Overview of prioritized substances

Content

Note: The Pillar numbers, Work Package numbers, and tasks will have to be adapted to the new outline of WPs and tasks.

1 Phthalates/DINCH

1.1 Introduction

Phthalates and their substitute Hexamoll® DINCH are a group of ubiquitous plasticizers some of which have adverse effects on the male reproductive tract of laboratory animals. Phthalates like di(2-ethylhexyl)phthalat (DEHP), di-n-butylphthalate (DnBP), di-iso-butyl phthalate (DiBP), and butlybenzylphthalate (BBzP) impede development of reproductive functions. Phthalates with a certain chemical structur (carbon side chain length of C3 to C 6) produce cumulative adverse effects (U.S. Congress, 2008). Mixtures of individual phthalates have direct additive effects on the foetal testosterone production and the course of pregnancy (Howdeshell et al 2008). Four of them (DEHP, DnBP, BBzP, DiBP) are classified as reproductive toxicants category 1B under Annex VI to the CLP Regulation, substances of high concern (Annex XIV EC 1907/2006) and subjected to authorization under REACh. The use of three of these phthalates (DEHP, DnBP, BBzP) are restricted in all toys and childcare articles with a concentration limit of 0.1% by entry 51 of Annex XVII to REACH. In addition, Diisononyl phthalate (DINP), Di-n-octyl phthalate (DNOP), Diisodecyl phthalate (DIDP) are restricted for all children's toys and child care articles that can be placed in children's mouth with a concentration limit of 0.1% by entry 52 of Annex XVII to REACH.

Plasticisers are taken up by ingestion, inhalation and dermal contact, the main source of exposure is via food originating from contamination and food contact materials. Inhalation, exposure via ingestion of house dust by children and dermal contact contribute to the overall exposure to a minor degree. Levels found in children at least in Germany have in the past been so high that an impact on health could have been no longer excluded with the sufficient probability. Phthalate metabolites are present in every urine sample investigated.

In regard to occupational exposure there is only limited data on the exposure of workers to different phthalates in the plastic industry. Also, phthalates used in the industry has changed dramatically during the past decade due to restrictions. Therefore, the exposure to old, well known phthalates (DEHP, DBP etc) in the industry has decreased. However, the workers may be significantly exposed to newer phthalates, like DINP and DINCH. According to the on-going study in Finland, DINP and DPHP are most often used.

1.2 Substance Classification

The phthalates and the latest substitutes on the market can be classified in 3 different categories : substances where a) sufficient data are already available, b) only insufficient data are available, and c) no data are available, published and/or no biomarkers have been established.

CATEGORY A: regulated: DEHP, DnBP, DiBP, BBzP,

non regulated: DEP

CATEGORY B: regulated: DiNP, DiDP, DnOP

non-regulated: DMP, DnPEP, DChP, DPHP, substitute Hexamoll® DINCH

CATEROGY C: DIPP (Diisopentylphthalate, CAS-No: 605-50-5; SVHC candidate, 57c), DHNUP (Di-C7-11-(linear and branched)-alkyl phthalate, CAS-No: 68515-42-4), DHEXP (di-n-hexyl phthalate, CAS-No: 84-75-3; SVHC candidate, 57c) and DEMP (Di(methoxyethyl) phthalate, CAS-No: 117-82-8

The aim is to move Cat C and B substances to Cat A, either by developing/integrating new methods, sharing new methods available in only one or two labs EU wide and/or by generating additional HBM exposure data. Desk research during year 1 and the following years will also be done the find evidence if the substance is not only theoretical of relevance.
When a substance has reached Cat A policy relevant conclusions can and will be drawn. For the whole group of phthalates this work will have to be done during the whole 5 years.
The assessment stages “introduce/share new methods”, “elaborate an efficient and targeted study design”, “measure additional HBM exposure data” and “ripe to draw conclusions” will necessarily differ for the Cat A, B and C substances.

1.3 Objectives

The overall goal of the plasticizer activities is to work out and extend research based information that can be transferred into mandatory and/ or recommended political and regulatory measures accompanied by a targeted communication of results and conclusions.
The objectives in detail differ for Cat A) and B) substances. In case of Cat A) the existing data should be made available on a European scale, assessed in comparison to each other and in relation to their geographical origin. They build a basis on which either direct conclusions for policy advice can be derived or research gaps identified. This advice is urgently needed because of the expected second approach to ban the 4 regulated Cat A phthalates under REACH.

Where no (Cat C) or not sufficient (Cat B) data are available the goals are to identify and prioritize knowledge and data gaps and related research needs as starting point for the development of research questions and goals for year 2 and following years, to identify missing analytical methods for move a substance in Cat. A, to start to establish available analytical methods in countries where this need is identified and to develop the basis for an ethical framework for data and biosample exchange, sample storage, etc. Furthermore, the potential health hazard of Cat. C phthalates will be explored.

1.4 Policy-Related Research Questions: for the Cat. A substances are:

1. How high is the current (year 2012 or more recent) exposure of the EU population to Cat. A substances?
2. Do the exposure levels of unregulated and regulated Cat. A substances differ significantly between countries? What are the main reasons for differences in exposure?
3. Is there a significant decrease of the regulated Cat. A substance levels (GM/median) in the population (general/children?) from year 2007 until today (2015)? (DEHP, DnBP, BBzP)
4. What are the high exposure groups? (Is there a statistical significant and toxicological relevant difference in mean concentration between adults and children? […] between occupational exposed and non-exposed adults? […] between male and female?)
5. Are the overall exposure levels in the general population and vulnerable groups as children and pregnant women above any health-relevant assessment levels (HBM guidance values - if existing; TDI)?
6. Can EU wide accepted HBM guidance values be derived for the single substances and for the additively acting phthalates?
7. Had the regulation under REACH the favorable impact, that is a reduction of GM/median concentrations of the already regulated (before 2015) phthalates (DEHP, BBP, DnBP, DiNP, DiDP, DnOP), especially for children?
8. What are knowledge gaps and related research needs for Cat. A substances to answer questions A 1-A 6 sufficiently in the following years (Year 2)? Which substances have to be moved to Cat. B (or even C)?

1.5 Description of work

In the first year collection, comparison and evaluation of available data will already be used to derive first recommendations for policy and information of the public. Existing HBM data will have to be collected, combined, harmonized if possible and compared across Europe to get an overview of current exposure levels (in general population, children, at the working place if still applicable). Data on time trends from the Swedish Biobank and the German Environmental Specimen Bank will be used to prove the success of the REACH risk reduction measures taken so far and thus also to evaluate if the rejection of the Danish proposal to ban phthalates was appropriate.

After evaluation of existing toxicological data and on the basis of the methodology developed by the German Human-Biomonitoring Commission toxicologically derived HBM guidance values have to be agreed upon on a European scale and newly developed for those still missing. In regard to the occupational exposure, the possibility of recommendations on biological limit values for those substances where no SCOEL or BLV exists should be explored and if possible missing values should be introduced. In parallel activities to develop a broader and harmonized applicability of existing new methods will be started in year 1.

If and to which extend further measurements of exposure in additional regions of Europe are necessary to conclude on the success of the authorisaton obligation under REACh will be one results of the first years analyses. In parallel training and harmonization of phthalate analyses methods including a round robin, preferably under the umbrella of the G-EQUAS run by University of Erlangen will be part of the extended harmonization, sharing of technical knowledge and training.
Also the concept developed by the German Human-Biomonitoring Commission to derive toxicologically based HBM guidance values should serve as a basis on which a EU-wide set of HBM values can be developed. After reaching agreement on a HBM guidance value for DEHP building on that derived by the German Human Biomonitoring Commission HBM values for the other Cat A phthalates and, subsequently, one which takes the additive effects into account will be developed. This can be started in year 1 and will be continued during

the 5 years of the project after prioritization of the Cat A, B and C substances according to the exposure levels observed and their toxicological potency. For Cat. B and C substances knowledge gaps and related research needs will be identified and filled as possible to subsequently move a Cat. B and C substance to Cat. A in order to answer the related research questions. Furthermore, the extend of occupational exposure, especially to "newer" phthalates and substitutes should be investigated

For Hexamoll®DINCH, the most prominent substitute for DEHP, the number of qualified laboratories will be extended by introducing as a first step a limited number of already specialised and qualified HBM laboratories in the methodology. This will be done by IPA (Holger Koch). In the next steps and in year 2 these 3-5 labs will then share their knowledge with additional labs which want to build up experiences and are up to now not specialized.
For DINCH and other Cat B substances new HBM data are to be measured. Following the scheme for the introduction in the application of the new methods which was tried out for DINCH the availability of labs being able to run these methods will have to be extended.
On the basis of the analysis of the exposure data for the Cat A phthalates in the second year a scheme will be developed to estimate from how many countries and from which regions exposure levels are needed to sufficiently include the variation of exposure in Europe. This will then be the basis for conducting additional HBM analyses in year 3.
Further research, monitoring, quality assurance, and harmonisation needs are to be identified and prioritiesed as starting point for the adjustment and, if needed development of new research questions and goals for year 2 and following years.
Simultaneously analytical methods, documents and study infrastructure have to be established, shared and/or developed in Europe. This includes the development of SOPs, quality assurance requirements and exchange of technical knowledge. Subsequently to identification and prioritization of knowledge and data gaps and related research needs the research and monitoring plan for year 2 and following years will be developed.

One important part of the work is to develop the basis for an ethical framework for data and biosample exchange, sample storage etc.

1.6 Deliverables

1st Year:

- Overview of available biomonitoring and exposure data on phthalates and DINCH relevant to the European population
- Overview of current exposure to phthalates & DINCH in Europe & exposure over time (by comparsion of German and Swedish time trends)
- Overview of high exposed population groups of phthalates & DINCH
- Report on spatial, temporal and knowledge gaps according to substance
- Map of the spatial and temporal variation in phthtalate & DINCH exposure across the EU based on use and available data to identify variability in exposure and risk
- Training and harmonization of phthalate analyses methods including a round robin
- Consolidated EU-wide health-based guidance value for DEHP, DINCH
- Extension of the number of qualified laboratories by introducing 2-3 already specialised and qualified HBM laboratories in the methodology for DINCH analysis

Years 2-5:

- Consolidated EU-wide reference values for phthalates & DINCH

- A number of qualified laboratories within EU able to measure phthalates & DINCH with a validated analytical methods according to SOPs
- Prove of the success of the REACH risk reduction measures (or not)
- Overview of potential health hazard of Cat. C phthalates
- Development of EU-wide SOPs, quality assurance requirements and exchange of technical knowledge, study infrastructure

1.7 Literature

Howdeshell K.L., Wilson, V.S., Furr, J., Lambright, C.R., Rider, C.V. , Blystone, C.R. Hotchkiss, A.K. and L.E. Jr., 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105, (1):153-165

U.S. Congress. House of Representatives. Committee on Energy and Commerce, Subcommittee on Commerce, Trade, and Consumer Protection. 2008. Hearing on Safety of Phthalates and Bisphenol-A in Everyday Consumer Products. June 10, 2008. Written Testimony of Leon Earl Gray, Jr., Senior Reproductive Biologist and Toxicologist, U.S. EPA, 2008.

Regulation (EC) No 1272/2008of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

2 Bisphenols

2.1 Introduction

Bisphenol A (BPA) is an endocrine disruptor and and it has been suspected to increase the risk of breast cancer after gestational or neonatal exposure. Studies have indicated that it could be associated with increased risk for cardiovascular disease, miscarriages, decreased birth weight at term, breast and prostate cancer, reproductive and sexual dysfunctions, altered immune system activity, metabolic problems and diabetes in adults, and cognitive and behavioural development in young children. It elicits a variety of endocrine disrupting effects targeting steroid hormones as well as thyroid hormones. It is used in certain plastics, epoxy resins and thermal papers and is among the highest volume of chemicals produced world-wide. There is a large literature on the toxicity of bisphenol A including at low doses and and solid evidence that a large majority of the human population is exposed to BPA.

Regulatory measures have been taken at the EU level while additional measures have been taken in certain countries. In the EU, bisphenol A is regulated under REACH (1907/2006/EC). EU law regulates BPA in plastic food containers, and the only EU restriction is for BPA in baby bottles (see section 2.1). The EU is considering additional regulation on metal food cans and screw caps. Additional measures have been taken in several countries. For example, France banned BPA in all food contact materials, other countries banned it in those materials intended for children under 3. There are also controversies between different agencies concerning the most protective TDI. Furthermore, BPA is also present in thermal papers and exposure of cashiers has been assessed and led to a proposal for restriction and substitution. Different committees of ECHA have analysed the benefits and costs of restrictions and sent their conclusion to the European Commission. BPA regulation is actively debated across the world. BPS and BPF are the major BPA substituents with distinct industrial applications. Much less is known about their putative toxicity and their presence in human matrices, although initial studies have indicated that they may display toxic effects that are similar to BPA (Rochester, EHP, 2015, 643; Thayer et al, EHP, 2016). Other bisphenol compounds are also manufactured and little is known about their toxicity and diffusion at this stage.

2.2 Objectives and questions

The two most critical questions concerning bisphenols are whether different regulations in different MS lead to different HBM values and whether current or putative substituents are safer than BPA.

Specific objectives are:

1. To follow the time trends and spatial trends for Bisphenols: what is the current body burden of exposure in the EU of BPA, BPS and BPF and possibly other bisphenols? What are reference values for EU population?

2. To determine whether different regulations in different EU MS lead to different exposures

3. To identify the most relevant analytical methods allowing to monitor BPA, BPS, BPF and possibly other bisphenols

4. To determine whether current or expected levels of BPS and BPF are of concern for health and to identify the relationship to the environment and workplace: What is the toxicity of substitutes compared to BPA? Is there a gender difference in relation to health risks? What are the most exposed subgroups? What is the evidence for low-dose effects?

5. To determine the effect of substance mixtures within the bisphenol family and with other families and whether this should impact health guidance.

6. To derive EU-wide health based guidance values.

7. To determine age and gender specific health effects of BPA

2.3 Substance classification

Substances have been classified based on data already available, Substances are classified into 3 categories based on decreasing level of knowledge:

CATEGORY A: BPA

CATEGORY B: BPS, BPF

CATEROGY C: BPB, BPAF, BPAP, BPBP, BPC, BPCl2, BPE, BPPH, BPM, BPP, BIS2, DHDPE, BPFL, BPZ, BP4,4’

2.4 Major activities

One of the major issues concerning the bisphenol family is whether the differences in regulation in different countries lead to differences in internal dose for BPA and its substituents. There are already data on exposure to BPA, but very few on BPS and BPF. Concerning BPA, a critical question is whether BPA levels tend to decrease more rapidly in countries where regulation is more stringent. Thus, time and space trends will be evaluated using available data from recent or ongoing studies. In cases where biosamples are available, additional assays may be required. Concerning BPS and BPF and possibly additional bisphenols, it would be relevant to assess whether they are detected and to which level. Depending on the observations made and on the knowledge gaps additional targeted studies could be designed and carried out at a later stage. Furthermore, it would be very relevant from both exposure and toxicity perspectives to determine whether BPA is in a free or conjugated (glucuronide and sulphate) form and in which matrix it is exactly detected (blood, urine, meconium, hair).

