA draft screening report (European Chemicals Agency, 2017)**, it was concluded for TCIPP that a LOAEL of 99 mg/kg is derived for developmental toxicity and effects on fertility.** In its recent report, US-EPA draws the same conclusion and classifies TCIPP as High hazard for Developmental and reproductive effects (Baker et al., 2015).

A LOAEL of 52 mg/kg was derived for carcinogenicity. We did not locate major new contributions, except for a cohort study that did not find a significant trend between levels of TCPP in dusts and odd ratios for thyroid cancer (Hoffman et al., 2017a).

tris[2-chloro-1-(chloromethyl)ethyl] phosphate **CAS: 13674-87-8**

TDCIPP

Recent scientific studies described below emphasize (1) its use as a flame retardant for polyurethane foam leads to significant use in products intended to be used for infants and young children, (2) TDCIPP is consistently detected in areas that directly lead to human exposure (e.g., indoor air, dust), (2) biomonitoring data suggest human exposure is increasing over the past 15 years, with higher exposure to children, and (4) TDCIPP is identified as having negative developmental and reproductive effects and high hazard for carcinogenicity. Thus the evidence of widespread human exposure suggests concern.

TDCIPP is frequently used as an additive flame retardant in foam products, particularly in the automotive industry and in some furnishings (van der Veen and de Boer, 2012). It is considered to be a replacement for now-banned pentaBDE, and was found in 36% of polyurethane foam samples collected from baby products on the North American market, at levels of up to 124 mg/g (Stapleton et al. 2011). TDCIPP is found at percent levels by weight in consumer products with direct use in residential indoor environments (Stapleton et al. 2009), and in indoor dust is at µg/g levels, compared to ng/g levels typically found for restricted flame retardants such as polybrominated diphenyl ethers, even during their time of major use.

TDCIPP is consistently detected in indoor dust in Europe and North America (Hoffman et al., 2015; Stapleton et al., 2014; Vykoukalová et al., 2017), including in 100% of 125 samples from homes of pregnant women in California (Castorina et al. 2017), and 100% of dust from school classrooms in Norway (Cequier et al. 2014). TDCIPP was the dominant organophosphate flame retardant in samples of automobile dust collected in the Netherlands (Brandsma et al., 2014), with levels of up to 1 mg/g of dust. TDCIPP was the dominant flame retardant detected in dust from German automobiles (Brommer et al., 2012). Levels of organophosphate flame retardants in indoor dust differ between countries, suggesting differences in product use and indoor environments, but TDCIPP is one of the major contributors to the signal of OPEs in indoor dust in all studies (Brandsma et al. 2014)

It is also consistently detected on hand wipes (Hoffman et al. 2015), indicating pathways for human exposure, and particularly for exposure to children, considering the higher rates of dust ingestion and frequency of hand-to-mouth behavior/mouthing of objects in young children. It is one of the highest median concentration organophosphate flame retardants detected in Swedish foods (Poma et al., 2017).

Urinary metabolites (BDCIPP) in US exposure studies have increased dramatically over the period of 2002-2015 (Hoffman et al., 2017b), and considering similarities in consumer product markets between North America and Europe, although lacking human biomonitoring evidence to show a similar temporal trend in Europe, this would suggest similar high and increasing exposure to the European population can be expected. A 15-fold increase in levels of BDCIPP in urine is seen in US studies when comparing 2015 to 2002, indicating a similar increase in human exposure to TDCIPP. Australian biomonitoring showed widespread detection of TDCIPP metabolites in urine, and higher levels in children's than adult urine, suggesting higher exposure to children (Van den Eede et al., 2014). A paired mother-child cohort in California found 15x higher urinary levels of BDCIPP in children than their mothers, and detection in 100% of urine samples suggesting widespread and elevated exposure to children (Butt et al., 2016). Concentrations of the metabolite BDCIPP in children's urine from a Norwegian study was significantly correlated with the levels of TDCIPP in air and dust from the homes of the children (Cequier et al., 2015).

It is concluded in the ECHA draft screening report (European Chemicals Agency, 2017) **that "there is no concern for effects on male fertility".** We think this should be reconsidered in the light of new information. In its recent report, US-EPA classifies TDCPP with high hazard for Reproductive toxicity based on effects on seminal vesicles (LOAEL 5mg/kg/d), testes and seminal product (Baker et al., 2015; Freudenthal and Henrich, 2000).

In addition, two recent cohort studies report a significant negative trend between paternal exposure to TDCPP and fertilization success (Carignan et al., 2018) or sperm quality (Meeker et al., 2013). Several studies also report effects on zebrafish fecundity upon exposure to low levels of TDCPP (Liu et al., 2013; Wang et al., 2015; Zhu et al., 2015). Finally, there are several evidences of endocrine disrupting activity, including two small cohort studies that report statistically significant associations between exposure to TDCPP and increased levels of prolactin (Meeker and Stapleton, 2010) or T3 and TSH (Meeker et al., 2013).

In the ECHA draft screening report, a LOEAL of 5 mg/kg/d was derived for carcinogenicity, with an unidentified, most likely non genotoxic, mode of action. Consistently, it is classified with High hazard for carcinogenicity by US-EPA (Baker et al., 2015) and it is included in the proposition 65 list of chemicals known to cause cancer (Kammerer, 2017). To our knowledge, no clear mode of action has been identified.

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