Substance report

June 2022

Flame Retardants

HBM4EU science and policy for a healthy future

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

Table of contents

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First version (December 2019) by RPA consultants, based on scoping documents produced by the chemical group leader (CGL) and colleagues. The EEA has since updated this document to reflect the work developed before the conclusion of HBM4EU, with the support of the CGL and other colleagues.

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Glossary

Abbreviations	
Agonist	a chemical that binds to a cellular receptor thus activating the receptor to produce a biological response
Adverse outcome pathways	The sequence(s) of biochemical changes which results ultimately in a toxic effect following exposure to a toxic agent.
Biomarker	The primary chemical or its metabolites that are used to estimate the extent of exposure of an organism.
Br	Bromine, one of the halogen group of elements.
Carcinogen	A chemical that induces or increases the risk of cancer.
Chronic effects	An adverse effect resulting from either long-term/ repeated exposure to a toxic agent or an adverse effect that is persistent (months, years or permanent) resulting from a short-term exposure.
Cl	Chlorine, one of the halogen group of elements.
CoRAP	The Community rolling action plan that specifies the substances that are to be evaluated over a period of three years.
Cytotoxin	A chemical that has an adverse effect on a cell, potentially leading to cell death.
EFSA	European Food Safety Authority.
Endocrine disruptor	A chemical that interferes with the normal functioning of the endocrine system which results in adverse effects on physical or neurological development, or on the functioning of the reproductive, immune, and other body systems.
FR	Flame Retardant.
GC-MS	Gas chromatography–mass spectrometry.
HBM	Human Biomonitoring.
HBCDD	Hexabromocyclododecane.
Hepatotoxicity	Adverse effects specifically on the liver as a result of exposure to a toxic agent (usually in relation to chemicals but potentially also microorganisms).
Homeostasis	In biology, this refers to the process by which a living organism, cell or physiological system to maintain conditions the same despite changes in the surrounding (internal or external) environment.

IARC	International Agency for Research on Cancer
Immunotoxin	Proteins that contain a toxin linked to an antibody (or growth factor) that binds specifically to target cells.
IPChem	Information Platform for Chemical Monitoring
LCMS	Liquid chromatography - mass spectrometry
Lipophilicity	The tendency of a compound to selectively partition into a lipophilic organic phase from a polar aqueous phase.
Nephrotoxin	A toxic agent that inhibits, damages, or destroys the cells and/or tissues of the kidneys.
Neurotoxins	Toxic agents that damage, destroy or impair the functioning of the cells of the nervous system.
NBFR	Novel Brominated Flame Retardant.
Obesogens	Chemicals that adversely affect lipid homeostasis and fat storage, changing fat metabolism balance or adversely modify regulation of appetite and satiety so as to promote fat accumulation and obesity.
OPE	Organophosphate esters
P	Phosphorous, is a non-metallic element, which only occurs in nature as an inorganic compound, frequently as a phosphate which is any salt or ester of phosphoric acid form, frequently as phosphate compound.
PBDEs	Polybrominated diphenyl ethers.
POPs	Persistent Organic Pollutants are organic compounds that are resistant to environmental degradation through chemical, biological or photolytic processes. Because of their persistence, POPs bioaccumulate with potential adverse impacts on human health and the environment.
REACH	a European Union regulation concerning the Registration, Evaluation, Authorisation, and restriction of Chemicals
Reproductive toxicant	Chemicals or other agents (e.g. radiation) that adversely impact on the sexual function, fecundity and/or fertility of a parent or on the development or viability of an offspring.
SOPs	standard operating procedures
Synergistic effects	The nonlinear effects of two or more chemicals that results in an overall effect greater than the sum of individual effects of any of them.
TBBPA	Tetrabromobisphenol A

TCEP	Tris(2-chloroethyl) phosphate.
Teratogen	An agent that can affect the development of the embryo or foetus resulting in malformations foetus.
TH	Thyroid hormone relates to hormones produced by the thyroid gland that has a wide range of effects on body systems such as to overall stimulate metabolic activities in most tissues, leading to an increase in basal metabolic rate. It also plays a role in foetal development. The 2 most important forms are thyroxine (T4) and triiodothyronine (T3).
WP	Work Package.

1 Key messages

- Exposure to flame retardants may result in, or contribute to, a range of adverse health effects.
- The contribution of flame retardants to endocrine disruption is of particular concern, especially in children.
- The general population is exposed to flame retardants via building materials and consumer products, such as electronics, textiles, furnishings, automobiles, insulation, etc.
- We do not have a comprehensive overview of the population's exposure to flame retardants.
- Increases in the levels of older flame retardants in breast milk of European population have ceased for flame retardants that were restricted in the early 2000s, indicating the efficacy of policy actions on reducing human exposures to flame retardants.
- Interlaboratory validation exercises identified good capacity within Europe for HBM of older flame retardants, but a lack of capacity for currently used FRs.
- European citizens are concerned about industrial chemicals such as flame retardants and largely support the use of HBM for risk assessment and policy, though awareness is still low.

2 Introduction

HBM4EU is a project funded under Horizon 2020 and runs from 2017 until June 2022. It generates knowledge to inform about the safe management of chemicals, and hence protect human health in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts to build upon existing evidence bases and improve chemical risk assessment. HBM4EU compares data from across Europe which allows an understanding of regional differences and can help to identify vulnerable groups in order to inform targeted measures to reduce exposure. The results of the HBM4EU project are aimed at supporting policy development, by providing a key evidence base in the understanding of exposure and impacts to toxic chemicals.

If you would like to read more about the project itself, please visit the HBM4EU website.

2.1 How to use this document

This substance report is based largely on the scoping document on FRs produced in 2017, the short overview report also published in 2017, the presentation on the main results for FRs at the Joint Meeting of Chemical Substance Group Leaders and Management Board, Presentation on 8th October 2019 and the deliverables produced to date. ECHA information from REACH registrations,

information in the C&L Inventory, and opinions and decisions from committees or authorities published in the ECHA website have also been used for this report.

This substance report is intended to inform scientists, relevant stakeholders and policy makers on the value of HBM to establish the EU population's exposure to flame retardants.

The focus of this document is on the exposure, health impacts and detection via human biomonitoring of flame retardants (FR), a term given to any compound or mixture added to a consumer product or building material to reduce the flammability and thus improve product safety.

2.2 Overview of Flame Retardants

There are two main groups of FRs in use, inorganics and organics. It is important to note that those addressed by HBM4EU are the synthetic organic FRs. These fall into three main categories based on their chemical composition, i.e. those containing bromine (Br), chlorine (Cl) or phosphorous (P) FRs.

The polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) have been used since the 1970s. However, due to concerns regarding their persistence, toxicity and bio-accumulative potential, these compounds are now regulated through various regulatory mechanisms including the Stockholm Convention. Consequently, a wide range of replacement compounds have been introduced globally, including novel brominated flame retardants (NBFR) and organophosphate esters (OPE), though in some cases there is already evidence of polymeric flame retardants' degradation and leak into the environment.

This report is intended to inform policy makers and other interested stakeholders about the potential value of HBM to establish the EU population's exposure to FRs, and to identify the following:

- the potential adverse health effects from exposure to FRs;
- the potential use of human biomonitoring (HBM) in EU policy development;
- the remaining challenges associated with use of HBM of FRs; and
- the main findings to date from HBM4EU relating to FRs.

3 Human exposure to Flame Retardants

FRs are widely used in building materials and consumer products, such as electronics, textiles, furnishings, automobiles, insulation, etc. Which FRs are used and at what concentration varies within and across these groups.

The information available on EU and/or global production of FRs is extremely limited. De Boer and Stapleton (2019) suggest a 3% annual increase in production. However, the provision of such data is challenging because of confidentiality issues such as the composition of FR mixtures, non-inclusion of certain amounts of FRs since many FRs enter the EU in consumer products manufactured in other regions, and the variability seen in the amounts of FR in the same products due to different manufacturing processes, rapidly changing regulations and shifts in product requirements.

The main human exposure pathways are via inhalation, ingestion (of food and/or dust) and dermal contact. The exposure pathways differ based on the chemical's properties and use. While adult exposure to some FRs is primarily through diet, for babies and toddlers the primary exposure pathway is through breast milk, ingestion of house dust due to hand-to-mouth behaviour and also

mouthing of toys. Higher exposure is associated with high-income regions, where people typically have more consumer products and electronics in the home (Demirtepe et al., 2019), regions with higher flammability standards resulting in higher use of FRs in products (Dodson et al., 2017), and more time spent indoors, or in vehicles (Reddam et al., 2020). Some occupations, particularly work in the e-waste sector, is also associated with high exposure to flame retardants.

The European Food Safety Authority (EFSA) identified 17 brominated FRs currently in use with detectable levels in environmental and/or human matrices. A further 10 FRs have concentrations over 0.1% in consumer products. However, there is as yet no comprehensive information on human and environmental levels (EFSA, 2012).

The main sources, pathways of exposure and health effects of flame retardants are shown in Figure 1.

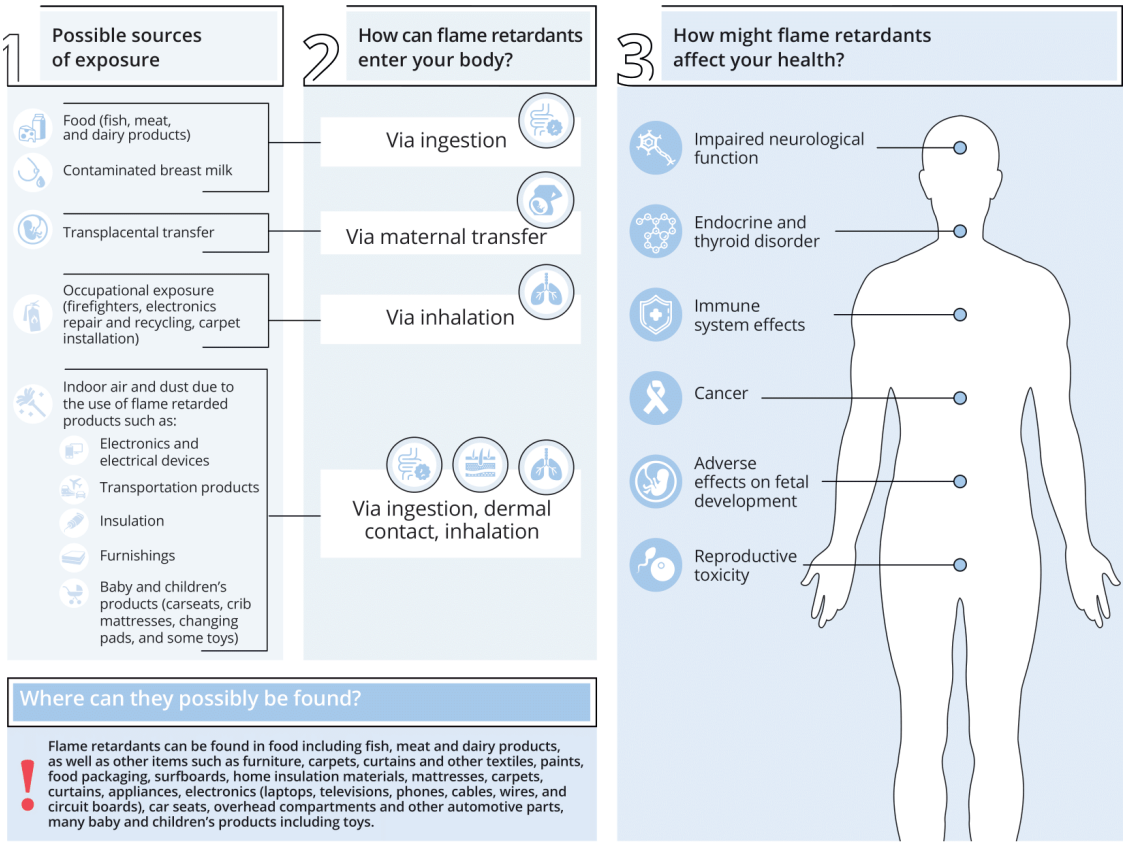


Figure 1. Overview of exposure routes and pathways for Flame Retardants

4 Health impacts of Flame Retardants

FRs are a cause of concern as several have been shown to adversely impact human health. The effects of selected FRs that were prevalent in the past are summarised below. However, due to their regulation under the Stockholm Convention, new replacement FRs are being introduced. Information on the extent of human exposure and the various exposure pathways are also summarised.

4.1 Overview of key health impacts from Flame Retardants

Brominated FR compounds, such as polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) have been identified as potentially possessing a wide range of toxic properties, including neurotoxicity and endocrine disruption (Figure 1). In addition, one of the most prevalent FRs, tetrabromobisphenol A (TBBPA) has been identified to have a range of potential hazardous properties. TBBPA is cytotoxic, immunotoxic, a thyroid hormone (TH) agonist, and a potential endocrine disruptor. It can cause a potential nephrotoxicity in infants, however, there is still controversy regarding these effects. TBBPA has been classified as probably carcinogenic to humans (Group 2A) by IARC.