The other critical issue to be addressed is whether substituents are safer than BPA. After mining the literature for studies in which bisphenol exposure is correlated to health effects, gaps will be identified and additional assays may be required; Particular focus will be given to birth cohorts and to occupational studies. Research work will be focused on cat B and C substances since much less is known about their toxicological endpoints or the routes of exposure. Low dose effects should be explored and possible mixture effects on both kinetics and toxicity with special focus on gender difference.

The gathered data should ultimately lead to the assessment of toxicological reference values for BPA, BPS and BPF.

2.5 Work plan Bisphenols

(this workplan includes only the tasks that are specifically related to the bisphenols in line with the objectives and questions to be addressed, not the tasks that are shared by all or most substances. This workplan will feed in the general workplan of the initiative and obviously the more general tasks will also be useful for bisphenols)

task	Activity and deliverables	objectives	time
Task 5.1: Development and consolidation of EU-HBM guidance values	- Collect exposure and tox data for health guidance - Derive reference values based on meta-analysis for BPA - Derive reference values for BPS and BPF ***Deliverables:*** *-Report on exposure and toxicity data relevant for health guidance BPA* *- consolidated reference values for BPA* *- Report on exposure and toxicity data relevant for health guidance BPS, BPF* *- reference values for BPS and BPF* *- Report on exposure and toxicity data relevant for health guidance Cat C if relevant)* *- update on reference values of BPs*	4,5,6	M1-60 M6 M9 M24 M36 M48 M60
Task 7.1: Identification of existing data and data gaps	-Develop criteria for the studies to be included in meta-analysis for BPA -Collect HBM data in EU, spatial and temporal categorization, study population and Identify data gaps to get an overall picture of EU exposure to bisphenols -Identify which samples/matrices are available for analysis of B&C substances ***Deliverables:***	1, 2	M1-12

	- *SOPs for the selected surveys* - *Guidelines for substance specific study design (Cat. B&C substances)* - *Guidelines for biobank sample usage for Cat. B&C* - *Guidelines for selection of participants (Cat. B&C substances)* - *Inventory of data gaps with respect to geographic regions, exposure groups, sensitive populations*		M3 M6 M6 M6 M6 M12
Task 7.2: Strategies for recruitment and sampling	-Develop a study design for future targeted studies: aim of studies, population, substances, outcome. Select MS with different regulations to appreciate the effect of regulations ***Deliverables:*** *Study design*	3	M1-12 M12
Task 8.1: Support for targeted field work of EU added value	-implement decisions and designs developed in task 7.2 *(details to follow)* ***Deliverables:*** *To be continued… as well as additional tasks of WP 8*	3	M?? M??
Task 9.1: Biomarkers, matrices and research needs for analytical methods	-Identify research needs for analytical methods for BPA (in blood), BPS, BPF and category C bisphenols in different matrices such as blood, urine, hair meconium and in both free and conjugated forms ***Deliverables:*** - *Inventory of research needs to develop analytical methods in different matrices*	3	M1-6 M6
Task 9.2: Network of Reference HBM laboratories	Establishment of a Network of Reference HBM Laboratories to perform Quality Control Programs at EU level and to carry out assays and development of the various bisphenols in various forms and in different matrices ***Deliverables*** -. *List of reference labs able to perform quality control program for Cat B and C*	3	M1-12 M12

Task 9.3: Developing of new methods	Develop methods for a robust quantitative assay of BPS, BPF and category C bisphenols as well as metabolites in different matrices (depends on task 9.1 conclusions) ***Deliverables*** *- Report and publications on assay methods for BPS, BPF and category C substances*	1	M1-24 M24
Task 9.5: Analytical phase	-Metaanalysis for BPA -Analyze available recent biobank samples for BPS, BPF and compare to BPA. Samples could originate from recent EU or national studies. - Analyze samples from new survey to assess levels of BPs depending on the country regulation. ***Deliverables*** *- Distribution of BPA internal dose across EU from initial metaanalysis* *- Distribution of BPS, BPF in available biosamples: initial studies* *- Distribution of BP cat C substances (when relevant) across the EU* *- Distribution of BPs in MS with different regulations (new assays and/or new studies*	1	M1-48 M6 M12 M24 M48
Task 10.2: Statistical analyses including the development of an analysis plan	Statistical analysis of BP data ***Deliverables*** *-Statistical analysis of available and generated data for BPA, BPS, BPF* *- Statistical analysis of available and generated data for category C BPs*	3	M1-48 M12 M48
Task 10.4: Generate the EU population reference values	Generate EU reference values for Bisphenols ***Deliverables*** *-EU reference values for BPA* *- EU reference values for BPS and BPF*	1	M1-12 M9 M12
Task 11.4: Demonstration studies	Include BPA in the demonstration studies establishing the feasibility of linking HBM and health surveys	1, 4	M1-36

Task 12.1: Adaptation and use of integrated exposure models and spatial modelling **Task 12.2: Inverse toxicokinetic modeling**	-Mine the literature for information on exposure models of BPA -Refine models for BPS and BPF using data to be collected during the initiative -Mixture effects on toxicokinetics ***Deliverables*** - *Determine exposure levels from HBM and compare to available TDI for BPA* - *Model routes of exposure* - *Exposure models for BPS and BPF* - *Refined models following new EU data*	4, 5	M1-48 M12 M12 M36 M48
Task 12.3: Refinement of toxicokinetic modeling,	Determine the tissue-level doses for Cat A and B substances using PBTK modeling ***Deliverables*** - *Report on PBTK models for BPA* - *Model applicationt for BPS, BPF* - *Model application for cat C if relevant*	4, 5	M1-60 M12 M36 M60
Task 13.1: Knowledge base on causal pathways from chemical exposure to health outcomes (Adverse outcome pathways)	-build a knowledge base for adverse outcome pathways of bisphenols (Cat A, B and C) -complete with studies on low dose effects of Cat B and C and compare to BPA. ***Deliverables*** - *Construction and development of the knowledge base for bisphenols* - *Low dose effects of BPS and BPF (additional studies)* - *Low dose effects of selected Cat C substances (additional studies)*	4	M1-60 M12 M36 M60
Task 13.2: Health effects in humans based on birth and adult cohorts	-Mine the literature for health effects and prioritizing where data is needed for Cat. A-C. - Mother child studies: correlation with neonatal parameters, child development, child obesity, reproductive development, neurological development, gender difference in health effects. Studies should be no earlier than 2012 and may require new assays for BPS and BPF.	1, 4	M1-60

	-Occupational studies: collect data from current studies in cashiers (Finland, France). Assess exposure to both BPA and BPS in other occupational settings (paint, plastic, etc.) ***Deliverables*** *- List of criteria for selecting studies* *- List of studies with available biosamples* *- Data collection from previous studies* *- Additional studies/assays*		M3 M6 M6 M12 M60
Task 14.1 and Task 14.2: Inventory of existing biomarkers of effect	Literature survey ***Deliverables*** *-Report on effect biomarkers of bisphenols*	4	M1-12 M12
Task 14.3: Development and validation of new biomarkers of effect	- Effect biomarkers derived from human clinical studies: targeted biomarkers, untargeted biomarkers (omics studies + metabolic network modeling). -effect biomarkers identified from relevant experimental studies and confirmation in human studies including occupational health biomonitoring - several toxic endpoints are relevant for bisphenols, including cancer, reproductive system, metabolic diseases and neurological diseases ***Deliverables*** *- list of newly identified effect biomarkers derived from human and experimental studies for BPA* *-list of newly identified effect biomarkers derived from human and experimental studies for other bisphenols*	4	M1-60 M36 M60
Task 15.1: Identification of the most relevant chemical mixtures for health risk assessment	-Determine currently available data implicating bisphenols in mixtures from epidemiological and toxicological studies ***Deliverables*** *- Report on available mixture data implicating bisphenols and ongoing projects and identification of knowledge gaps* *- list of relevant mixtures identified in human studies*	4, 5	M12 M12 M12

Task 15.3: Identification of mixture health effects	-Assess whether within the bisphenol family, independent, additive or interactive models should be used and whether this is dependent on the target effect and pathway of toxicity -Study the effects of mixtures including bisphenols determined by statistical analysis of epidemiological data (see mixture program) ***Deliverables*** *- Report on mixture effect models within the bisphenol family* *- Report on the toxicological effects of the relevant mixtures*	4, 5	M1-60 M36 M60

2.6 Suggested work on bisphenols for the first annual work plan

During the first year two main types of activities will be carried out:

- First, there is a clear need to collect and interpret the available data on both exposure to the various bisphenols and on their toxic effects. This will help establish the research needs for the following years of the initiative
- Second, it is important to start working on policy relevant issues that should be focused and well defined and based on the information that we already have. We will focus on the safety and actual exposure of the EU population to 2 substituents of BPA: BPS and BPF. The work will develop along two subtracks:
    - Determination of exposure to BPS, BPF and BPA: it would be very useful to rapidly assess the current exposure to these chemicals and to provide policy makers with an initial evaluation. Larger and more representative studies could be conducted in the future. The initiative will fund the assays of these chemicals in recent or ongoing studies (EU or national studies) if samples are available. Different types of studies could be considered: well characterized samples such as Cophes/Democophes, studies including several samples per individual to account for intra-individual variability, studies with available or planned health outcomes. This project is relevant to tasks 9.5 and 13.2.
    - Targeted assessment of toxic effects of BPS/BPF as compared to BPA. Only available in vitro/in vivo experimental settings in which BPA AOP have already been explored will be used to assess the effects of BPS and BPF. Targets priority will be given to cancer, reproductive, hormonal, metabolic, immune and neurological effects.
      This project is relevant to task 13.1 primarily

Such studies could be either selected through an internal call that could be planned in the first months of the initiative or through other transparent procedures if a limited number of interested partners are involved.

task	Activity and deliverables	time
Task 5.1: Development and consolidation of EU-HBM guidance values	- Collect exposure and tox data for health guidance - Derive reference values based on meta-analysis for BPA ***Deliverables:*** *-Report on exposure and toxicity data relevant for health guidance BPA*	M1-12 M6

	- *consolidated reference values for BPA*	M9
Task 7.1: Identification of existing data and data gaps	-Develop criteria for the studies to be included in meta-analysis for BPA -Collect HBM data in EU, spatial and temporal categorization, study population and Identify data gaps to get an overall picture of EU exposure to bisphenols -Identify which samples/matrices are available for analysis of B&C substances ***Deliverables:*** - *SOPs for the selected surveys* - *Guidelines for substance specific study design (Cat. B&C substances)* - *Guidelines for biobank sample usage for Cat. B&C* - *Guidelines for selection of participants (Cat. B&C substances)* - *Inventory of data gaps with respect to geographic regions, exposure groups, sensitive populations*	M1-12 M3 M6 M6 M6 M6 M12
Task 7.2: Strategies for recruitment and sampling	-Develop a study design for future targeted studies: aim of studies, population, substances, outcome. Select MS with different regulations to appreciate the effect of regulations ***Deliverables:*** *Study design*	M1-12 M12
Task 8.1: Support for targeted field work of EU added value	-implement decisions and designs developed in task 7.2 *(details to follow)* ***Deliverables:*** *To be continued… as well as additional tasks of WP 8*	M?? M??
Task 9.1: Biomarkers, matrices and	-Identify research needs for analytical methods for BPA (in blood), BPS, BPF and category C bisphenols in different matrices such as blood, urine, hair meconium and in both free and conjugated forms	M1-6

research needs for analytical methods	***Deliverables:*** *- Inventory of research needs to develop analytical methods in different matrices*	M6
Task 9.2: Network of Reference HBM laboratories	Establishment of a Network of Reference HBM Laboratories to perform Quality Control Programs at EU level and to carry out assays and development of the various bisphenols in various forms and in different matrices ***Deliverables*** *-. List of reference labs able to perform quality control program for Cat B and C*	M1-12 M12
Task 9.3: Developing of new methods	Develop methods for a robust quantitative assay of BPS, BPF and category C bisphenols as well as metabolites in different matrices (depends on task 9.1 conclusions) ***Deliverables*** *- First Report and publications on assay methods for BPS, BPF and category C substances*	M1-12 M12
Task 9.5: Analytical phase	-Metaanalysis for BPA -Analyze available recent biobank samples for BPS, BPF and compare to BPA. Samples could originate from recent EU or national studies. ***Deliverables*** *- Distribution of BPA internal dose across EU from initial metaanalysis* *- Distribution of BPS, BPF in available biosamples: initial studies*	M1-12 M6 M12
Task 10.2: Statistical analyses including the development of an analysis plan	Statistical analysis of BP data ***Deliverables*** *-Statistical analysis of available and generated data for BPA, BPS, BPF*	M1-48 M12
Task 10.4: Generate the EU population reference values	Generate EU reference values for Bisphenols ***Deliverables*** *-EU reference values for BPA* *- EU reference values for BPS and BPF*	M1-12 M9 M12

Task 12.1: Adaptation and use of integrated exposure models and spatial modelling **Task 12.2: Inverse toxicokinetic modeling**	-Mine the literature for information on exposure models of BPA -Refine models for BPS and BPF using data to be collected during the initiative -Mixture effects on toxicokinetics ***Deliverables*** - *Determine exposure levels from HBM and compare to available TDI for BPA* - *Model routes of exposure for BPA*	M1-12 M12 M12
Task 12.3: Refinement of toxicokinetic modeling,	Determine the tissue-level doses for Cat A and B substances using PBTK modeling ***Deliverables*** - *Report on PBTK models for BPA*	M1-12 M12
Task 13.1: Knowledge base on causal pathways from chemical exposure to health outcomes (Adverse outcome pathways)	-build a knowledge base for adverse outcome pathways of bisphenols (Cat A, B and C) -complete with studies on low dose effects of Cat B and C and compare to BPA. ***Deliverables*** - *Construction and development of the knowledge base for bisphenols* - *Low dose effects of BPS and BPF (additional studies)*	M1-12 M12 M12
Task 13.2: Health effects in humans based on birth and adult cohorts	-Mine the literature for health effects and prioritizing where data is needed for Cat. A-C. - Mother child studies: correlation with neonatal parameters, child development, child obesity, reproductive development, neurological development, gender difference in health effects. Studies should be no earlier than 2012 and may require new assays for BPS and BPF -Occupational studies: collect data from current studies in cashiers (Finland, France). Assess exposure to both BPA and BPS in other occupational settings (paint, plastic, etc.) ***Deliverables*** - *List of criteria for selecting studies* - *List of studies with available biosamples*	M1-12 M3

	- *Data collection from previous studies* - *Additional studies/assays*	M6 M6 M12
Task 14.1 and Task 14.2: Inventory of existing biomarkers of effect	Literature survey ***Deliverables*** -*Report on effect biomarkers of bisphenols*	M1-12 M12
Task 14.3: Development and validation of new biomarkers of effect	- Effect biomarkers derived from human clinical studies: targeted biomarkers, untargeted biomarkers (omics studies + metabolic network modeling). -effect biomarkers identified from relevant experimental studies and confirmation in human studies including occupational health biomonitoring - several toxic endpoints are relevant for bisphenols, including cancer, reproductive system, metabolic diseases and neurological diseases ***Deliverables*** - *First list of effect biomarkers derived from human and experimental studies for BPA*	M1-12 M12
Task 15.1: Identification of the most relevant chemical mixtures for health risk assessment	-Determine currently available data implicating bisphenols in mixtures from epidemiological and toxicological studies ***Deliverables*** - *Report on available mixture data implicating bisphenols and ongoing projects and identification of knowledge gaps* - *list of relevant mixtures identified in human studies*	M12 M12 M12

3 Per-/Polyfluorinated compounds

The overall aim of the PFASs related activities in EHBMI is to identify knowledge gaps in the context of human exposure and health risks of these compounds, and to answer the policy questions related to these substances in order to identify appropriate regulatory measures to sufficiently protect human health.

