Prioritised substance group: Flame retardants (FR)

Lead author	Jana Klanova, Lisa Melymuk (MU - CZ)
Contributors	Jana Klánová, Lola Bajard, Garry Codling

Short overview of results of the activities carried out within HBM4EU in 2020 to answer the policy questions with reference to corresponding deliverables.

Policy question	Results
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?	In WP10, five legacy/regulated FRs were identified as the focus for statistical analysis. These are four polybrominated diphenyl ethers (BDE 47, 99, 153 and 209) and hexabromocyclododecane (HBCDD). Insufficient data was available through HBM4EU to evaluate spatial trends as planned, as well as insufficient data to evaluate temporal trends, although temporal trends have been evaluated and published for Norway (Thomsen et al. 2002; Thomsen et al. 2007) Sweden (Fängström et al. 2008; Norén et al. 2000; Meironyte et al., 1999; Darnerud et al. 2015; Lignell et al. 2015; Gyllenhammar et al. 2016) and Rome, Italy (Alivernini et al. 2011). These are summarised in the WP10 data analysis plan for flame retardants. Thus, the smaller set of data available through HBM4EU has been supplemented with literature data to allow 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 is continuing in 2020, with the focus on maternal milk as a target biomonitoring matrix. A data analysis plan (task 10.4) on “Geographic Variations in Category A Flame Retardants in the European Population” reflects the planned analysis for these analyses. Further analysis on geographic differences in current-use FRs as well as determinants of exposure is planned for data generated by aligned studies. The combined interpretation of the legacy and current-use FR population levels will serve as a baseline to eventually evaluate whether declines due to chemical regulation are 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)?	Under WP8, new aligned data is being generated for FR exposure in children age 6-11, for urinary biomarkers of organophosphate ester FRs, and serum biomarkers of BFRs by the end of 2020. Data will cover all four regions of Europe (North: Norway (300 urine and 300 serum), Denmark (300 serum); East: Slovakia (300 urine); South: Slovenia (150 serum), Greece (150 serum); West: France (300 urine), Germany (300 urine, 300 plasma), Netherlands (300 urine)). This

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	will provide sufficient data to analyse exposure of the children to current flame retardants. Currently there is insufficient available data to evaluate this.
3 & 13. 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	Following the production of new aligned data under WP8, this analysis can be performed in WP10 in 2020. There is currently insufficient data to evaluate this question. This question is further being addressed through the pharmacokinetic (PK) modelling being conducted in WP12. 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 modeling is crucial to enable comparison of the legacy and emerging FRs.
4 & 12. How does exposure to FRs differ between adults and children, males and females? What are the population groups most at risk?	There is not currently sufficient data to address this question, nor will sufficient data be produced under the harmonised WP8 framework, as the generation of new FR data will be limited to children ages 6-11. Therefore, this question is being addressed through integrated exposure modeling in WP12 (AD12.3). Exposure modeling for TCEP has identified highest estimated exposure to infants, however discrepancies between modeled exposure and measured urinary metabolites, particularly in infants and toddlers, indicate uncertainties and data gaps in FR exposure in infants and children. Toxicokinetics of TCEP exposure were assessed through INTERGRA PBTK model (AD12.5).
5. How does exposure differ by geographic area within Europe? Do countries/regions have different FR exposure levels?	This question is being addressed from WP10, initially for the restricted FRs for which there is sufficient data (4 PBDEs and HBCDD), and subsequently also for current use FRs when new data is generated through the aligned studies. The initial analysis will incorporate records of maternal milk for 10 European countries, and compare the geographic trends evaluated by the different matrices.
6. 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 (D4.2) has identified occupations with potentially elevated exposure to FRs (e.g., e-waste processers, computer repair, construction workers, some chemical industry workers, carpet installers). Occupational exposure to FRs has not been further addressed within the project. Occupational exposure will not be addressed in the aligned studies as the FR data will be only for children ages 6-11.
7 & 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?	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.
9. Do certain flame retardants co-occur in HBM	Yes, there is strong evidence based on existing HBM data (so far reviewed in literature during updating of scoping

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matrices?	document, D4.2) that FRs occur in mixtures. A framework and statistical analysis plan has 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.
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?	Under WP13, FRs 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. Molecular targets, health outcomes and potential AOPs identified for the 9 priority FRs with toxicological concern. The toxicity of FRs in mixtures has not yet been addressed.
11. Can exposure to FRs be linked with any adverse health effects?	This is the focus of WP13 and WP14. Under WP13, TBBPA was addressed as a first case, summarising existing toxicity information on TBBPA to link with adverse outcome pathways (AOPs) (D13.2) Evidence was found linking TBBPA exposure with thyroid hormone homeostasis, hepatotoxicity, carcinogenicity, neurotoxicity and teratogenicity. Similar exercises were completed for TDCIPP, linked with reproductive toxicity, and TPhP, linked with reproductive toxicity. Under WP14, a literature search was completed for biomarkers of effect for BFRs and OPEs. For BFRs 74 relevant publications were identified, covering 58 molecular/biochemical markers. Of those, 23 biomarkers were identified in at least 2 studies. For OPEs, the literature search identified 23 relevant publications. Ten biomarkers were proposed for implementation in Human Biomonitoring studies. Effect biomarkers were related to neurotoxicity, reproductive toxicity, and cardiovascular function. It was identified that there is a lack of information related to neurodevelopment.
14. What additional FRs should be prioritised for further information regarding exposure and/or toxicity? How can use and risk information be combined to identify and prioritise knowledge gaps for further assessment?	The scoping document (D4.2) 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.
15. Can reference values be established for any FRs?	Based on the exclusion and partitioning criteria set by WP10, there is insufficient current 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).