4.1.1 Health impacts of replacement FRs and FR mixtures

Overall, there is a concern that the short- and long-term hazard profiles of the novel (newer) FRs may have not been adequately characterised.

Thus, in the case of a number of novel brominated flame retardants (NBFRs) there is some evidence to suggest that they possess similar toxic effects to the older brominated forms. However, as of yet the datasets available are inadequate to fully characterise their properties.

There is also evidence of mammalian toxicity for several OPEs.

A further concern is the possibility that some FR mixtures may show additive or synergistic toxicity. Many flame retardants are used as mixtures (e.g. technical mixtures of the PBDEs and Firemaster® 550).

Firemaster® 550 (FM550) is a chemical mixture currently used as an additive flame retardant in commercial products, and comprises 2-ethylhexyl-2,3,4,5-tertrabromobenzoate (EH-TBB), bis(2-ethylhexyl) tetrabromophthalate (BEH-TEBP), triphenyl phosphate (TPHP) and isopropylated triphenyl phosphate (iP-TPP). There is some evidence that Firemaster 550 may be an endocrine disruptor and obesogen[1], contributing to metabolic syndrome[2] (Patisaul, 2013).

Little attention has been given to the potential toxic effects of FR mixtures indoors where humans are exposed. Further investigation is considered necessary, particularly in relation to carcinogenicity (via hormonal effects), chronic toxicity, reproductive health and endocrine disruption.

4.2 Vulnerable target groups

Young children are identified as a vulnerable target group with respect to FR risk because of the combined impact of higher exposures and sensitive developmental period. Children's behaviours, particularly higher accidental ingestion of dust and hand-to-mouth and mouthing behaviour, can contribute to higher exposures. Breastfeeding can also lead to a higher body burden of flame retardants, particularly for the older, more persistent flame retardants (e.g. PBDEs, HBCDD). In combination with this higher exposure, exposure to FRs in utero or in childhood has been associated with neurodevelopmental effects such as ADHD (Lam et al., n.d.; Moore et al., 2022). People are most susceptible to the potential endocrine-related effects when exposures are in early-life (Ghassabian et al., 2022).

[1] Artificial chemicals believed to contribute to obesity.
[2] A collective term for a set of comorbid risk factors (including obesity, elevated fasting glucose, and impaired glucose tolerance) that together increase the risk for coronary artery disease, stroke, and type 2 diabetes.

4.3 Societal concerns

Concerning the use of Human Biomonitoring of toxic chemicals, 87 % of the respondents of the HBM4EU citizens' survey supported the use of HBM and said it should be used more, with 50 % saying it should be undertaken as regularly as food and water quality tests, with a stronger coordination at the European level, and near 60 % considered it should be included in the National Health Surveys.

Over 65 % of the respondents strongly supported the importance of HBM studies for the purposes of: evaluating chemical exposure of the population, study the health impacts of chemical exposure, the development of health policy that promote the safe use of chemicals, to support occupational health policies and the safe use of chemicals at work, to raise awareness/understanding the impact of chemical exposure amongst the population and to raise awareness/understanding of the impact of chemical exposure amongst health professionals and policy makers.

Overwhelmingly, citizens chose food, the environment and drinking water as priority areas of chemical exposure to be addressed by human biomonitoring studies (see Figure 2)

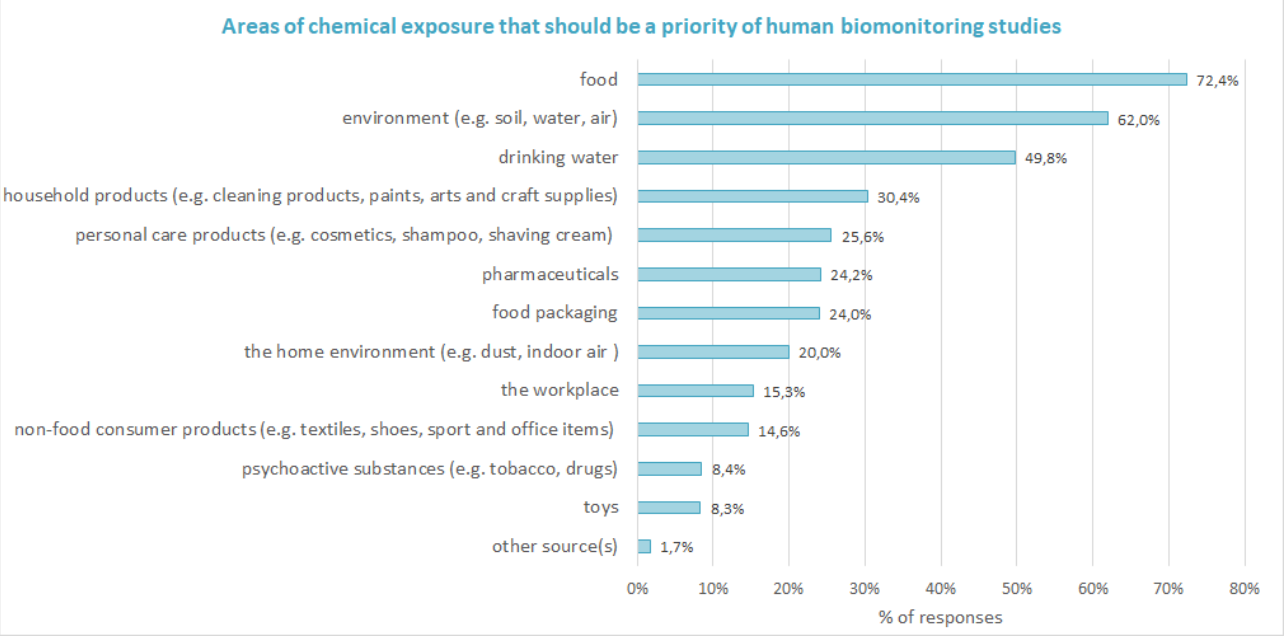


Figure 2 Priority areas in human biomonitoring

It is also noteworthy that, conversely, 13 % of the survey respondents supported the idea that HBM should not be done at all. A round of focus groups in several countries that were also part of the survey provided additional insights. Notably, the level of awareness about human biomonitoring was relatively low across countries and was not related with educational attainment. Moreover, beyond human biomonitoring, the awareness of the potential ill health effects from chemical exposures was also low, underscoring the importance of awareness raising and public education activities and policies.