3.1 Introduction

Per- and polyfluoroalkyl substances (PFASs) have been in use since the 1950ies as ingredients of intermediates of surfactants and surface protectors for assorted industrial and consumer applications. Within the past decade, several long chain perfluoroalkyl acids have been recognized as persistent, bioaccumulative and toxic. Many have been detected globally in the environment, biota, food items, and in humans (OECD, 2015). Current regulatory actions within the European Union and elsewhere mainly concern PFOS and PFOA, while other widely used substances are still under evaluation[1]. PFOS and PFOA are classified as carcinogenic (Cat2, suspected human carcinogens), reprotoxic (Cat 1B, presumed human reproductive toxicants), Lact [may cause harm to breast-fed children], and toxic to specific target organs (STOT RE 1, specific target organ toxicity – repeated exposure), acute toxicity cat 3-4 for different exposure routes. Whether other non-regulated PFAS exert similar toxicity is currently less well established. PFASs have also been recognized as a new emerging policy issue for strategic International Chemicals Management Actions under SAICM[2]. PFASs are also relevant within EFSAs remit; as food contact materials on one hand and food contaminants on the other[3].

Human exposures to PFAS have been reported in numerous studies world wide. Most of these studies have focused on blood or breast milk concentrations of PFOS and PFOA, while others have also included PFBS, PFHxS, PFDS, PFBA, PFPeA, PFHxA, PFHpA, PFNA, PFDA, PFUdA, PFDoA, PFTrDA, PFTeDA and some FOSA, MeFOSA, N-EtFOSA, N-EtFOS, di PAP. Human exposures to 8:2 diPAP, 6:2 diPAP, 8:2 PAP, 6:2 PAP, PFDPA, PFOPA, PFHxPA have, on the other hand, been minimally addressed. Several knowledge gaps also exist regarding alternatives currently used by industry (Danish EPA, 2013, Wang et al. 2013). These gaps need to be addressed, particularly in light of findings suggesting potential adverse health consequences in humans at current exposure levels to some PFASs. These include increased risk of miscarriage, reduced fetal growth and increased weight and reduced fertility among offspring as a result of early life exposures (Halldorsson et al. 2012, Joensen et al. 2013, Timmermann et al. 2014, Jensen et al., 2015). Postnatal exposures have also been associated with thyroid hormone imbalances and reduced immune response to vaccination (Grandjean and Budtz-Jørgensen 2013)

.3.2 Substance classification

The PFASs can be classified in 3 different categories based on data availability: substances where A) sufficient data are already available, B) only insufficient data are available, and C) no data or very limited are available.

The aim is to ideally move all compounds found in categories B and C into category A. When a compound is classified as category A it is considered to have enough information than an informed decision on appropriate use and/or necessary regulation may be made. Preliminary year 1 work will be gathering, analysis and synthesis of existing data to evaluate the appropriateness of the preliminary classifications and/or move chemicals between categories based on available data, Data gathering in year 1 will also identify any compounds where production, use and toxicity data preclude the need for biomonitoring.

[1] [1] http://echa.europa.eu/information-on-chemicals
[2] [2] http://www.saicm.org/
[3] [3] http://www.efsa.europa.eu/de/efsajournal/pub/653

CATEGORY A: perfluoro-1-butanesulfonate (PFBS; CAS-No: 375-73-5), perfluoro-1-hexanesulfonate (PFHxS; CAS-No: 355-46-4), perfluoro-1-decanesulfonate (PFDS; CAS-No: 335-77-3), perfluoro-n-butanoic acid (PFBA; 375-22-4), perfluoro-n-pentanoic acid (PFPeA; CAS-No: 2706-90-3), perfluoro-n-hexanoic acid (PFHxA; CAS-No: 307-24-4), perfluoro-n-heptanoic acid (PFHpA; CAS-No: 375-85-9), perfluoro-heptanesulfonate (PFHpS; CAS: 60270-55-5), perfluoro-n-nonanoic acid (PFNA; CAS-No: 375-95-1); perfluoro-n-decanoic acid (PFDA; 335-76-2), perfluoro decanesulfonate (PFDS; CAS-No: 67906-42-7), perfluoro-n-undecanoic acid; (PFU(n)dA; CAS-No: 2058-94-8), perfluoro-n-dodecanoic acid (PFDoA; CAS-No: 307-55-1), perfluoro-n-tridecanoic acid (PFTrDA, CAS-No: 376-06-7), perfluoro-n-tetradecanoic acid (PFTeDA; CAS-No: 376-06-7)

CATEGORY B: perfluoro-1-octaperfluoro-1-octanesulphonamide (FOSA; CAS-No: 754-91-6), N-methylperfluoro-1 octanesulphonamide (N-MeFOSA; CAS-No: 31506-32-8), N-ethylperfluoro-1-octanesulphonamide (N-EtFOSA; CAS-No: 4151-50-2), N-ethyl-perfluorooctane sulphonamidoethanol (N-EtFOSE; CAS-No: 1691-99-2) , N-ethyl-perfluorooctane sulfonamidoacetate (EtFOSAA, CAS-No:) , polyfluoroalkyl phosphoric acid diesters (8:2 diPAP, CAS-No: 678-41-1)

CATEGORY C: polyfluoroalkyl phosphoric acid diesters (8:2 diPAP, CAS-No: 678-41-1), 6:2 polyfluoroalkyl phosphoric acid diesters (6:2 diPAP), 8:2 polyfluoroalkyl phosphoric acid monoesters (8:2 PAP), 6:2 polyfluoroalkyl phosphoric acid monoesters (6:2 PAP) , 2 polyfluoroalkyl phosphoric acid monoesters (PFDPA), Perfluorooctylphosphonic acid (PFOPA), Perfluorohexylphosphonic acid (PFHxPA), hexafluoropropylene oxide (HFPO), 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid (HFPO-DA, C6HF11O3, GenX), Perfluoroalkyl ether potassium sulfonate, F-53B Ammonium 4,8-dioxa-3H-perfluorononanoate (ADONA)

Further work from years 1 to 5 will involve identifying where laboratories may have developed methods for PFASs screening in human matrices. Should laboratory method development be needed identifying a lab with the capacity to develop these methods and ensure the method is transferred across the group to create a harmonized strategy will be a part of year 1-2.Assessment stages to introduce and share new methods, design efficient and targeted studies to measure additional HBM exposure data and draw conclusions will necessarily differ for the Cat A, B and C substances.

3.3 Objectives

The overall aim of the PFASs related activities within the EHBMI is to identify and address current knowledge gaps in the context of human exposure and potential health risks of these compounds; to answer the policy questions and to identify appropriate regulatory measures needed to sufficiently protect human health. Main goals include establishing baseline levels of exposure and follow time trends in support of existing regulations, as well as developing new biomarkers of exposure where needed; and finally to assess potential health effects including exposures to PFASs mixtures. As there is a trend amongst global manufacturers to replace long-chain PFASs with chemicals containing shorter perfluoroalkyl chains these short-chain compounds and other substitutes are of particular interest within the EHBMI initiative. To fill some of the data gaps on properties of alternatives will be an important task. Based on production volume, bioaccumulation potential and the evidence derived from new toxicity studies substances shall be prioritised. In order to support regulation baselines of exposure and follow time trends shall be established.

Specific objectives are:

1. To perform inter-laboratory comparison tests in order to assess if already existing data are comparable throughout Europe; and to establish training courses and organization of inter-laboratory comparisons tests and proficiency testing schemes for sustainability of the initiative (WP9).
2. To assess for which Cat B and C substances methods should be developed.

3. To identify the current (year 2012 or more recent) exposure of the EU population to Cat. A substances based on existing data (WP7) and establish reference values (WP10)
4. To investigate time trends of the differently regulated, recently regulated and not regulated Cat A substances (WP7, WP10)
5. To identify differences in the exposure levels of unregulated and regulated Cat. A substances (and Cat B substances if data are available) between countries and to identify the main reasons for differences in exposure (WP 7, 8, 9)
6. To identify high exposure groups, - where sources of exposure may relate to life-style or living in contaminated areas (WP 5); or occupation (WP 4, 7, 13). Human exposures to PFAS have been reported in numerous studies world wide. Furthermore, to examine if these high exposure groups are more at risk of adverse health taking into consideration exposures form early life to adult age (WP 5).
7. To identify if the overall exposure levels in the general population, children, and pregnant women exceed any health-relevant levels (HBM guidance values - if existing; TDI, DNELs)
8. To assess if current TDIs, DNELs and HBM values include also effects on hormone and immune system (WP 5).
9. To identify the knowledge gaps and related research needs for all substance categories taking production volumes and bioaccumulation potential into consideration (especially for Cat B and C substances) (WP 7, 13). This includes developing new biomarkers of exposures, for example by examining urine versus serum concentrations for the short chain carboxylates and other more rapidly excreted compounds (WP 7, 8, 9, 10)
10. To identify risks for adverse outcome pathways for selected PFASs.
11. To address questions related to mixture effects (due to similar Mode of Action and potential over-additive effects of combined exposures e.g. peroxisome proliferation, mitochondrial toxicity, cytotoxicity, and transcriptome profiles of key metabolic pathways of the liver) (WP 13, 14, 15)

3.4 Policy-related research questions

- What current information is available regarding human exposure to PFASs, both past and present? How well does the information cover the European population, spatially and temporally?
- What are current human levels of legacy PFASs (e.g., PFOS and PFOA)? 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?
- How do the levels of legacy PFASs compare to levels of PFASs using as substitutes? Is any temporal or spatial trend observed? Can we relate this to use patterns and/or production volume?
- What are the population groups most at risk?
- What compounds 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 studies?
- Which biomarkers of effects can be used in order to identify the risk of additive or synergistic effects of PFASs mixtures?

3.5 Description of work

In the beginning the policy related research questions shall be updated with the input of current national, international and European PFASs activities as well as consultation of experts in this field (including EFSA, ECHA and Commission) (WP4). Within the first year a detailed and thorough assessment of the available studies shall be performed in order to address the objectives listed above (WP 4, 5, 7). Further, an inventory of ongoing studies shall be established in order to see which gaps will already be filled within the next years

(WP7). Reference and HBM-values for Cat A substances will be derived (WP 10) and already stipulated health-based limit values (external and internal exposure) will be evaluated.

Research on contamination issues will be started: based on the knowledge available within member states a map with known, suspected and probable affected regions shall be established and options for risk assessment and management shall be developed (WP 5)

An inter-laboratory comparison test will be performed in order to assess if already existing data are comparable throughout Europe (WP9).

Collection of new data during the first or second year will primarily focus on examining new biomarkers of exposure for the more rapidly excreted PFAS (that may have been used to replace regulated PFAS). A small scale pilot study comparing concentrations of PFASs in urine versus blood (and possibly also breast milk) shall be performed in e.g. 4 countries covering a broad geographical coverage (e.g. Spain, Denmark, Iceland, and Austria). This exercise is necessary in order to draw conclusions if more rapidly excreted PFASs should be assessed in urine rather than blood in future European monitoring studies (WP 7, 8, 9).

Prioritization of future research efforts for group B and C substances will be done according to production volume, bioaccumulation potential and new toxicity studies. Information from the OECD PFC Steering Group on production volumes will be used (WP4). "In case of data gaps "in-silico" methods, such as quantitiative structure activity relationship (QSAR) analyses, will support the identification of AOPs (WP 13).

3.6 Deliverables

Year 1:

- Compilation of existing HBM data and results of the assessment
- Inventory of existing and ongoing HBM studies
- Catalogue of data gaps for Cat A, Cat B and Cat C substances
- Map of known and suspected contaminated sites across Europe
- Results and evaluation of the round robin interlaboratory test on PFASs
- Development of a pilot study of short chain and less persistent PFASs in urine versus blood
- Preliminary results on in silico models and AOPs
- Preliminary results on health risks assessment
- Proposal of work plan for year 2

Years 2-5:

- Baseline levels of exposure and follow time trends in support of existing regulations
- Filling of data gaps identified in the first year/ in the following years
- Development of new biomarkers of exposure
- Results on MOA and AOPs
- Development of biomarkers of effects
- Health relevance of exposure levels/ health risk assessment
- Health effects of PFASs mixtures
- HBM values and reference values for Cat A and where possible Cat B substances
- Network of laboratories providing comparable results
- Integration of study results into IPCheM

3.7 References

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4 Flame Retardants

4.1 Introduction

Flame retardant (FR) is the term given to any compound or mixture added either bound or unbound to a consumer product or building materials to reduce the flammability. While a range of both inorganic and organic FRs are in use, of concern with respect to the European Union 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).

Human exposure to flame retardants can occur through a variety exposure pathways, mainly 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 (Harrad et al., 2010). The exposure pathways differ based on the compound properties and flame retardant use. In addition to use as FRs, a number of these compounds (particularly the phosphorus-based FRs) also act as plasticizers (van der Veen and de Boer, 2012), and thus may be added to synthetic materials for this purpose as well. Nevertheless, the potential for human exposure remains whether the intended purpose was as flame retardant or plasticizer.

Since the 1970s, the primary flame retardant compounds used were the polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD). However, due to concerns regarding the persistence, toxicity and bioaccumulative potential, some of these compounds have been added to the Stockholm Convention on Persistent Organic Pollutants (www.pops.int). Although these compounds are regulated under the Stockholm Convention and 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. 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 (European Food Safety Authority, 2012). In conjunction with a lack of exposure data, there also is a lack of toxicological information for many of these compounds, and what information is available for some compounds is based on the chemical properties and estimates rather than direct evidence. This makes it difficult for regulatory bodies and legislative agencies to make informed decisions.

PBDEs and HBCDs have been identified to have a range of adverse health effects, including potential neurotoxic, endocrine, and carcinogenic effects (*inter alia* Chevrier et al., 2010; Covaci et al., 2006; Herbstman et al., 2010). Early evidence suggests that a number of the replacement FRs may have similar health concerns (Dishaw et al., 2011; Patisaul et al., 2013; Springer et al., 2012), and moreover, insufficient evidence exists to evaluate toxicity for many of these new FRs. Thus, the EHBMI provides a platform to initially provide human exposure data, epidemiology and toxicity data and 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.

Many flame retardants exist primarily 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 in addition to as individual compounds (Darnerud et al., 2001), and there is evidence of Firemaster 550 as an endocrine disrupting compound and obesogen (Patisaul et al., 2013). 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. The issue of mixture toxicity remains a large data gap within the toxicological knowledge on FRs.

4.2 Substance Classification

The flame retardants can be classified in 3 different categories based on data availability: substances where A) sufficient data are already available, B) only insufficient data are available, and C) no data or very limited are available.

The aim is to ideally move all compounds found in categories B and C into category A. When a compound is classified as category A it is considered to have enough information than an informed decision on appropriate use and/or necessary regulation may be made. Preliminary year 1 work will be gathering, analysis and synthesis of existing data to evaluate the appropriateness of the preliminary classifications and/or move chemicals between categories based on available data, Data gathering in year 1 will also identify any compounds where production, use and toxicity data preclude the need for biomonitoring.

CATEGORY A: Tetrabromodiphenyl ether (tetraBDE; CAS-No: 5436-43-1); Pentabromodiphenyl ether (pentaBDE; CAS-No: 60348-60-9); Hexabromodiphenyl ether (hexaBDE; CAS-No: 36355-01-8); Heptabromodiphenyl ether (heptaBDE; CAS-No: 189084-67-1); Hexabromocyclododecane (HBCD; CAS-No: 3194-55-6, 25637-99-4); Perchloropentacyclodecane (mirex; CAS-No: 2385-85-5); 2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether (BDE-209; CAS-No: 1163-19-5)

n.b. the term BDE refers to congeners grouped in this table by the number of Br atoms. Not all 209 BDEs were produced industrially as an FR but those listed are the most common homologue groups that were produced and are detected in the environment..

CATEGORY B: Bis(2-ethylhexyl)tetrabromophthalate (BEH-TEBP; CAS-No: 26040-51-7); 2-ethylhexyl-2,3,4,5- tetrabromobenzoate (EH-TBB; CAS-No: 183658-27-7); 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE; CAS-No: 37853-59-1); Decabromodiphenylethane (DBDPE; CAS-No: 84852-53-9); Tetrabromoethylcyclohexane (DBE-DBCH; CAS-No: 3322-93-8); Hexachlorocyclopentenyldibromocyclooctane (DBHCTD; CAS-No: 51936-55-1); Hexabromobenzene (HBB; CAS-No: 87-83-2); Octabromotrimethyphenyl indane (OBTMPI; CAS-No: 1084889-51-9, 1025956-65-3, 893843-07-7, 155613-93-7); Pentabromobenzyl acrylate (PBBA; CAS-No: 59947-55-1); Pentabromotoluene (PBT; CAS-No: 87-83-2); 1,2,5,6-tetrabromocyclooctane (TBCO; CAS-No: 3194-57-8); 2,3,5,6-tetrabromo-*p*-xylene (TBX; CAS-No: 23488-38-2); Pentabromoethylbenzene (PBEB CAS-No: 85-22-3); Dechlorane Plus (DDC-CO; CAS-No: 135821-03-9); Tetrabromobisphenol A (TBBPA; CAS-No: 79-94-7); Tris(2,3-dibromopropyl) phosphate (TDBPP; CAS-No: 126-72-7); Triphenyl phosphate (TPHP; CAS-No: 115-86-6); Tricresyl phosphate (TMPP; CAS-No: 1330-78-5);

	Tri(2-butoxyethyl) phosphate (TBOEP; CAS-No: 78-51-3); Tris-2-chloroethyl phosphate (TCEP; CAS-No: 115-96-8); Tris(1-chloro-2-propyl) phosphate (TCIPP; CAS-No: 13674-84-5); Tris(1,3-dichloropropyl)phosphate (TDCIPP; CAS-No: 13674-87-8); Triethyl phosphate (TEP; CAS-No: 78-40-0); Tri-n-butyl phosphate (TNBP; CAS-No: 126-73-8); Tri-iso-butyl phosphate (TIBP; CAS-No: 126-71-6); Tris(2-ethylhexyl) phosphate (TEHP; CAS-No: 78-42-2); 2-ethylhexyl diphenyl phosphate (EHDPP; CAS-No: 1241-94-7); Tri-n-propyl-phosphate (TnPP; CAS-No: 513-08-6); Cresyl diphenyl phosphate (DCP; CAS-No: 26444-49-5)
CATEGORY C:	2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate (HEEHP-TEBP; CAS-No: 20566-35-2); Pentabromophenoxy-nonabromodiphenyl ether (4'-PeBPO-BDE208; CAS-No: 58965-66-5); Tribromoneopentyl alcohol (TBNPA; CAS-No: 1522-92-5); Hexabromocyclodecane (HBCYD; CAS-No: 25495-98-1); Dibromoneopentylglycol (DBNPG; CAS-No: 3296-90-0); Dibromostyrene (DBS; CAS-No: 31780-26-4); Tris(2,3-dibromopropyl)isocyanurate (TDBP-TAZTO; CAS-No: 52434-90-9); 1,3-bis(2,3-dibromopropyl)-5-(2-propen-1-yl)-1,3,5-triazine-2,4,5(1H,3H,5H)-trione (BDBP-TAZTO; CAS-No: 75795-16-3); 1-(2,3-dibromopropyl)-3,5-diallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (DBP-TAZTO CAS-No: 57829-89-7); 2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine (TTBP-TAZ CAS-No: 25713-60-4); N,N'-ethylenebis(tetrabromophthalimide) (EBTEBPI; CAS-No: 32588-76-4); Bisphenol A bis(diphenylphosphate) (BPA-BDPP; CAS-No: 5945-33-5); Resorcinol bis(diphenylphosphate) (RBDPP; CAS-No: 125997-21-9); 2,4,6-tribromophenol (2,4,6-TBP; CAS-No: 118-79-6) Pentabromophenol (PBP; CAS-No: 608-71-9); 2,4-dibromophenol (DBP; CAS-No: 615-58-7); 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) (Dec 602; CAS-No: 31107-44-5); 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) (Dec 603; CAS-No: 13560-92-4); Dechlorane 604 (1,2,3,4,7,7-hexachloro-5-(2,3,4,5-tetrabromophenyl)-bicyclo[2.2.1]hept-2-ene) (HCTBPH/Dec 604; 34571-16-9); Tris(tribromoneopentyl)phosphate (TTBNPP; CAS-No: 19186-97-1); Isopropyl triphenyl phosphate (ip-TPP; CAS-No: 68937-41-7) 2,2-bis(chloromethyl)trimethylenebis[bis(2-chloroethyl) phosphate] (V6; CAS-No: 38051-10-4); Melamine polyphosphate (CAS-No: 20208-95-1); Diethylphosphinic acid (CAS-No: 813-76-3)

Further work from years 1 to 5 will involve identifying where laboratories may have developed methods for FR screening in human matrices. Should laboratory method development be needed identifying a lab with the capacity to develop these methods and ensure the method is transferred across the group to create a harmonized strategy will be a part of year 1-2.

Assessment stages to introduce and share new methods, design efficient and targeted studies to measure additional HBM exposure data and draw conclusions will necessarily differ for the Cat A, B and C substances.

4.3 Objectives

Given the existing regulations on flame retardants both at the international (e.g., Stockholm Convention) and European level (e.g., REACH), the EHBMI can contribute information on the effect of regulation on concentrations in the European human population, particularly with respect to establishing baseline exposure concentrations for current-use flame retardants. Evaluating temporal trends for banned/restricted/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 or HBM values, or knowledge of the mass of a specific compound in use thus the inclusion of this compound class in the EHBMI will serve to address these knowledge gaps.

4.4 Policy-related Questions

The following are the major questions that should be addressed for FRs:

- What current information is available regarding human exposure to FRs, both past and present? How well does the information cover the European population, spatially and temporally?
- 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?
- What are current human levels of legacy FRs (e.g., PBDE and HBCD)? 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?
- 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?
- What are the population groups most at risk?
- What compounds 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 study?

4.5 Description of work

Primarily, the initial focus will be on analysis and synthesize of existing data regarding biomonitoring and exposure for all target FRs (Annex 1 list) and identification of additional compounds based on production and use. Information of FRs may include individually presented results on a regional/national level, and currently there lacks any holistic overview of the status of the European population, both in terms of regional variation and population sub-groups that may be at greater risk, (e.g.. occupational exposure). The overview and assessment of currently available biomonitoring data will allow a more complete understanding of current status and streamline work to avoid targeting compounds where there is sufficient information already or where the use is restricted. Moreover, this will allow clear elucidation of data gaps with respect to region and/or compound, which can be addressed with more targeted approach. Statistical evaluation of average concentrations, time trends and potential variance between population subgroups both regional and at risk (meta-analysis) will be initiated. In conjunction with the evaluation of exposure data, toxicity data will also be evaluated, in terms of the compounds, which have currently available information of relevance to typical human exposure levels.

Known in-use and legacy FRs have been given a provisional classification according to current information on data availability. Those placed in Category A (section 4.2) have sufficient human biomonitoring data; this does not mean that Cat. A compounds require regulatory action, rather that there is enough knowledge on their use, exposure and toxicity for informed decision-making. Those placed in Cat. B have some information but not enough for adequate understanding and decision-making, and those in Cat. C lack any significant information. Thus, the end goal of the FR work should be to move all compounds to Cat. A by producing sufficient information for decision-making, or, to exclude compounds which are in such limited use that they do not warrant inclusion and investigation. An additional and on-going task throughout the project will be re-evaluation of the current classification according to the complete synthesis of existing European data and fully develop what is considered ‘sufficient’ for informed decision making.

From year 1 onwards a strategy for additional HBM will be implemented, if needed based on information gaps identified in year 1 for both exposure data and toxicity. In particular, toxicity will be investigated with respect to the mixtures of FRs to which Europeans are typically exposed. This will build on existing toxicity information which as yet is largely focussed on individual substances and does not consider any synergistic or mixture effects. Exposure assessment will, where possible, use existing HBM projects or biobank archives rather than generate new samples. However, should a region of the EU lack sufficient information with no existing HBM, a targeted approach will be used. This targeting may be aimed at people considered at risk due to age, gender or exposure. The aim by year 5 will be to have the majority of FRs in use moved to category A.

4.6 Deliverables

Year 1:

- Overview of available biomonitoring and exposure data on FRs relevant to the European population
- Report on data gaps according to substance, region and/or population
- Map of the spatial and temporal variation in FR exposure across the EU based on use and available data to identify variability in exposure and risk.
- Inventory of research needs for development of analytical methods in different matrices
- Inventory of toxicity data for individual FRs and FR mixtures
- Consolidated EU-wide reference values of known (Cat. A) substances
- Harmonized SOPs for substances with known/validated analytical methods
- Study design for the determination and quantification of FRs in human matrices across Europe that can create comparable data

Years 2-5:

- SOPs for determination of compounds with identified data gaps (e.g., insufficient biomonitoring data – Cat. B and C substances)
- Exposure biomarker database for FRs
- Summary indicators to describe the exposure and body burdens of FR mixtures
- Toxicological evaluation of HBM data (comparison with assessment values and/or TDI values) and HBM guidance values for those compounds without guidance values
- Report on EU-wide understanding of FR human exposure, identifying compounds of highest concern and any highly exposed population subgroups
- Risk profile on emerging FRs for the European population (incorporating use, toxicity and exposure data)
- Database of FR information that will allow informed decision making on emerging FRs, to be linked with existing database infrastructure (e.g., IPCheM).

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5 Cadmium and chromium(VI)

5.1. Introduction

5.1.1 Cadmium

Cadmium (Cd) is a toxic metal found as an environmental contaminant, both through natural occurrence and from industrial and agricultural sources. Foodstuffs are the main source of cadmium exposure for the non-smoking general population. Anthropogenic sources have increased the background levels of cadmium in soil, water and living organisms. Cadmium is released into the environment by wastewater and waste incineration, and the contamination of agricultural soils can occur by the use of fertilizers, by air deposition and by cadmium-containing sewage sludge. Exposure in general population is primarily through diet, drinking water, and tobacco smoke. The mean exposure of adults in Europe through food is close to or slightly exceeding the TWI of 2.5 µg/kg b.w. Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI by about 2-fold.

Cadmium is primarily nephrotoxic and carcinogenic to humans (Group 1) lung, endometrium, bladder, and breast. Cd seems to increase the risk of common cardiovascular events, such as stroke and myocardial infarction in the US and European general populations (Tellez-Plaza et al, 2013). Cd also causes bone demineralisation. After 2009, effects on bone have been shown at low-level exposure in several studies. Many of these are discussed in the review by Akesson (2014).

The main rational for action/inaction lies in Regulation (EC) No. 1881/2006 of 19 December 2006 that sets maximum levels for certain contaminants in foodstuffs contains the most recent maximum levels for cadmium in foodstuffs. These levels continue to be reviewed by the Commission. An updated scientific basis is therefore of great importance.

A number of issues are are still to be addressed in HBM for Cd. For example, a selection of exposure biomarkers: blood vs. urinary Cd, where the reliability of U-Cd as a long-term (nonoccupational!) exposure biomarker is questioned as studies report no difference in U-Cd level between never smokers and past-smokers, while B-Cd level can be influenced by long-term exposure (past-smokers!). In HBM programmes a normalization of Cd in urine by chreatinine or specific gravity has been a subject of several studies. Confounding factors, such as markers of kidney dysfunction (tubular and glomerular) may influence U-Cd data. Changes in kidney reabsorption function may play a role as well. Cd in blood plasma is mostly bound to metallothionein (Cd-MT) and in this form, follows the same urinary excretion pathway as LMWP that are used as renal biomarkers. Co-excretion of Cd-MT* and renal proteins increased urine level of U-Cd and renal proteins and their positive correlation, irrespective of Cd exposure (Akerstrom et al, 2013; Akesson et al, 2014; Chnaumont et al, 2013; Chaumont et al, 2012). Cd co-exposure and effects in mixtures of chemicals has not been addressed sufficiently.

Levels in urine are widely accepted as a measure of the body burden and the cumulative amount in the kidneys, plasma. At the European level biomarker are collected in national HBM programmes such as GerES, FLEHS, ENNS, NHANES, CHMS, PROBE, CZ-HBM, Uppsala, KHNANES, National HBM Slovenia, and international projects such as PHIME and COPHES/DEMOCOPHES.