5 EU policies on Flame Retardants

Some FRs are restricted within the EU as well as at the international level. PBDEs and HBCDD are restricted under the Stockholm Convention on Persistent Organic Pollutants (POPs) and therefore now have very limited use. Dechlorane Plus was recommended for risk management evaluation by

the Persistent Organic Pollutants Review Committee. Many replacement/alternative FRs are registered under REACH, but there are currently no regulations for a number of FR compounds.

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 identified by HBM4EU, one is registered under REACH under the 10,000-100,000 t/y tonnage band, 7 are at 1,000-10,000 t/y and 9 are at 100-1,000 t/y. Three FRs are not registered under REACH but listed under CoRAP based on (among others) high aggregated tonnage and wide dispersive use. Twenty eight of the 62 FRs are not registered under REACH.

EFSA is working on an update of the EFSA scientific opinions on brominated flame retardants, taking into account new occurrence data and any newly available scientific information.

6 Policy questions for Flame Retardants

6.1 Introduction

For each of the HBM priority substances stakeholders were asked to identify policy related questions that HBM4EU should address to contribute to the strengthening of policy ambitions on emerging chemicals. Further background detail on emerging chemicals and how the policy questions were selected is available in the scoping document and the report on stakeholder consultation and mapping of needs.

The current situation for flame retardants' policy questions is summarised in the next section and they were based on a document (AD5.7 Reporting CGLs 2022) updated by the CGLs and work package leader (WPL).

6.2 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?

Meta-analysis of existing biomonitoring data of FRs in the European population indicates an impact of restrictions on PBDEs and HBCDDs on population levels. PBDE levels in breast milk show a decline in selected lower brominated PBDE congeners (BDE 47, 99), however, higher brominated PBDE congeners (BDE-153, BDE-209) do not yet show a decline. This reflects the later restrictions on BDE-209.

Existing biomonitoring data of HBCDD in breast milk in the European population suggest a decline after 2010, however this trend is not yet conclusive due to the scarcity of data.

New biomonitoring data collected in the HBM4EU Aligned Studies show that PBDEs and HBCDD continue to be detected in serum of European children, however it is not possible with the available data to distinguish if this concerns legacy exposure from maternal transfer or new exposure from

flame retarded products. The HBM4EU Aligned Studies data will form baseline European exposure levels for FR in children, allowing follow up studies to monitor increased or decreased usage.

6.3 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)?

For many current-use FRs we lack biomonitoring data. New data collected in the HBM4EU Aligned Studies demonstrate widespread children's exposure to metabolites of TPHP, TDCIPP and TCIPP across all regions of Europe, with detection of DPHP (metabolite of TPHP and other OPFRs) in 99% of children.

P50 and P95 of DPHP concentrations are in the range of 1.43-2.43 µg/g crt and 5.16-9.70 µg/g crt respectively.

P50 of urinary BDCIPP concentrations are in the range of 0.38-0.64 µg/g crt across studies in children with 2 studies with a P50 value < detection limit (range: 0.09-0.5 µg/L). P95 of urinary BDCIPP concentrations are in the range of 0.70-4.55 µg/g crt across studies in children.

P50 of urinary BCEP concentrations is 0.12 µg/g crt for 1 study, the other 2 studies have a P50 < detection limit (0.3 µg/L). P95 of urinary BCEP concentrations range from 0.86-4.01 µg/g crt across studies in children.

P50 of urinary BCIPP concentrations is 0.09 µg/g crt in 1 study, all other 5 studies have a P50 value < detection limit (range: 0.19-0.9 µg/L). P95 of urinary BCIPP concentrations are in the range of 0.39-5.04 µg/g crt.

There are no health-based guidance values available for organophosphate flame retardants.

P50 of serum BDE-209 concentrations is 0.041 µg/L in 1 study in children, the 2 other studies have a P50 < detection limit (range: 0.0016-0.05 µg/L). P95 of serum BDE-209 concentrations are in the range of 0.06-0.58 µg/L across studies in children with 1 study with a P95 < detection limit of 0.0016 µg/L.

P50 and P95 of serum TBBPA concentrations are both < detection limit of 0.7 µg/L in one study in children.

All P50 of serum DBDPE concentrations are < detection limit (range: 0.01-1.9 µg/L) and P95 concentrations are in the range of 0.56-2.61 µg/L across studies in children.

P50 and P95 of serum 2,4,6-TBP concentrations are both < detection limit of 0.7 µg/L in one study in children.

P50 of serum BDE-47 concentrations is 0.003 µg/L in 1 study, the 3 other studies have a P50 < detection limit (range: 0.0001-0.002 µg/L). P95 of serum BDE-47 concentrations are in the range of 0.002-0.01 µg/L across studies in children.

P50 of serum BDE-153 concentrations are in the range of 0.0005-0.001 µg/L across studies in children with two studies with P50 < detection limit (range: 7x10-4-0.001 µg/L). P95 of serum BDE-153 concentrations are in the range of 0.004-0.007 µg/L.

P50 of serum DP-syn concentrations is 0.009 µg/L in 1 study in children, the 3 other studies have a P50 < detection limit (range: 0.001 - 0.05 µg/L). P95 of serum DP-syn concentrations are in the range of 0.003-0.08 µg/L across studies in children with 1 study with P95 < detection limit of 0.03 µg/L.

P50 of serum DP-anti concentrations is 0.01 µg/L in 1 study in children with 3 studies that have a P50 < detection limit (range: of 0.001 - 0.04 µg/L). P95 of serum DP-anti concentrations are in the range of 0.006-0.16 µg/L across studies in children with 1 study with P95 < detection limit of 0.0188 µg/L.

P50 of serum α-HBCDD concentrations are all < detection limit (range: 0.0075 - 0.01 µg/L) across studies in children. P95 of serum α-HBCDD concentrations are in the range of 0.03-0.13 µg/L across studies in children with 1 study with P95 < detection limit of 0.01 µg/L.

P50 and P95 of serum γ-HBCDD concentrations are all < detection limit (range: 0.0075 - 0.01 µg/L) across studies in children.

The HBM-I values for α-HBCDD and γ-HBCDD (both 1.6 µg/L) are not exceeded. For the other FRs, no HBM-GVs are available.

6.4 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? As FR market shifts towards replacement/alternative FRs, does human exposure reflect that trend? E.g., DBDPE as replacement for BDE209

OPFRs are widely marketed and used as alternatives to now restricted PBDEs and HBCDDs. There are comprehensive data for a small subset of these OPFRs (notably TCIPP, TCEP, TDCIPP), however for the majority of current-used flame retardants the knowledge and data gaps extend across the spectrum from analytical methods for HBM to toxicity and determinants of exposures and effects.