5.1.2. Chromium (VI)

Chromium (Cr) is an element that occurs in nature. The two environmentally relevant forms of chromium are

trivalent chromium (Cr(III)) and hexavalent chromium (Cr(VI)). Cr(III) is considered an essential nutrient. Cr(VI) is the toxic form. The primary focus of EHMBI is on Cr(VI). There is an extensive body of literature on Cr(VI) (ATSDR, 2012 and EFSA, 2014). The Office of Environmental Health Hazard Assessment (OEHHA) developed Reference Exposure Levels (OEHHA, 2001) and a Public Health Goal (OEHHA, 2011) for Cr(VI). OEHHA (2009a) also reviewed the developmental and reproductive toxicity of Cr(VI). In recent report EFSA also provided information on benchmark dose, margin of exposure (MOE), tolerable daily intake (TDI) for the European population (EFSA, 2014).

Inhalation is one of the major pathways of exposure. Sources to be considered include chrome-plating, fumes generated during welding of steel and dust from erosion of subway rails. Cr(VI) is found in tobacco smoke, and indoor air concentrations of Cr(VI) can be orders of magnitude higher, due to smoking, compared to outdoor air concentrations (ATSDR, 2012).

Cr(VI) can occur naturally in groundwater and as releases to water due to industrial sources (textile dyes, wood preservation, and anti-corrosion processes). Chromium can be present in food and drinking water arising from both natural and anthropogenic sources for which exposure estimates of concern for high consumers such as infants, other children and toddlers have been identified. Other sources of exposure need to be considered for general population including corrosion of orthopedic implants made from stainless steel and cobalt-chromium alloys releases chromium, with Cr(VI) as the predominant species. Dermal exposure through leather articles and oral exposure of children through toys have been reported.

Cr(VI) is carcinogenic to humans (Group 1) with respect to the cancer of the lung and also cancer of the nose and nasal sinuses. Cr(VI) compounds are mutagenic and known to cause male and female reproductive toxicity, and developmental toxicity. Cr(VI) is a respiratory toxicant and can adversely affect the hematopoietic system. It causes skin sensitization, such as in contact with contaminated leather.

Because Cr(VI) is largely reduced to Cr(III) in the body, speciation of chromium is not useful in HBM programmes. Elevated levels in blood or urine can be indicative of Cr(VI) exposures, but other factors may complicate interpretation such as for example individuals who take Cr(III) supplements can have elevated levels of urinary chromium. To interpret elevated chromium urinary and/or blood levels, additional information, such as from an exposure questionnaire, is of fundamental importance. Cr(VI), but not Cr(III), can be taken up by red blood cells (RBCs). Cr(VI) is reduced inside the RBC to Cr(III), which can remain there for the life of the cell. Measuring chromium in RBCs, and determining the ratio with levels in plasma/serum, may be a more specific indicator for Cr(VI) exposure. To separate plasma/serum from RBCs, fresh (preserved but never frozen) blood has to be available.

Policy driven action can Rational for action also driven by policy as follows:

- There are several CrVI compounds on the REACH Authorisation List (latest application for authorisation dates are in 2016 or 2017): http://echa.europa.eu/web/guest/addressing-chemicals-of-concern/authorisation/recommendation-for-inclusion-in-the-authorisation-list/authorisation-list
- Background documents explaining why they are on the Authorisation list : http://echa.europa.eu/addressing-chemicals-of-concern/authorisation/recommendation-for-inclusion-in-the-authorisation-list/previous-recommendations
- When a suitable substitute substance is not available and granting the authorisation is recommended to the Commission, the ECHA Risk Assessment Committee's opinion may recommend that the applicant uses biomonitoring as supporting evidence to demonstrate safe use and to include such information in any potential subsequent application toward the review. This is already the case in the opinion relative to certain lead-chromium pigments (although biomonitoring only proposed for lead). For those considerations the relation of the biomonitoring values to exposure levels on one hand and to risk of adverse health outcome on the other hand needs to be known.
- SCHER opinion on Cr(VI) in toys: http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_167.pdf

- Since 1 May 2015 a restriction on Cr(VI) in leather is in place and applicable at EU level, limit 3 ppm according to the opinion of RAC. That threshold is expected to be 80 % effective in reducing the occurrence of new chromium VI-related allergic dermatitis cases due to chromium VI in leather articles. However a review clause was included which mentions: 'The effectiveness of the restriction on the number of cases of chromium allergy can be determined by monitoring cases of chromium VI-related allergic dermatitis. Should the prevalence of the allergy not decrease, or should an analytical method to detect lower content of chromium VI become available and be recognised as reliable, this restriction should be reviewed.'
- Non-regulated in food: Maximum limit of 50 µg Cr/L for total chromium in water intended for human consumption and natural mineral waters are laid down in Council Directive 98/83/EC and in Commission Directive 2003/40/EC, respectively.
- Technical aspects: As compared to other biomarkers of exposure, RBC-Cr has two main advantages: (i) it is species specific since only Cr(VI) is able to cross RBC membranes; (ii) it is long-lived as compared to plasma Cr(III), once inside the RBCs Cr(VI)remains trapped and is very slowly released from RBCs: RBC-Cr could be used to assess absorption of Cr(VI) escaping reduction by gastric juice and plasma, and accumulating in RBC.

At the European level in biomarkers are rarely reported. Urinary markers are collected in some programmes such as GerES, ENNS, PROBE, Uppsala. Some information is also available from national studies (Austria, Belgium, Denmark, Finland, Greece, Lithuania, Italy, Poland, Slovenia, Spain and the United Kingdom).

5.2 Substance classification

Cadmium: CAS IDCAS ID #: 7440-47-3

Chromium: CAS IDCAS ID #: 7440-43-9

5.3. Objectives and questions

General questions for both, Cd and Cr(VI) are as follows:

1. Synthesize an overview of available biomonitoring and exposure data on Cd and Cr(VI) relevant to the European population.
2. Overview toxicological data on Cd and Cr(VI) available for European population
3. Identify data and analytical gaps
4. Identify the key groups at risk considering:
    - *life-style, nutritional status and genetic background*
    - *gender, age; postmenopausal women, elderly*
    - *regions with elevated levels in the environment*
    - *occupational settings*
    - *co-exposure to chemical mixtures*
5. Based on the information above, develop a plan for population-based cross-European and/or targeted HBM studies (demonstration studies) within 2-5 years EHBMI program.

In addition the following issues will need to be addressed for Cr(VI) in the first year:

1. Provide information on the value of Cr concentration in urine as regards risk of local effects (e.g. lung cancer) where not all exposures but only inhalation exposures seem relevant
2. Provide information how Cr compounds other than hexavalent Cr might bias the biomonitoring in occupational/environmental setting

3. Provide information on the quantitative relationship between urine Cr concentration and Cr exposure levels (Cr mg/m^3).
4. Provide information on the quantitative relationship between urine Cr concentration and cancer risk.
5. Provide information on any differences between the Cr(VI) compounds as regards relevance and reliability of the urine Cr concentration measurements as a biomonitoring tool.
6. Monitor effectiveness of Cr(VI) restriction in leather articles on allergic dermatitis – if no decline analytical tools to assess lower than 3 ppm values needed.
7. To improve risk assessment related to food safety. Unfortunately, no data are available on chromium concentration in RBCs from the general population. If available, such data would provide a straightforward way to demonstrate that indeed ingested water soluble Cr(VI) can escape reduction in the gastro-intestinal tract, giving rise to systemic exposure. It might be feasible to get something useful with a careful literature search and also using national measurement databases quite quickly.

5.4 Policy related questions

1. What is the current (last 5 years) exposure to Cd of the European population?
2. What is the level of exposure, environmentally and occupationally relevant to Cr(VI) in EU population?
3. Do the exposure to Cd and Cr(VI) levels differ significantly between countries and population groups? What are the main reasons for differences in exposure?
4. Is there a significant time trend of Cd and Cr(VI) levels in the population studies?
5. What are the groups at risk?
6. Are the overall exposure levels in different population groups above any health-relevant assessment levels (HBM guidance values, TDI)?
7. Has the regulation under REACH had the favorable impact, that is a reduction of GM/median concentrations?
8. What are knowledge gaps and related research needs to answer questions A1-A7 in the following years?

5.5 Description of work

In the first year collection, comparison and evaluation of available data and studies will be used to derive recommendations for policy and general public. Recent EFSA, 2014 reports for Cr(VI) will also be taken into account. In addition, existing HBM data across Europe will be evaluated and combined, taking agreed quality criteria into account. This will provide an overview of current exposure levels in population groups identified under general goals for the 1st year. The population groups will include different general population strata and exposures at work place, particularly for Cr(VI).

Data from time trends will be used from HBM programmes that provide data sets over extended period of time (Germany, Sweden, Czech Republic and others if data are available).

The data available from different countries will be statistically evaluated to derive average concentrations, time trends and potential differences between population subgroups (meta-analysis) and different countries/regions. If possible, this will result in European-wide reference values.

After evaluation of the recent toxicological data and on the basis of agreed methodology toxicologically derived HBM guidance values have to agreed upon on a European scale and existing values re-evaluated.

Along with data acquisition the first year will also serve to identify and prioritize knowledge and data gaps and related research needs as starting point for the development of research questions and goals for year 2 and following years (including identification of relevant effect and susceptibility markers).

Analytical methods used for trace element determination are mostly obtained by multi-elemental ICP MS methods for which numerous laboratories demonstrate sufficient analytical proficiency. Methodological development in terms of proper sampling, sample handling, and proper use and interpretation of biomarker data will be addressed. This is particularly important for Cr(VI) for which the protocols and methodologies will need to be reviewed and evaluated.

5.6 List of main deliverables

1st year

- Establishing of a Working group for Cd and Cr(VI) and mode of operation within management structure of the EHBMI
- An acquisition of available biomonitoring data (exposure, effects, susceptibility) on Cd and Cr(VI) relevant to European populations – report and contribution to a database
- A review of toxicological data on Cd and Cr(VI) available for European populations – report
- Identify the key groups at risk considering: life-style, nutritional status and genetic background; gender, age; postmenopausal women, elderly; regions with elevated levels in the environment; occupational settings, particularly for Cr(VI); co-exposure to chemical mixtures – report and series of publications
- Inventory of available SOPs (for all stages of HBM) – report
- Inventory of knowledge and analytical gaps (especially appropriate biomarkers!), needs, cost estimates, - report
- Toxicological evaluation of HBM data (comparison with HBM or reference values/doses) – report and publication
- Mapping spatial and temporal distribution across Europe – report and publication
- Report on exposure levels across EU and comparison to available HBM or reference values – a report and publication
- Report on selection of appropriate biomarkers of exposure, effect and susceptibility – report
- Identification of data and knowledge gaps – a report progress during EHBMI implementation (communication materials for stakeholders, etc..)
- Inventory of existing biomonitoring infrastructure and studies in Europe – database and report

From 1st to the 5th year

- Updated report on updated guidelines, protocols and research results, relevant policies and activities for Cd and cr(VI) for Cd and Cr(VI) – reports
- Contribution to common deliverables listing users of EHBM outputs relevant policies and research and practical needs and gaps – reports
- Updates on action plan for policies, measures and suggestions for further research – contribution to common deliverables
- Contribution to common deliverables related to:
    - Identification of possible national, EU and international funding mechanisms; training needs; meetings with stakeholders to identify short and long-term needs.
    - Institutionalization of national HBM programmes (from planning, implementation, interpretation and communication stages).
    - Development of national strategic plans
- Report on support for targeted field work in Europe and the use of existing samples from biobanks and collection and analysis of new samples
- Reports on quality assurance support to ongoing recruitment and implementation HBM activities related to C and Cr(VI)
- Statistical analysis of newly acquired data
- Yearly reports on data included in the IPChem
- Inventory of health studies for Cd and Cr
- Inventory of biological samples from health studies in biobanks
- SOPs and guidelines for inclusion of HBM in health studies
- Use of biological samples for adding health studies to HBM
- Contribution to a common report on the Workshop

- Report on HBM and health survey based on existing data
- Report on HBM and health surveys in newly conducted studies
- Refinement of PBTK model, estimation of elimination half-lives and risk characterization for Cd and Cr(VI)
- Creation of knowledge base on causal pathways from chemical exposure to health outcomes (Adverse outcome pathways) including Cd and Cr(VI) where appropriate
- Health effects in humans based on birth and adult; literature search on cohorts in European countries
- Development and validation of new biomarkers of effect for Cd and Cr(VI) in combination with other substance groups
- Strategy and plans for population-based cross-European and/or targeted HBM studies within 2-5 years EHBMI program – report.

5.7 References

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6 PAHs and air pollutants

6.1 Introduction

An overview of currently available exposure data indicates that PAHs are ubiquitous pollutants. They are present in the aromatic fraction of some coal- and petroleum-derived products and through these can lead to exposure of consumers (e.g., via some plastic and rubber articles), in the use of solvents or indirectly via the environment or food and water. Many PAHs are known or suspected carcinogenic and mutagenic compounds (e.g., benzo (a) pyrene, dibenzo (a,h) anthracene, etc.). They are the reason for inclusion in the candidate list under article 59 of REACH of a number of complex substances derived from petroleum and coal such as: coal tar pitch, high temperature (CTPHT) – EC 266-028-2; anthracene oil EC 292-602-7 and other anthracene related fractions. The reasons for inclusion are the PBT, vPvB and carcinogenic properties of the PAHs which are present as constituents in these UVCB substances.

Relevant individual PAHs to monitor, where feasible via their specific metabolites, include:

1. 8 carcinogenic PAHs in entry 50 of Annex XVII to REACH: Benzo[a]pyrene, Benzo[e]pyrene, Benzo[a]anthracene, Chrysen, Benzo[b]fluoranthene, Benzo[j]fluoranthene, Benzo[k]fluoranthene and Dibenzo[a,h]anthracene

2. 16 USEPA priority PAHs, included in numerous EN and national standards:

Naphthalene (CAS No. 91-20-3); Acenaphthene (CAS No.83-32-9); Acenaphthylene (CAS No.208-96-8); Fluorene (CAS No.86-73-7); Anthracene (CAS No.120-12-7); Phenanthrene (CAS No. 85-01-8); Fluoranthene (CAS No.206-44-0); Pyrene (CAS No.129-00-0); Benzo(a)anthracene (CAS No.56-55-3); Chrysene (CAS.No.218-01-9); Benzo(b)fluoranthene (CAS No. 205-99-2); Benzo(k)fluoranthene (CAS No.207-08-9); Benzo(a)pyrene (CAS No.50-32-8); Indeno(1,2,3-cd)pyrene (CAS No.193-39-5); Dibenzo(ah)anthracene (CAS No.53-70-3); Benzo(ghi)perylene (CAS No.191-24-2)

3. Potentially also alkylated PAHs: 7,12-dimethylbenzo(a)anthracene; 1-methylphenanthrene; 2,3,5-trimethylnaphthalene; 1-methylnaphthalene; 2-methylnaphthalene and 2,6-dimethylnaphthalene.

Enhanced public concern is demonstrated by the strong public opposition to planned industrial activities such as oil and gas drilling (conventional and unconventional). Strong public interest was observed during the development by the Commission of a restriction on certain PAHs in consumer articles (plastic and rubber components), based on a dossier submitted by Germany. Special concerns have been expressed in particular due to exposure of children to PAHs, such as in toys, and its possible link with the development of cancer in children.

PAHs are regulated on the basis of the National Emission Ceilings Directive 2001/81/EC. Moreover, Regulation (EU) 1272/2013 on PAHs in articles for supply to the general public, amended entry 50 of Annex XVII to REACH. Subject to the detailed scope of the restriction, a limit of 1 mg/kg is established for the rubber and plastic parts of many types of consumer articles. In the case of toys and childcare articles the limit is lowered to 0.5 mg/kg for each of 8 carcinogenic PAHs. The restriction enters into force in December 2015. Anthracene oil and coal tar pitch are included in the 6th recommendation of the European Chemicals Agency, of 1 July 2015 for the inclusion of substances in Annex XIV to REACH.

From the technical point of view, methods already exist for the determination of some PAHs (such as BaP) in urine. Further methodological developments may be necessary however; that need can be served by EHBMI cost-effectively. The impacts of polyaromatic hydrocarbon activities on public health are poorly understood. HBM information would be extremely useful in determining the overall exposure of the general population or of sensitive sub-populations, particularly children, to carcinogenic PAHs. It should also serve to determine whether the existing restrictions and limitations (in articles, in certain foods, in water, in ambient air) have a positive effect in reducing exposure to this ubiquitous family of chemicals or not. Finally, EHBMI can also be very relevant in assessing worker exposure to these chemicals in certain activities (petrochemical plants, manufacture of anodes, etc).

6.2 Objectives

The overall objectives for polyaromatic hydrocarbons (PAHs) during the whole duration of the project can be summed up as follows:

- To get a better insight into the overall human exposure to PAHs through HBM. One-go monitoring should be envisaged for as many compounds as possible.
- To understand the impact of PAHs on public health.

With regard to airborne pollutants, the main objective of EHBMI should be to discover and validate biomarkers of exposure and effect, providing thus valuable support to the refined assessment of the association between airborne pollutants and public health beyond the current epidemiological knowledge.

On the basis of current state of knowledge PAHs and airborne pollutants of interest have been grouped into two groups as follows: (a) substances for which existing data are sufficient for preliminary exposure analysis (data-rich substances); and (b) substances for which additional data and knowledge is needed to perform exposure assessment (data-poor substances).

In particular, the following questions should be addressed during year 1 for PAHs and airborne pollutants for which there is sufficient data for preliminary exposure analysis:

- How high is the current (year 2012 or more recent) exposure (both external and internal) of the EU population to data-rich substances?
- Do the exposure levels of data-rich substances differ significantly between countries? Do spatial and temporal analyses of available data reveal hot spots or time patterns of exposure? What are the main reasons for differences in exposure? What are the most important determinants of aggregate exposure (e.g. are PAH and benzene exposure primarily driven by lifestyle factors, by environmental factors or by workplace environments?)
- Is there a significant change of the regulated data-rich substance levels (GM/median) in the population (both in terms of general population and in terms of susceptible population sub-groups such as children) over the last ten years?
- What are the high exposure groups? Do available HBM data reveal differences in sub-groups that depend on gender, age group, socio-economic status, etc.?
- Are the overall exposure levels in the general population, children, and pregnant women above any health-relevant assessment levels (reference dose or HBM guidance values)?
- What are the policy or socio-economic drivers that may have significant impacts on the exposure levels of the European population to these substances?
- What are knowledge gaps and related research needs for data-rich substances to answer the questions above satisfactorily in the following years (Year 2)? Can the identified knowledge gaps be mended based on existing data or by extension of current good HBM practices?

On the basis of these questions the following specific objectives have been formulated:

- Collect, combine, harmonize and compare existing HBM and exposure data on data-rich substances across Europe to get an overview of current exposure levels (in general population, children, workers…)
- Associate air quality measurements across the EU with available HBM data as appropriate
- Statistically evaluate average concentrations, time trends and potential differences between population subgroups (meta-analysis)
- Derive EU-wide reference values
- Toxicologically evaluate HBM data (comparison with assessment values and/or Reference Dose values) and HBM guidance values for those still missing
- Identify and prioritize knowledge and data gaps and related research needs as starting point for the development of research questions and goals for year 2 and following years

For data-poor substances the questions to be addressed during year 1 are as follows:

- What are knowledge gaps and related research needs for data-poor substances to be considered data-rich and answer the related research questions? How can knowledge gaps be mended by improved methods for data aggregation and analysis of existing data?
- Can some substances be considered as having sufficient data for exposure analysis?
- What analytical methods, documents and study infrastructure have to be established and/or developed in Europe to render a substance data-rich and answer the related research questions?
- How can available HBM methods be improved to allow data collection to be extended to vulnerable subgroups (i.e. children)? What novel HBM approaches should be implemented to allow policy-related research questions to be answered?

On the basis of these questions the following specific objectives have been formulated:

- Identify and prioritize knowledge and data gaps and related research needs as starting point for the development of research questions and goals for year 2 and following years
- Identify missing analytical methods for rendering a substance data-rich.
- Start to establish available analytical methods necessary to render a substance data-rich.
- Develop the basis for an ethical framework for data and biospecimen exchange, sample storage, etc.

6.3 Description of work

Primarily, the initial focus will be on analysis and synthesis of existing data regarding biomonitoring and exposure for all target PAHs and airborne pollutants (Annex 1 list). Information of FRs may include individually presented results on a regional/national level, and currently a holistic overview of the status of exposure of the European population is lacking, both in terms of regional variation and population sub-groups that may be at greater risk, (e.g. occupational exposure). The overview and meta-analysis of currently available biomonitoring data will allow a more complete understanding of current status and streamline work to avoid targeting compounds where there is sufficient information already or where the use is restricted. This effort will comprise the statistical evaluation of exposure levels at the general population and susceptible population sub-group levels. Moreover, it will allow the elucidation of data gaps and the identification of opportunities, which can be addressed with a more targeted approach.

6.4 Deliverables

- Overview of available biomonitoring and exposure data on PAHs and airborne pollutants relevant to the European population
- Toxicological evaluation of HBM data (comparison with assessment values and/or reference dose values) and HBM guidance values for those still missing
- Inventory of reference dose, HBM values for each substance and derivation of EU-wide reference values
- Inventory of SOPs for data analysis including for sharing, harmonizing, analyzing data (which software to use, methods, protocols)
- Inventory of relevant actors and of relevant policies to come for non-regulated PAHs and airborne pollutants
- Inventory of current needs/gaps/cost estimates/analytical gaps including training for PAHs and airborne pollutants
- Compilation of HBM data for use in health impact analysis, in chemical/food safety policy; in environmental policy (e.g. revision of air quality guidelines); in burden of disease estimates
- Indicators for extrapolation to different exposure groups or to prediction of EU exposure
- Mapping of the spatial and temporal variation across the EU to identify variability in exposure and risk.
- Inventory of available biomarkers (incl. metabolites) for PAHs and airborne pollutants
- Validated list of criteria for biomarker and biological matrix sampling prioritization
- Prioritized list of biomarkers and matrices for PAHs and airborne pollutants
- First version of questionnaire for assessment of exposure to PAHs and airborne pollutants
- Guideline for laboratory analyses (analytical phase) for PAHs and airborne pollutants
- SOPs for data management and statistical analysis of results

- List of HES and epidemiological studies that could be used to link health outcomes with exposure data for data-rich substances
- Report on exposure assessment taking into account all pathways based on spatial and PBPK modeling
- Report on determination of exposure levels from available HBM data and comparison to available reference doses using PBPK modeling
- Report on existing biomarkers of effect for PAHs and airborne pollutants

Table x: Classification of PAHs and airborne pollutants according to available data

A) Substances where sufficient data are already available	Regulated: • Particulate matter (PM10 and PM2.5) • NOx (NO2) • SOx (SO2) • O3 • CO
B) Substances where only insufficient data are already available	Regulated: • PAHs (Acenaphthene, Acenaphthylene, Anthanthrene, Antracene (Ant), Benzo(a)anthracene, Benzo(a)pyrene (BaP), Benzo(b)fluoranthene, Benzo(b)fluorine, Benzo(b)naphthothiophene, Benzo(e)pyrene (BeP), Benzo(ghi)fluoranthene, Benzo(ghi)perylene (BgP), Benzo(j)fluoranthene (BjF), Benzo(k)fluoranthene (BkF), Biphenyl, Coronene, Cyclopenta-(cd)-pyrene, Dibenzo(ac)anthracene, Dibenzo(ac)antracene, Dibenzo(ah)anthracene, Fluoranthene (Flu), Fluorene, Chrysene/Benzo(a)phenanthrene , Indeno(123-cd)pyrene, Naphtalene, naphthalene, Perylene (Per), Phenantrene (Phe), Pyrene (Pyr), Retene, Triphenylene) and metabolites (1-OH-pyrene) • Methyl-PAHs (1, 2-Dimethylnapthalene, 1, 3-Dimethylnapthalene, 1, 4-Dimethylnapthalene, 1, 5-Dimethylnapthalene, 1, 8-Dimethylnapthalene, 1-Methylfluoranthene, 1-Methylfluorene, 1-Methylchrysene, 1-Methylnapthalene, 1-Methylphenanthrene, 2, 3-Dimethylnapthalene, 2, 6-Dimethylnapthalene, 2,7-Dimethylnapthalene, 2-Methyl anthracene, 2-Methylchrysene, 2-Methylnapthalene, 2-Methylphenanthrene, 3-6-Dimethylphenanthrene, 3-Methylchloanthrene, 3-Methylchrysene, 5- Methylchrysene, 6-Methylchrysene, 7.12-Dimethylbenz(a)anthracene, 7-Methyl[a]pyrene, 9-Methyl anthracene)and metabolite • Nitro-PAHs (6-Nitrochrysene (6NCHRY), 1-Nitropyrene, 4-Nitropyrene (4NP), 2-Nitropyrene (2NP), 2-Nitronapthelene, 9-Nitroanthracene, 2-Nitrofluorene (2NFLU), 2-nitrofluoranthene (2NFL), 3-Nitrofluoranthene (3NFL), 3-Nitrophenanthrene, 6-Nitrobenzo[a]pyrene (6NBAP), 7-Nitrobenzo[a]anthracene (7NBAA) and metabolites • C6H6 (benzene) • VOCs (toluene, ethylbenzene, xylene(s)) • Carbonyls (formaldehyde and acetaldehyde) • Non-methane semi-VOCs
	Non-regulated: • Biologicals (mould, pollen) • Particulate matter (PM1) • Ultra-fine particles (UFP)

6.5 Work plan PAHs and Air Pollutants

The following table gives an overview of the workplan for year 1 and the challenges for years 2-5 on PAHs.

Pollutant	**Parent substance**	**Biomarker and biological medium**	**Year-1 Analyze status quo, identify opportunities for next**	**Year 2-5 Challenges**

			steps and decide on challenges for Year 2-5	
Regulated	PAH (parent)	OH-PAH metabolites in urine	Extend from 1-OH-pyrene to additional OH-PAH biomarkers to characterize mixture profile and allow source apportionment	Establish reference values for selected OH-PAH parent metabolites in urine for general population (adults/children, smokers/non-smokers) and for worker's populations (smokers/non-smokers)
	PAH (derivate)	OH-PAH derivate metabolites in urine	Assess feasibility of introducing available OH PAH derivate biomarkers	Establish reference values for selected OH-PAH derivate metabolites in urine for general population (adults/children, smokers/non-smokers) and for worker's populations (smokers/non-smokers)
	Benzene	Benzene in blood Benzene in exhaled air Benzene in urine Metabolites in urine	Decision on preferred methods of HBM for benzene for the general population and for subpopulations (e.g. workers)	Establish reference values for benzene biomarker of choice in general population (adults/children, smokers/non-smokers) and for worker's populations (smokers/non-smokers)
	CO	Carboxyhemoglobin (CO-Hb)	Assess feasibility to acquire available clinical data and consider less or noninvasive method (e.g. analysis of exhaled air). Validate noninvasive HBM method by establishing suggested high correlation with blood CO Hb.	Harmonize on choice of available sensor technology for noninvasive CO measurement Establish reference values for CO in exhaled air for general population (adults/children, smokers/non-smokers) and for worker's populations (smokers/non-smokers)
Non-regulated	VOC	VOC in exhaled air VOC metabolites in urine VOC in blood headspace	Decision on preferred methods of HBM of VOC for the general population and for worker's populations	Define method of sample collection, decide on available VOC mixture standards for calibration and nontargeted screening approaches for screening purposes; Establish EU reference values for smokers and non-smokers (cf results from BIOMONECS project)

7 Anilin family: MOCA

7.1 Introduction

Aniline is the simplest member of the aromatic amines, in which one or more hydrogen atoms of the benzene ring are replaced by amino (-NH2) group. Derivatives of aniline include a wide variety of different substances. Some of these (like benzidine and MOCA) are composed of two combined aromatic rings.

Aromatic amines may cause methemoglobinemia in humans and aniline and many of its derivatives are known or suspected human carcinogens. Classical members of this family are bladder carcinogens 2-naphtylamine and benzidine, which use has already ceased in EU. Other members of the family include anisidine, o- and p-toluidine, 4-chloroaniline, 4,4-methylenebis(2-chloroaniline) (MOCA), 4,4-methylenedianiline (MDA), 4,4'-methylenedi-o-toluidine, 4,4'-oxydianiline, 4-aminoazobenzene, 4-methyl-m-phenylenediamine, 6-methoxy-m-toluidine and e.g. 5-nitro-o-toluidine. All of these are registered in use in EU and have use especially in the chemical industry in the manufacture of other chemicals. In addition to workers, exposure to general population via the environment is possible. For aniline and many aniline derivatives, skin is a relevant route for exposure in occupational settings. This emphasizes the role of biomonitoring in exposure assessment.