The understanding of exposure to legacy FRs is much more comprehensive than the understanding of trends in the replacement emerging FRs. Meta-analysis of legacy FRs in breast milk completed under WP10 has identified declines in BDE-47 and 99, and either decline or plateau in BDE 153, BDE-209 and HBCDD in European populations. The breakpoints in the temporal trends coincide with the introduction of restrictions on these compounds, indicating the impact of restrictions and market shifts on HBM levels.

However, there is a lack of data on the levels of replacement FRs. Metabolites of chlorinated FRs used as replacements from some PBDEs have been detected in 64% of children from Belgium, Denmark, Germany, France, Slovenia, and Slovakia in the HBM4EU Aligned Studies. DBDPE is a key alternative FR used to replace BDE 209. It was detected between 8-16% of children from France, Greece and Slovenia, however, the limitation in provision of new HBM data may be due to the analytical capacity of many European laboratories in targeting these emerging FRs.

6.5 4 & 12. How does exposure to FRs differ between adults and children, males and females? What are the population groups most at risk?

Under WP12, PBTK modelling has indicated higher TCEP intake and urinary metabolite levels in infants and young children, attributed to exposure to consumer products through mouthing of objects and direct dermal contact.

New biomonitoring data generated for children in the HBM4EU Aligned Studies do not indicate any gender difference for either legacy FRs or current use OPFR metabolites.

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

Based on literature review and meta-analysis for PBDEs conducted under WP10, there are no substantial differences within Europe in PBDE levels in breast milk. However, in a global context, European breast milk levels of PBDEs are around 10x lower than North American levels, which is attributed to the higher flammability standards and PBDE use in North America compared to Europe.

In contrast, the literature review and meta-analysis for HBCDDs has indicated comparable global levels of α-HBCDD in breast milk, but differences within Europe, with lower levels in Northern Europe; this is attributed to earlier restrictions on the use of HBCDD introduced in Nordic countries.

New data generated under the HBM4EU Aligned Studies also indicate regional differences in serum levels of Dechlorane Plus when compared across France, Norway and Slovenia (SI>NO>FR), but no clear cause for the regional differences has been identified. Similarly, regional differences exist for OPFRs (DPHP: SI>DE,FR,NO), also without a clear cause. There appears to be an incomplete understanding of the major determinants of exposure for OPFRs.

Focused multimedia studies including potential exposure pathways (dust, diet) in conjunction with HBM are recommended to provide insight into the regional differences in exposure, particularly for Dechlorane Plus, which is under consideration for inclusion in the Stockholm Convention on Persistent Organic Pollutants, and the chlorinated OPFRs, which have substantial evidence of toxicological concern.

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

The literature review completed within the framework of the scoping document (D4.9) has identified occupations with potentially elevated exposure to FRs (e.g., e-waste processers, computer repair, construction workers, some chemical industry workers, carpet installers). Workers in these settings are typically exposed to both legacy and current-use flame retardants at higher levels than the general population due to emissions of gaseous and particulate flame retardants during the dismantling of electrical and electronic waste.

6.8 What are the relevant exposure pathways for FRs, e.g., diet, air, water, indoor environmental exposure? Is elevated exposure to FRs associated with particular consumption patterns or lifestyles?

Human biomonitoring studies address the exposure of OPFR mainly through indoor environment via air and dust since it is detected in high amounts in those matrices. Only recently, a few studies focused on the dietary exposure to OPFRs. The concentration in house dust is approximately three magnitudes higher than its occurrence in food. In contrast to this, a child consumes approximately 1.2 kg food per day compared to 30 mg of dust. It can be assumed that the dietary intake might be equal or even a greater contributor to the total human exposure to OPFR.

This is supported by modelling under WP5 (D5.11), which identified that dietary contributions to children's exposure to selected OPFRs (TDCIPP, TCEP, TCIPP) is substantial, and in some cases may be the dominant exposure pathway (Plichta et al., 2022). The estimated daily and dietary intake of TCEP did not exceed health-based guidance values. However, there is limited information on dietary exposure for most of the prioritized FRs, and the data that exist are from a small subset of countries. Therefore, OPFR exposure sources remain uncertain. Further research on e.g. the oral bioavailability and occurrence data are necessary to determine which exposure pathways (dietary or dust uptake) contribute the most to the general exposure.

In the scoping document, FRs were categorized in Cat. A-E according to the availability of data regarding exposure, HBM and toxicity. Categories C, D, and E contain 40 FR compounds, and for these, almost no data are available to estimate the exposure from indoor environment (air and dust) and dietary uptake.

6.9 Do certain flame retardants co-occur in HBM matrices?

There is strong evidence based on existing HBM data and new data generated via the HBM4EU Aligned studies that FRs occur in mixtures. Exposures to individual PBDEs are correlated, and exposure sources (diet, dust ingestion) are common to most FRs, suggesting that highly exposed populations (particularly infants and children) will be highly exposed to a mixture of FRs.

Moreover, there is concern that mixture exposure posed a hazard that is not well-captured with compound-specific hazard evaluations and risk assessments. Under WP13, it was identified that many FRs have similar endocrine disrupting effects, suggesting potential for additive effects of exposure to multiple FRs (Bajard et al., 2021).

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?

A comprehensive literature search showed that toxicological data was either incomplete or critically lacking for many flame retardants in use.

A systematic search for data availability focused on the FRs used as substitutes, such as OPFRs and showed that for the majority of these 52 replacement FRs, in vivo toxicological data, mechanistic data and in vitro data on ED activities were either missing or insufficient for proper hazard characterization. For 9 FRs (TCEP, TCIPP, TDCIPP, TPhP, TMPP, TBBPA, EHDPP, TNBP, TBOEP), substantial data allow some level of hazard identification and raises a toxicological concern. Literature search on ED activities combined with in silico predictions reveals that most of the 52 FRs may share antiandrogenic properties, raising concerns for mixture effects of combined exposure (Bajard et al., 2021). This was confirmed in vitro for 7 FRs.

Apart from these results obtained within WP 13, no information on the toxicity of typical FRs mixtures was identified.

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

For 9 replacement FRs, in vivo data, combined with mechanistic information from in vitro testing and AOP knowledge highlighted the main effects on male fertility, neurotoxicity, and hepatotoxicity. However, solid human epidemiology studies are critically missing to establish the health risks associated with exposure to replacement FRs (Bajard et al., 2019).

Additional in vitro studies performed within WP13 identify potential mechanisms underlying male reproductive toxicity and hepatic steatosis.