4,4-methylenebis(2-chloroaniline) (MOCA) and 4,4-methylenedianiline (MDA) are currently authorized under REACH and there is a lot of effort in industry to substitute these chemicals with other chemicals. Both of these chemicals are genotoxic carcinogen to which a threshold for carcinogenic effects cannot be assigned. Both MOCA and MDA are easily absorbed via the skin. This underlines the relevance of biological monitoring. Both for MOCA and MDA methods for biological monitoring has been established. As MOCA is not a ubiquitous environmental contaminant or natural body constituent, any noticeable excretion above the detection limit points to occupational sources. Biomonitoring has been taken into account in REACH authorization process of these compounds and ECHA's Risk Assessment Committee (RAC) has established "biomonitoring equivalents" for different cancer risk levels (see: https://echa.europa.eu/documents/10162/13641/rac_32_notes_moca_en.pdf ; https://echa.europa.eu/documents/10162/13641/dose-response-carc-moca_en.pdf).

Aniline has been assessed under the existing chemicals regulation in EU. It is currently classified as a suspected carcinogen (carc cat 2) in EU. It is used e.g. in pH regulators, water treatment products and in the manufacture of other substances. EU risk assessment report from 2008 concludes that there is a need to limit to risk especially for workers but also to general population near the point sources due to its carcinogenicity and genotoxicity (http://echa.europa.eu/documents/10162/d537626b-e5b6-43e9-a7d2-582468edcc24). Aniline has been recently assessed also by SCOEL. There are validated biomonitoring methods available for aniline and it is possible to set a biological limit value for aniline. Limited data are, however, available on the urinary aniline levels among occupationally exposed population and general population. o- and p-Toluidines are currently in SCOEL working list. Although there are published methods for the biomonitoring of toluidines, limited biomonitoring data is available on these compounds.

In addition to MOCA and MDA, several other aniline derivatives has been included in the candidate list of future authorization in EU. These include anisidine, o-toluidine, 4,4'-methylenedi-o-toluidine, 4,4'-oxydianiline, 4-aminoazobenzene, 4-methyl-m-phenylenediamine, 6-methoxy-m-toluidine and 4-o-tolylazo-o-toluidine.

7.2 Substance classification

CATEGORY A/B: There are occupational exposure data available on MOCA, MDA and aniline at least from some countries. This data have to be evaluated and its representativeness for current use of these substances has to be evaluated. Although they are in borderline category B (Substances where some data are available to generalize), they may be upgraded (based on data gathering and evaluation) to category A (Substances where sufficient data are available to generalize). Exposure of general population to MOCA and MDA is very limited. In addition, due to the authorization of MOCA and MDA, the relevance of these compounds in EU may be very limited in future. However, these may be substituted by other aromatic amine compounds and there may be a need to assess hazards and exposure potential of these compounds in future. There are some biomonitoring data available also on aniline itself, but the data is scattered and needs to be collected and the representativeness of it have to assessed.

CATEGORY B/C: other aniline derivatives mentioned above. E.g. toluidines can be considered as category B substances. There are established biomonitoring methods for toluidines but the available biomonitoring data is limited.

7.3 Objectives

The main emphasis under the group anilines will be on aniline itself and toluidines. Also available data on MOCA and MDA will be gathered to support possible REACH authorization process. However, since it seems that their use has been significantly decreased, the main emphasis will be in these other compounds. The aim is to answer the following questions:

- Availability of methods for the biomonitoring of these aniline derivatives?
- Is there any biomonitoring data available on occupational exposure to aniline compounds (aniline, toluidines, MOCA and MDA) in different industries/occupations? How has the exposure changed over time?
- General population exposure to especially aniline? Are there sufficient data available to set EU-wide reference limits?

- Any specific data gaps identified?
- Availability of biological limit values and availability of data for the setting of health based biomonitoring limit values?
- Are there new aniline derivatives coming into the market to substitute authorized MOCA and MDA? What are the possibilities to biomonitor these compounds?

7.4 Policy-Related Research Questions

Several aniline derivatives are either already authorized or are in the candidate list for authorization. Background data is needed to support REACH authorization process. Also aniline itself and e.g. 4-chloroaniline and p-toluidine, which are currently not in the candidate list, are suspected carcinogens and information on exposure is limited. Aniline has been assessed under the existing chemicals regulation in EU and there are concerns related to occupational and environmental risks. Toluidines are currently evaluated by SCOEL. The main policy related research questions are:

What is the current exposure to these chemicals in EU on the basis of biomonitoring data?

What are the related risks, and the recommended health based biomonitoring values/biomonitoring equivalents for these chemicals?

7.5 Description of Work

- Collect, combine and analyze existing biomonitoring data on these compounds across Europe to get an overview of current occupational exposures and evaluate if there has been decline in the exposure over the time. Identify possible data gaps in biomonitoring methods and data available. Filling of most relevant data gaps with targeted surveys among workers to identify what are the levels currently achievable with the use of best available techniques to control the exposure.
- Identify the labs with analytical capacity for aniline derivatives. Identify the needs to harmonize/develop methodology further. Prepare recommendations for the biomonitoring among occupationally exposed population.
- Identify possible exposure of general population to aniline and aniline derivatives. Collect information on background exposure of general population and identify the sources (e.g. smoking) and their relevance. Setting of reference values for the relevant aniline derivatives.
- Recommendations for the health based limit values or "biomonitoring equivalents" for the different cancer risk levels.
- Identify possible new related compounds coming to substitute authorized aniline compounds (especially MOCA and MDA). Need for the development biomonitoring methods in future?
- Assess the role of HB-adducts in the biomonitoring of exposure to anilines

In the first year, it is planned to collect existing data on:

1) Availability of validated biomonitoring methods for prioritised aniline derivatives (especially aniline, toluidines, MOCA, MDA)
2) Laboratories with analytical capability for the biomonitoring of these compounds
3) Occupational exposure to aniline derivatives among different industries
4) Possible exposure of general population to aniline derivatives and sources
5) Reference/guidance values available and the availability of toxicokinetic/toxicity data for the setting of health based limit values/biomonitoring equivalents

and to identify the data gaps and prioritize further research activities related to the activities during the following years. Priority is in aniline, toluidines but also existing data on MOCA and MDA is collected immediately in the beginning of the project.

Activities during the following years:

1) targeted surveys for the collection of new data

2) harmonization of methods, creation of SOPs
3) development of new biomonitoring methods for the relevant aniline compounds with no existing methods
4) setting of reference values, health based biomonitoring values, or "biomonitoring equivalents" for the prioritized aniline derivatives

7.5 Deliverables

1st year

- Inventory of the available biomonitoring methods for prioritised aniline compounds, inventory of laboratories and procedures. Analysis of available reference/health based guidance values within EU and their basis.
- Report on the current occupational and general population exposure to prioritised aniline compounds in the light of biomonitoring data.
- Analysis of data gaps and needs for further research.

2nd -5th year

- Possible updates on the exposure data on the basis of new data
- Recommendations on health based guidance values/biomonitoring equivalents (on the basis of toxicological evaluation, analysis of causal pathways, and possible PBPK modelling)
- Possible new methods for aniline compounds; standard operating procedures and recommendations for use

8 Chemical mixtures

8.1 Introduction

The phenomenon of mixtures (in the context of HBM) refers to the common occurrence of chemical xenobiotic substances in the body. There is no broadly accepted operational definition of mixtures. In principle, every single substance, once it enters the body, will exhibit its health effects in interaction with a person's genetic makeup and acquired characteristics, and in concert with all other (xenobiotic) substances from previous and simultaneous exposures. These combined and/or simultaneous may come involuntarily or voluntary through different exposures routes from ambient environments, indoor and occupational environments, food, food additives, consumer products, medication, (medical or voluntary) implants, recreational drugs, performance enhancing drugs and food supplements, tattoo ink, etcetera. These mixtures thus form a challenge to (experimental and observational) science, to scientific assessment of risks and to regulation of substances and general risk management policies. The EHBMI project addresses how HBM can contribute to both the science and policy/regulation of dealing with the phenomenon of mixtures. Within the EHBMI project, the focus for chemical mixtures will be on chemicals with exposure routes through the environment, food, occupation and/or consumer products.

The proposed activities on mixtures in EHBMI were developed by a working group of experts from the Member States (c.f. Wiki). This comprised a first inventory in MS of available data, a preliminary inventory of policy needs in EC institutions combined with a preliminary inventory of specific policy needs in member states, a discussion at the Workshop EHBMI Proposal Development (16-17th of November 2015, Utrecht), a EEA Workshop Activities on Mixtures under the European Human Biomonitoring Initiative (11th February 2016). In the latter, experts and policy makers jointly outlined the challenges that mixtures pose to science and policymaking. The proposed activities on mixtures in EHBMI were further developed through e-mail exchanges, with periodic presentations to the EHBMI Steering Group Meetings.

Some research issues

Dealing with mixtures in research poses specific challenges <add some references here>. In toxicological research working mechanisms, mode of action and adverse outcome pathways can be studied in details, but typically only a few permutations of possible mixtures can be assessed. This does not do justice to the wide array of substance to what populations are exposed to. On the other hand, observational studies in humans may

capture these multiple substance, but often fall short in characterizing the dynamics of exposure and ADME characteristics (absorption, distribution, metabolism, and excretion) and typically cannot document mechanisms and causality. Developments in modern techniques such as in sensor technologies, and in epigenomics, transcriptomics, metabolomics, as well as development in biostatistics now allow more in depth research of multiple exposures, body burdens and their effects in humans. To optimally benefit from these developments new forms of cooperation between traditionally separated research communities and projects need to be build. EHBMI provides an excellent opportunity and platform to build such alliances.
Also existing data merit re-evaluation from a mixture perspective. In many HBM projects, as well as in cohort studies and biobank studies, multiple (groups) of pollutants have been studied; yet the reporting is typically restricted to distributions and central tendency measures of single compounds or groups of compounds. The groups are often clustered on:

- chemical families, e.g. phthalates, bisphenols, dioxins, PCB's, PAH's, VOC's
- exposure routes, e.g. food, household dust
- type application such as plasticisers, flame retardants, pesticides
- supposed working mechanisms e.g. endocrine disruptors, carcinogens, neurotoxins.

If few cases, the distribution of a measure/indicator of cumulative body burdens in individuals is reported. If so, this only summarizes body burdens within the clusters mentioned above and hardly ever overarching indicators are used and reported. Thus, it is largely unknown whether specific profiles of high exposures exist, i.e. individuals high in PCB's are also in pesticides, flame retardants or poly fluorinates compounds or mycotoxins. Meaningful indicators to capture such profiles need to be developed for mixtures in the wider meaning of the word. With such aggregated mixture indicators exposure profiles of concern and potential hotspots or risk groups can then be identified in existing data and in new studies.

Some policy issues
Dealing with mixtures also poses substantial regulatory challenges, with numerous pertinent EU and national regulations, as illustrated in the table below.
<add table here from EEA presentation Stephany Bopp, JRC)

In the European Directive 396/2005 EFSA was appointed to be responsible for establishing the methodology for risk assessment of mixtures. It states among other things *"…It is also important to carry out further work to develop a methodology to take into account cumulative and synergistic effects. In view of human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic effects on human health, MRLs should be set after consultation of the European Food Safety Authority…."*. Since 2005 EFSA has published 4 Opinions and 1 Guidance on how to perform risk assessment for pesticide mixtures. The full methodology was discussed during an EFSA info session organized to discuss the methodology with the stakeholdersi. Also JRC has published several reports on assessment of mixtures, that advocate a new test strategy to define the relevant mixturesii. EFSA takes pesticides as a concrete point of departure to develop strategies for dealing with mixtures. Such strategies, once developed, will then be generalized to other forms of mixtures. Central in this approach is the grouping of substances into CAG's, cumulative assessment groups of substance with a common mode of actions. Such CAG's are developed on the basis of adverse outcomes by organ system, e.g. liver. <add refs>

Several Member States (MS) also have issues reports and opinions on dealing with mixtures. For instance in the Netherlands, avoidance of cumulative exposures (of all environmental agents, not just substances) is one of the corner stones of modern environmental policy[iii]. In France, the new health law (currently under consideration) indicates that the identification of risks health should be done relying on the Exposome concept, integrating the effects of exposures to all non-genetic factors<add French reference>.

While there is a clear information need articulated from the side of policy makers, there is less insight in the possible action perspectives for policy makers and stakeholders in dealing with mixtures. Moreover, it is difficult to assess "value of information" for HBM data on mixtures: at what point would additional information on HBM and exposure to mixtures (based on HBM data, or the combined knowledge base) lead to other decisions and other/further policy actions? Should exposure to all substances in the mixtures be reduced, or the one with the highest impact on adverse health outcomes, the one with easy and safe

alternatives/replacements, or the ones with the least costs to reduce, or should the cost-benefit ratio of each source/exposure route be taken into account. One can imagine that the cost-benefit ratio to reduce BPA exposure for babies, children, shop personnel, or in medical (emergency) equipment, may vary substantially. Moreover, when mode of action (MoA) and adverse outcome pathways (AOP) are taken as point of departure to assess acceptability of the combined health impacts of exposure to mixtures, there may well be a need to compare across substances emerging from different types of applications, e.g. flame retardants, pesticides, plasticizers, and food additives/contaminants. For HBM data on mixtures to be meaningful for policy development, it is necessary get further insight in and articulation of the expectations and primary policy needs already in the design phase of the research.

8.2 Substance Classification

Mixtures as a group fall into category C <add description of cat C>. While single chemicals, or even chemical family groups such as PCB's may warrant a category A or B classification, the essence of the mixture issue is the many unknowns about joint and cumulative exposure, combined mode of actions and overall adverse outcomes and health risks and impacts.

8.3 Objectives

The **overall aim** of the mixtures-related activities in EHBMI is to improve the efficacy of HBM to inform science, policy and regulatory actions with respect to dealing with mixtures.

Specific objectives include:

1 The development of summary indicators to describe the exposure and body burdens of mixtures
2 The re-evaluation of existing HBM data with respect to mixtures
3 To further develop practical approaches to identify and assess the potential health risks and impacts of mixtures
4 To inform policy makers, stakeholders and the public at large about mixture exposures and associated health risks

The EC through the H2020 programme has funded several new projects on mixtures pertinent to HBM, e.g. EuroMix, EDC-MixRisk, Denamic, Solutions and several relevant exposome projects, such as Exposomics, Heals, Helix, Chrome). The EHBMI project seeks to cooperate with these project and to build and capitalise on the expertise and data generated in these projects.

8.4 Policy-related research questions

The EHBMI project will address a number of policy-related research questions, as outlined below.

1 What are the more specific information needs from policy makers from different domains with respect to the management of mixtures?
2 How do these specific needs translate into functional criteria for generation and interpretation of HBM?
3 What is the population distribution of the relevant mixture profiles in Europe?
4 Are there hotspots or specific risk groups identifiable on the basis of existing and new HBM data?
5 What health risks are associated with these exposures to mixtures and what are the dominant uncertainties?
6 What action perspectives and policy scenarios are available in different domains to reduce health riks, for stakeholders and policy makers?
7 What are the recommendations for further sustainable research and policy development for mixtures within the EHBMI?