Within WP14, a literature search identified biomarkers of effect related to neurotoxicity, reproductive toxicity, and cardiovascular function that have been associated with OPFRs exposure.

The association between FR exposure, molecular and clinical biomarkers of effect (including the novel biomarker BDNF), and neurodevelopment is currently evaluated in child cohorts included in the HBM4EU Aligned Studies.

6.11 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?

Broad data gaps remain for many currently used FRs. For the majority of the 52 replacement FRs listed in HBM4EU, in vivo toxicological data, mechanistic data and in vitro data on ED activities were either missing or insufficient for proper hazard characterization. Uncertainties also extend to analytical capacities, with a very limited set of European laboratories with capacity for HBM of current use FRs, and inconsistencies in analytical methods.

The risk assessment on TCEP demonstrated that when sufficient exposure and HBM data are available, we can improve our understanding of risk. However, this is also influenced by uncertainty in hazard evaluation, as the risk assessment identified low risk according to one EU hazard threshold, but possible risk based on US EPA threshold; uncertainty in both the hazard and exposures to TCEP leads to uncertainty in the risk assessment.

6.12 Can reference values be established for any FRs?

There is currently insufficient data to establish general population reference values for FRs.

7 HBM4EU outputs to date

7.1 Categorisation

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 1.1 Categorisation of Flame Retardants

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	BDE-28[3]	2,4,4'-Tribromodiphenyl ether	41318-75-6	Restricted under REACH and listed on Stockholm Convention
A	BDE-47	2,2'4,4'-Tetrabromodiphenyl ether	5436-43-1	Restricted under REACH and listed on Stockholm Convention
A	BDE-99	2,2',4,4',5-Pentabromodiphenyl ether	60348-60-9	Restricted under REACH and listed on Stockholm Convention
A	BDE-100	2,2',4,4',6-Pentabromodiphenyl ether	189084-64-8	Restricted under REACH and listed on Stockholm Convention
A	BDE-153	2,2',4,4',5,5'-Hexabromodiphenyl ether	68631-49-2	Restricted under REACH and listed on Stockholm Convention
A	BDE-154	2,2',4,4',5,6'-Hexabromodiphenyl ether	207122-15-4	Restricted under REACH and listed on Stockholm Convention
A	BDE-183	2,2',3,4,4',5',6-Heptabromodiphenyl ether	207122-16-5	Restricted under REACH and listed on Stockholm Convention
A	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
A	**HBCDD**	Hexabromocyclododecane	3194-55-6, 25637-99-4, 1093632-34-8	On REACH Authorisation List and listed on the Stockholm Convention
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)
B	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.
B	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)
B	TCIPP	Tris(1-chloro-2-propyl) phosphate	13674-84-5	Registered under REACH
B	TDCIPP	Tris(1,3-dichloropropyl)phosphate	13674-87-8	Registered under REACH, Entered onto CoRAP for evaluation in 2019 as potential endocrine disruptor
B	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
B	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.)
B	TBOEP	Tri(2-butoxyethyl) phosphate	78-51-3	Registered under REACH under 1000-10000 T/y tonnage band

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

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
B	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)
B	EH-TBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate	183658-27-7	None
B	BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane	37853-59-1	Not registered under REACH
B	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
C	EHDPP	2-ethylhexyl diphenyl phosphate	1241-94-7	Registered under REACH under 1000-10000 T/y tonnage band
C	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
C	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).
C	TEP	Triethyl phosphate	78-40-0	Registered under REACH
C	HBB	Hexabromobenzene	87-82-1	Not registered under REACH
C	DBE-DBCH	Tetrabromoethylcyclohexane	3322-93-8	Not registered under REACH
C	DBHCTD	Hexachlorocyclopentenyldibromocyclooctane	51936-55-1	Not registered under REACH
C	PBEB	Pentabromoethylbenzene	85-22-3	Not registered under REACH
C	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
C	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)
C	PBT	Pentabromotoluene	87-83-2	Not registered under REACH
C	PBB-Acr	Pentabromobenzyl acrylate	59947-55-1	Registered under REACH under 100-1000 T/y tonnage band
C	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

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
D	BPA-BDPP	Bisphenol A bis(diphenylphosphate)	5945-33-5	Registered under REACH
D	TBCO	1,2,5,6-tetrabromocyclooctane	3194-57-8	None
D	PBP	Pentabromophenol	608-71-9	Not registered under REACH
D	DBP	2,4-dibromophenol	615-58-7	Not registered under REACH
D	TIBP	Tri-iso-butyl phosphate	126-71-6	Registered under REACH under the 1000-10000 T/y tonnage band
D	TnPP	Tri-n-propyl-phosphate	513-08-6	Not registered under REACH
D	TDBPP	Tris(2,3-dibromopropyl) phosphate	126-72-7	Restricted under REACH
D	CDP	Cresyl diphenyl phosphate	26444-49-5	Not registered under REACH
D	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
D	OBTMPI	Octabromotrimethyphenyl indane	1084889-51-9, 1025956-65-3, 893843-07-7, 155613-93-7	Not registered under REACH
D	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
E	TDBP-TAZTO	Tris(2,3-dibromopropyl)isocyanurate	52434-90-9	Not registered under REACH
E	RBDPP	Resorcinol bis(diphenyl phosphate)	57583-54-7	Not registered under REACH
E	TTBNPP	Tris(tribromoneopentyl)phosphate	19186-97-1	Registered under REACH under the 100-1000 T/y tonnage band
E	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)
E	HEEHP-TEBP	2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate	20566-35-2	Registered under REACH under 100 – 1000 T/y
E	TTBP-TAZ	2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine	25713-60-4	Not registered under REACH
E		Melamine polyphosphate	20208-95-1, 218768-84-4	Not registered under REACH
E		Diethylphosphinic acid	813-76-3	Not registered under REACH
E	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

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
E	4'-PeBPO-BDE208	Pentabromophenoxy-nonabromodiphenyl ether	58965-66-5	Not registered under REACH
E	TBNPA	Tribromoneopentyl alcohol	1522-92-5	Registered under REACH under 100 – 1000 T/y
E	HBCYD	Hexabromocyclodecane	25495-98-1	None
E	DBS	Dibromostyrene	31780-26-4	Not registered under REACH
E	DBP-TAZTO	1-(2,3-dibromopropyl)-3,5-diallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	57829-89-7	None

7.2 Key outputs

Current HBM levels and trends of legacy/regulated FRs (e.g., PBDEs and HBCDD)

In WP10, five legacy/regulated FRs were identified as the focus for statistical analysis of existing HBM data. These are four polybrominated diphenyl ethers (BDE 47, 99, 153 and 209) and hexabromocyclododecane (HBCDD). The European HBM dashboard provides summary statistics for HBM data from different European countries, with 8 aggregated datasets including legacy FRs exposure data in blood serum or plasma. These data, covering different age groups from largely Western and Northern European populations, were insufficient to evaluate spatial and temporal trends as planned. Thus, a comprehensive literature review was conducted to gather literature data for a joint analysis of spatial and temporal trends in Europe and on a global scale, to place European population levels in a broader context. Literature data mining and statistical analysis focused on maternal milk as a target biomonitoring matrix. The HBM4EU Aligned Studies (2014-2021) have measured brominated FR in serum samples from children between 6 and 11 years of age from 4 different sampling sites in Europe representing 711 individuals. This has improved the data coverage of current knowledge on FR exposure to children within Europe, with new data generated for PBDEs in children from France, Greece, Slovenia and Norway and new data on HBCDDs in France, Greece, and Slovenia.

Exposure of the European population to current use FRs

The HBM4EU Aligned Studies (2014-2021) have measured halogenated FR (10 biomarkers) in serum samples from children between 6 and 11 years of age from 4 different sampling sites in Europe (Norway, Slovenia, Greece, and France) representing 711 individuals and organophosphate FR (4 biomarkers) in urine samples from children between 6 and 11 years of age from 7 different sampling sites in Europe (Norway, Denmark, Slovakia, Slovenia, France, Belgium and Germany) representing 1770 individuals. Not all biomarkers were analyzed in all contributing studies, therefore number of sampling sites and data points can vary per biomarker. To support current and future HBM studies, HBM4EU developed a variety of publicly available groundwork materials for a harmonised approach to study planning and conduct in Europe. (WP7, HBM4EU online library)

A prioritised list with most suitable biomarkers, matrices and analytical methods has been produced (WP9, D9.2, D9.7).

The HBM4EU Aligned Studies have substantially improved the coverage of current knowledge on FR exposure within Europe, with new data generated for Dechlorane Plus in children from France, Slovenia, and Norway.

Levels of legacy FRs vs levels of new/emerging FRs

To ensure comparability across newly generated biomonitoring data in the HBM4EU Aligned Studies, four rounds of interlaboratory validation exercises were carried out. The intercomparison exercises identified a significant core network of comparable European laboratories for HBM of halogenated flame retardants (PBDEs, HBCDD, Dechlorane Plus). On the other hand, the data revealed a critically low analytical capacity in Europe for HBM of currently-used flame retardants (e.g., TBBPA, DBDPE, 2,4,6-TBP, and the OPFR biomarkers).

In addition, as biomarkers of legacy FRs are typically quantified in serum/plasma, while many of the new/emerging FRs (i.e., organophosphate esters) biomarkers are quantified in urine, the measured levels cannot be directly compared. Therefore, PK modelling is necessary to enable comparison of

the legacy and emerging FRs. PK modelling has been performed under WP12 for both legacy (BDE 47) and current use FRs (TCEP), however not on identical populations, so the outcomes cannot be used to directly compare legacy and current use FRs.

Differences in exposure to FRs between adults and children, males, and females

There are very limited data to address this question, as the data produced under the HBM4EU Aligned Studies were limited to children ages 6-11. Young children typically have higher exposure due to transplacental transfer, flame retardants in breast milk, and behaviour. Children accidentally ingest indoor dusts which have high levels of FRs and are exposed due to mouthing of objects and hand-to-mouth transfer. Exposure modelling for TCEP under WP12 has provided an indication of age-related differences in exposure. Toxicokinetics of TCEP exposure were assessed through INTERGRA PBTK model (AD12.5), however discrepancies between modelled exposure and measured urinary metabolites, particularly in infants and toddlers, indicate uncertainties and data gaps in FR exposure in infants and children.

Differences in exposure by geographic area within Europe

This question has been addressed under WP10, both through the literature review and meta-analysis conducted for existing data on legacy FRs, and for children's populations through new data generated by the HBM4EU Aligned Studies.

Occupationally exposed sub-groups

The answer to this question is supported by the questionnaires developed in WP7, among others for the 2nd occupational studies. A framework for a study on exposure of e-waste workers to a wide range of chemicals, including FRs, has been prepared, covering the target matrices, questionnaires and framework for comprehensive biomonitoring and exposure assessment. Occupational exposure has not been addressed in the HBM4EU Aligned Studies as FR have only been measured in children ages 6-11.

Relevant exposure pathways for FRs, e.g., diet, air, water, indoor environmental exposure

To answer questions on exposure levels and sources and further support current and future HBM studies, WP7 has produced a variety of materials to provide the groundwork for a harmonised approach to study planning and conduct in Europe.

When identifying exposure levels and sources as well as groups at risk, WP7 questionnaires are of great value. They can be used to set up new studies and allow the harmonized collection of data on a participant's individual characteristics and their potential exposure pathways from different sources (sociodemographic characteristics, residential environment/home exposures, dietary habits, lifestyle, occupational exposure and health status) with flame retardants. For flame retardants, questionnaires for adults, adolescents and children are available. Questionnaires for the 2nd occupational study on e-waste (incl. FRs as a biomarker) have also been developed.

Under the framework of WP12, a web-based exposure database has been developed to support the modelling of exposure towards better HBM data interpretation. Chemical-specific data include information related to the contamination levels in several environmental matrices such as ambient air, indoor air, water, soil, dust, as well food residues in various food items, and concentration in consumer products. In the current iteration of the exposure database this is available for brominated flame retardants, with geographically disaggregated data from Austria, Germany, Greece, Norway, Spain, Sweden and UK for environmental exposure, and Norway + general EU for dietary exposure, and general data for consumer products.

This tool has been used in estimating population exposures, e.g, exposure through ingestion, inhalation and dermal contact was evaluated for TCEP (AD12.3, 12.5), highlighting non-dietary ingestion of dust as a major exposure pathway.

For various OPFRs, WP5 estimated the daily intake based on HBM data of TDCIPP, TCIPP and TCEP measured in urine samples from children in Germany, Belgium, Denmark, France, Slovenia and Slovakia and toxicoknetic modelling.

Co-occurrence of flame retardants in HBM matrices

A framework and statistical analysis plan have been developed within WP15 (AD 15.3) to provide a general concept and structure for how mixtures can be addressed. Mixture profiles for 26 flame retardants have been evaluated (D15.3) based on simulated data to gain insight into the determinants of mixture profiles in HBM data, but thus far is only simulated data and does not indicate direct biological relevance of these FR mixtures. Under WP10, correlations between biomarkers of BFR and OPFR exposure have been investigated within the new HBM4EU Aligned Study data.

Toxicity of FRs typically occurring in indoor environments and diet

Under WP13, 52 FRs used as replacement (such as OPFRs) were classified and prioritised according to the availability of toxicological information and potential toxicity, as follows: 10 FRs with substantial toxicological information, 9 of which have toxicological concern (TCEP, TCIPP, TDCIPP, TPhP, TMPP, TBBPA, EHDPP, TNBP, TBOEP), 20 FRs without toxicological data in mammals, and 22 FRs with only scarce toxicological data. In addition, systematic search (WP13) for in vitro information on endocrine disruptive (ED) activities of the 52 replacement FRs highlights the absence of data for 24 of them. Complemented with structure-based predictive models, the search shows that antiandrogenic activity is reported and/or predicted for most of the 52 replacement FRs. In a follow up screening performed within WP13, the predicted antiandrogenic activity was confirmed for one FR, TDBP-TAZTO. This raises concerns regarding possible mixture effects that were confirmed in vitro. Besides, no information on the toxicity of FRs as mixtures was identified.

Linkages between exposure to FRs and adverse health effects

Under WP13, decrease in male fertility, neurotoxicity and hepatotoxicity were identified as the main health effects for 9 prioritized FRs, based on toxicological data combined with AOPs. In addition, evidence was found linking TBBPA exposure with thyroid hormone homeostasis, carcinogenicity, and teratogenicity. The data collected also indicate that TPhP and TDCIPP may be considered as endocrine disruptive chemicals (EDCs). An AOP-based in vitro screening also highlighted the potential of 4 FRs to induce hepatic steatosis. Under WP14, a literature search was completed for biomarkers of effect for BFRs and OPEs. For BFRs 23 biomarkers were identified in at least 2 studies. For OPEs, the literature search identified ten biomarkers proposed for implementation in human biomonitoring studies. Effect biomarkers were related to neurotoxicity, reproductive toxicity, and cardiovascular function. A review of the literature further supported the association of selected FRs with ADHD.

Prioritisation of additional FRs for further information regarding exposure and/or toxicity

The scoping document (D4.9) highlighted 20 of 62 flame retardants with evidence of toxicity but insufficient HBM data. These are also candidate compounds to be prioritised for exposure assessment. These compounds are TPHP, TMPP, TCEP, TCIPP, TDCIPP, TNBP, TBBPA, and TBOEP (Cat. B), TEHP, EHDPP, DDC-DBF, ip-TPP, V6, 2,4,6-TBP and TDBPP (Cat. C and D) and DBNPG, TDBP-TAZTO, RBDPP, melamine polyphosphate and EBTEBPI are Cat. E. See D4.2 Section 5. WP5 built on the prioritisation of the scoping document by further classifying and investigating regulatory, risk evaluation and data availability for the 20 highlighted FRs. TCEP emerged as the most urgent FR to address. An HBM-based risk assessment was performed for TCEP aimed at the general population, using model-reconstructed external exposure starting with HBM data.

Establishment of reference values be established for any FRs

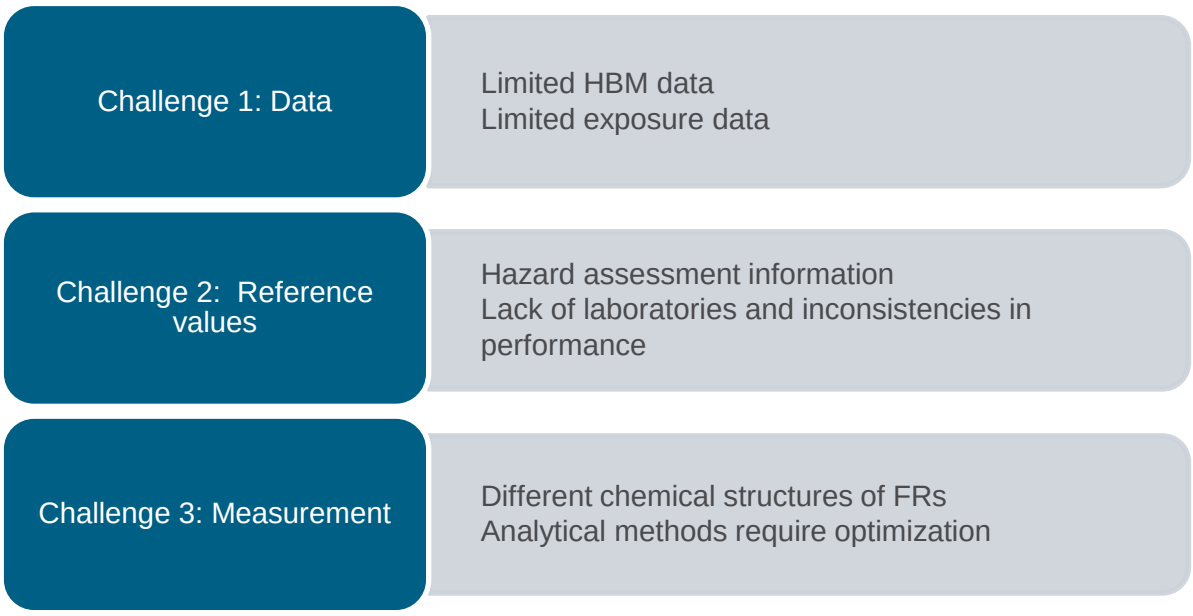
Based on the exclusion and partitioning criteria set by WP10, there are currently insufficient data to establish reference values (limiting to general population, exclusion of hot spots, infants, children, adolescents and pregnant women/partitioning by matrix – serum or milk).

7.3 Key data gaps

Additional short- and long-term toxicity data are needed, including information data on synergistic and additive effects.

There are inconsistencies between laboratory analyses for NBFRs and OPEs.

Analytical methods vary for different sub-groups of FRs due to differences in chemical structure and there is a general need for methods to be optimised.



8 Future recommendations

Flame retardants are a complex chemical group to address, covering many hundreds of chemicals, some with prioritary structures and unknown toxicity. Given the challenges of lack of data, reference values and harmonized methods, clear prioritization and grouping strategies are needed to ensure that the resources dedicated to FR biomonitoring, exposure, and risk assessment are focussed on those in substantial use and with indication of toxicity. Grouping strategies can ensure that the long-list of FRs can be coherently addressed.

Improvements to laboratory capacity are needed to allow HBM for a broad set of OPFRs across Europe. More information on the hazard of OPFRs is needed to allow generation of health-based guidance values.

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