8.5 Description of work

The work on chemical mixtures will involve activities in Pillars 1, 2 and 3 and consist of workshops/activities with policy makers and stakeholders to articulate the information needs, as well as, later on, the translation of the results to policy makers and stakeholders (Pillar1), the compilation of data from existing studies on HBM to re-analyse data on multiple chemicals collected in the same individuals (Pillars 2-3), the collection of new targeted HBM mixture data in 3-5 countries (Pillars 2-3), the assessment of health effects, risks and health impacts of mixtures <?emerging chemicals?> (Pillar 3).

The project will make an inventory of various approaches and conventions within MS to deal with mixtures in policies, e.g. derivation of references values, or TTC for mixtures, focussing on the priority substance groups (phthalates, biphenols, per/polyfuorinated compounds, flame retardants, elements (Cd, Cr), PAH's and air pollution, and emerging substances). Since pesticides play a major role in the development of an EC approach to dealing with mixtures as spearheaded by EFSA, the CAG approaches will also be included. Based on these alternative approaches a statistical, data driven approach on existing data on mixtures will be performed. A key set of aggregated mixture indicators will be developed, compared and evaluated with respect to value of information for policy support. To this end, we will liaise with related projects with HBM information on mixtures. Also, we will adopt approaches from mixture toxicology. Aggregated mixture indicators to be considered include aggregation on chemical family, application, exposure route, and/or MoA/AOP. This will lead to a key set of indicators to describe the cumulative exposure and body burden to mixtures. For these indicators, population distributions from existing data will be developed, and data gabs identified. Patterns in distribution, e.g. from hotspots and specific risk groups will be analysed, building on approached like e.g. Phenol Explorer/Exposome Explorer.

Procedures for exposure reconstruction from HBM mixture profiles will be developed to identify particular exposure pathways of concern and/or source apportionment.

In addition to the compilation, analysis and evaluation of existing HBM data on mixtures, new data will be generated in a joint 3-5 country survey. Countries will be enrolled based on expected exposure gradients to the mixtures of concern. A protocol for mixtures will be developed, with special emphasis on hotspots for multiple exposures and repeated measures designs to assess the variability and dynamics of exposures and body burdens. Candidate substance groups will be selected from the priority substance groups on the basis of relevance to mixture risk assessment and on the basis of interests from MS and EC institutions. Again, given the prominence of pesticides in the EC/EFSA approach to mixtures, these compounds are candidates for a joint survey. Execution of a joint survey is expected to take place in years 2 or 3.

The mixture activities in the EHBMI project will also entail approaches to identify mixture health effects. This will be done in close association with the groups working on the other priority substances and also in close cooperation with EU funded studies, like EuroMix and EDC-MixRisk and exposome projects. We will also liaise with EFSA activities and CAG approaches for pesticides and interact with relevant mixture toxicity groups and projects. The use of effect biomarkers for mixture effects will be explored, both from an inventory of existing effect biomarkers, as well as the exploration of new effect biomarkers. Topical case studies will be performed as proof of concept.

In the final phase of the EHBMI project, the adopted approaches and developed methodology will be applied for an overarching assessment of mixtures on the basis of existing and newly collected data from the EHBMI database on priority substances. Results will be translated to policy recommendations and recommendations for future research.

Activities in year 1

Activities in year 1 will focus on elucidation of the information needs from policy makers and stakeholders, the compilation of existing data, the development of a statistical analysis plan for re-analysis of existing mixture data, and preparation of a protocol for a joint survey on mixture exposures and body burdens.

1. Initial description and further articulation of information needs from policy makers
2. Translation of policy needs in terms of functionality of HBM data to inform the policy development; translation of specific research
3. Development of a set of approaches for meaningful aggregated indicators (on application, on exposure route, on MoA/AOP) to describe the cumulative body burden to mixtures
4. Development and compilation of an operational database of existing HBM mixture data
5. Preparation of the development of procedures for exposure reconstruction from HBM mixture profiles for exposures of concern and/or source apportionment to contributing sources
6. Preparation of the development of a protocol for the joint collection of HBM data of mixtures in 3-5 countries
7. Preparation of the development of approaches to identify mixture health effects and description of the functionality of mixture effect biomarkers

8.6 Deliverables

Deliverables for the first year

1. Report on information needs from policy makers and translation of policy needs in terms of functionality of HBM mixture data (M12)
2. Database on existing HBM data on mixtures measured in same individuals
3. Plan of analysis for existing HBM data
4. Report a core set of aggregated mixture indicators

Deliverables within five years

5. Protocol for a joint survey
6. Report on procedures for exposure reconstruction from HBM mixture profiles for exposures of concern and/or source apportionment to contributing sources
7. Report approaches to identify mixture health effects and description of the functionality of mixture effect biomarkers
8. Report existing effect biomarkers and the functionality of new mixture effect biomarkers
9. Case study reports on mixture health effects
10. Report on aggregated HBM mixture indicators, including profiles across MS and specific risk groups and/or hotspots
11. Report on the results of joint mixtures survey
12. Report on exposure reconstruction, exposure pathways and source apportionment of observed mixtures
13. Report on overarching analysis of existing and newly collected data across priority substance groups
14. Report policy recommendations and future research avenues

8.7 Critical risks for implementation

In addition to more generic risks, the mixture related activities carry some additional risks. For the compilation and re-analysis of existing data, cooperation of MS to provide access to earlier collected data is a prerequisite (low). For aggregation of mixtures based on MoA/AOP, availability of knowledge on such MoA's of all relevant components of the observed mixtures is necessary (high). It is likely that the availability of such knowledge will be limited for many substances; therefore it may be necessary to develop expert elicitation procedures to provide best expert judgement on the relevant MoA to use in the aggregation process. Since mixtures are classified in category C, knowledge about mixture exposure, and particularly health effects and risks is extremely limited. Case studies and risk and impact assessments will therefore carry substantial uncertainty. There is the risk that existing effect biomarkers for pertinent mixtures are scarce (high);

development time for new biomarkers of effects may well exceed the duration of the 5 year projects, and may only reach fruition when a sustainable continuation of EHBMI is realised.

8.8 References

9 Emerging chemicals

9.1 Introduction

Conventional chemical monitoring activities are basically focused on targeted analysis of particular chemicals or their direct metabolites which were pre-selected based on potential concerns stemming from known hazard properties, exposure scenarios and production and/or use volumes. This approach is however limited by the pre-existence and availability of information regarding the hazardous properties and use of these chemicals. For some of these known chemicals which are not routinely measured and for which no data on human exposures exist, their presence (parent chemical and/or their known metabolites) has to be searched in human samples by "suspect screening". Such suspect screening can make use of the currently existing initiatives and can be informed by concatenating information and data mining on the use of chemicals, their occurrence in media relevant for human exposure (food, water, air, soil) together with toxicological data. Another approach is non- targeted screening, where there is no pre-established list of chemicals to be screened against. In that case, the "unknown" chemicals can be identified based on a number of properties, including the accurate (molecular) mass. Such methods cover a much wider range of chemicals and, moreover, offer the possibility to re-analyse existing data rather than having to re-analyse the samples when searching for new chemicals or metabolites/biomarkers thereof.

The work on emerging chemicals is motivated by the need of policy makers for markers of early signalling of the presence of chemicals in humans and to prioritize for the monitoring of populations for chemicals currently not included in existing biomonitoring programmes. Matrices of focus are urine, blood, breast milk, cord blood, but alternative matrices (hair, nails, or meconium) may also be investigated. Currently, there are three challenges in the application of suspect and non-targeted screening approaches in HBM. First is the extraction of the relevant information from the extensive raw data files. This involves pre-processing of the data and searching data files for large numbers of substances, their potential metabolites, and/or certain molecular features. Second is the lack of databases/libraries that would facilitate targeted searches in the data. Third is the lack of guidelines in validation and quality control of non-targeted methods. For all these three challenges, lessons learned from the use of other non-targeted applications (such as metabolomics) can be implemented here and adjusted for the specific needs of emerging chemicals.

9.2 Objectives

- Inventarise and prioritize already known emerging chemicals associated to a potential HBM concern, based on exposure information from environmental organisms and occupational exposures.
- Improve screening methods and screen for these known emerging chemicals in human matrices (suspect screening) including sample preparation, information extraction, data processing and provide guidelines for method validation.
- Develop and improve methods and screen for yet unknown chemical hazards by untargeted screening approaches including sample preparation, information extraction, data processing and provide guidelines for method validation
- Obtain information on which emerging chemicals and which chemical combinations are present in human matrices and may turn into chemicals with emerging concerns.

9.3 Description of work

Task 1 – Make an inventory of emerging chemicals relevant for EHBMI and for which to date no biomonitoring data exists. This task has to be strongly informed by the current on-going initiatives within other projects and networks and the relevant scientific literature.

1.1 Collate existing lists of emerging chemicals e.g. generated by ECHA, EFSA (food), NORMAN network (aquatic environment), occupational settings (yr1). (IRAS-NL)

1.2 Prioritize chemicals for inclusion in EHBMI by linking occurrence to toxicological properties (yr1). (IRAS-NL)

1.3 Collate existing data on mammalian metabolism/distribution/excretion. If not available: Predict potential metabolites for each prioritized chemical using computer models/software and existing data (yr1) (synergism with Task 12.3)

Task 2 – Method development and harmonisation of methods for suspect screening of known emerging compounds and for non-target screening of yet unknown compounds

2.1 Inventarise existing protocols and uniformization/standardisation of methods, including the associated data processing. Development of a proposal for harmonized workflow, this should be informed with existing initiatives such as metabolomics standardization initiatives (yr1)

2.2 Generate databases for identification of prioritized chemicals and metabolites in human samples based on mass spectral information (yr1-5).

2.3 Inventarise existing approaches for untargeted "fishing" of yet unknown markers of exposure on the basis of particular chemical signature (inc. for instance halogenated compounds in HRMS). Develop appropriate data processing strategies for revealing such relevant signals of interest from the generated untargeted profiles. (CEA-FR, INRA/LABERCA-FR (6PM), UAntwerp-BE, UFZ)

Task 3 – Generation of new HBM data

3.1 Generate new mass-spec data for samples from and selected populations, such as occupationally exposed individuals for detecting both known emerging and yet unknown compounds on the basis of the previously developed methods. To start , already collected samples (>2014) will be used. Later on suitable samples will be collected from cohort studies scheduled in the EHBMI. Analysis will be done using current state-of-the-art instruments (yr 2-5). (INRA/Toxalim-FR, INRA/LABERCA-FR (6PM), UAntwerp-BE)

3.2 Mine spectra for metabolites of emerging chemicals according to optimised protocols methodologies and develop accurate mass MS and and MS/MS-databases/libraries for biomarkers of emerging chemicals and their human metabolites. (yr 2-5). This will result in a dedicated exposure biomarker database based on or developed in collaboration with existing platforms (Exposome Explorer, Norman MassBank, M/z-cloud, etc) or add-ons to these existing databases (INRA-TOXALIM-FR, CEA, UAntwerp-BE))

3.3 Exploration of alternative biological matrices (hair, nails, meconium, teeth) for screening of emerging chemicals, with the aim to cover exposures over time (yr 2-5). (synergism with task 9.3)

Task 4- Identify new chemicals of emerging concern and their combinations in selected human samples

4.1. Integration of chemical screening data and toxicological data. (yr 2-5) . Development of a method for prioritisation of screening for unknown features. (yr 2-5). This will build on approaches that are being developed in several centers and also in the U.S.A (ToxCast).

9.4 Deliverables

Deliverables (brief description and month of delivery)

	Y1	Y2	Y3	Y4	Y5	deliverable
Task 1	x					List of potential exposure biomarkers
Task 2	x					Standardised workflows for broad chemical screening
					x	Exact mass MS and and MS/MS -databases/libraries for biomarkers of exposure
Task 3					x	Exposure biomarker database based on screening of new samples
					x	Suitable matrix for screening over time
Task4			x		x	Priority chemicals for emerging concern

Gantt Chart

	Y1	Y2	Y3	Y4	Y5
1.1 List of emerging chemicals based on occurrence data	x				
1.2 Prioritisation based on toxic properties	x				
1.3 Identification of metabolites of emerging chemicals	x				
2.1 Inventory of existing protocols , harmonise and optimize workflow	x				
2.2 Generate database for identification of chemicals and metabolites	x				
3.1 Generate new data from samples based on developed workflows		x	x	x	x
3.2Development of exact mass and MS/MS databases of exposure biomarkers		x	x	x	x
3.3 Screening of alternative biological matrices		X	X	X	X
4.1 Integration with tox data		x	x	x	x

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Task 4.1b: Identification of information needs from internal bodies

To identify needs for developing analytical HBM methods , IRAS will collate existing lists of emerging chemicals e.g. generated by ECHA, EFSA (food), NORMAN network (aquatic environment) , occupational settings (yr1). Further prioritization will occur by linking occurrence to toxicological properties .

Task 12.3: Toxicokinetic properties

Collate existing data on mammalian metabolism/distribution/excretion. If not available: Predict potential metabolites for each prioritized chemical using computer models/software and existing data

Task 15.3: Development of methods for combined and non-targeted screening for chemicals of emerging concern

Inventarise existing protocols and uniformization/standardisation of methods, including the associated data processing. Development of a proposal for harmonized workflow, this should be informed with existing initiatives such as metabolomics standardization initiatives

Inventarise existing approaches for untargeted “fishing” of yet unknown markers of exposure on the basis of particular chemical signature (inc. for instance halogenated compounds in HRMS).

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Task 9.3: Developing of new methods

Exploration of alternative biological matrices (hair, nails, meconium, teeth) for screening of emerging chemicals, with the aim to cover exposures over time (yr 2-5

Task 15.4: Development of methods for combined and non targeted screening for chemicals of emerging concern

Generate databases for identification of prioritized chemicals and metabolites in human samples based on mass spectral information (yr1-5).

Develop appropriate data processing strategies for revealing signals of interest from the generated untargeted profiles. (CEA-FR, INRA/LABERCA-FR (6PM), UAntwerp-BE, UFZ)

Generate new mass-spec data for samples from selected populations, such as occupationally exposed individuals for detecting both known emerging and yet unknown compounds on the basis of the previously developed methods. To start , already collected samples (>2014) will be used. Later on suitable samples will be collected from cohort studies scheduled in the EHBMI. Analysis will be done using current state-of-the-art instruments (yr 2-5). (INRA/Toxalim-FR, INRA/LABERCA-FR (6PM), UAntwerp-BE)

Mine spectra for metabolites of emerging chemicals according to optimised protocols methodologies and develop accurate mass MS and and MS/MS-databases/libraries for biomarkers of emerging chemicals and their human metabolites. (yr 2-5). This will result in a dedicated exposure biomarker database based on or developed in collaboration with existing platforms (Exposome Explorer, Norman MassBank, M/z-cloud, etc) or add-ons to these existing databases (INRA-TOXALIM-FR, CEA, UAntwerp-BE))

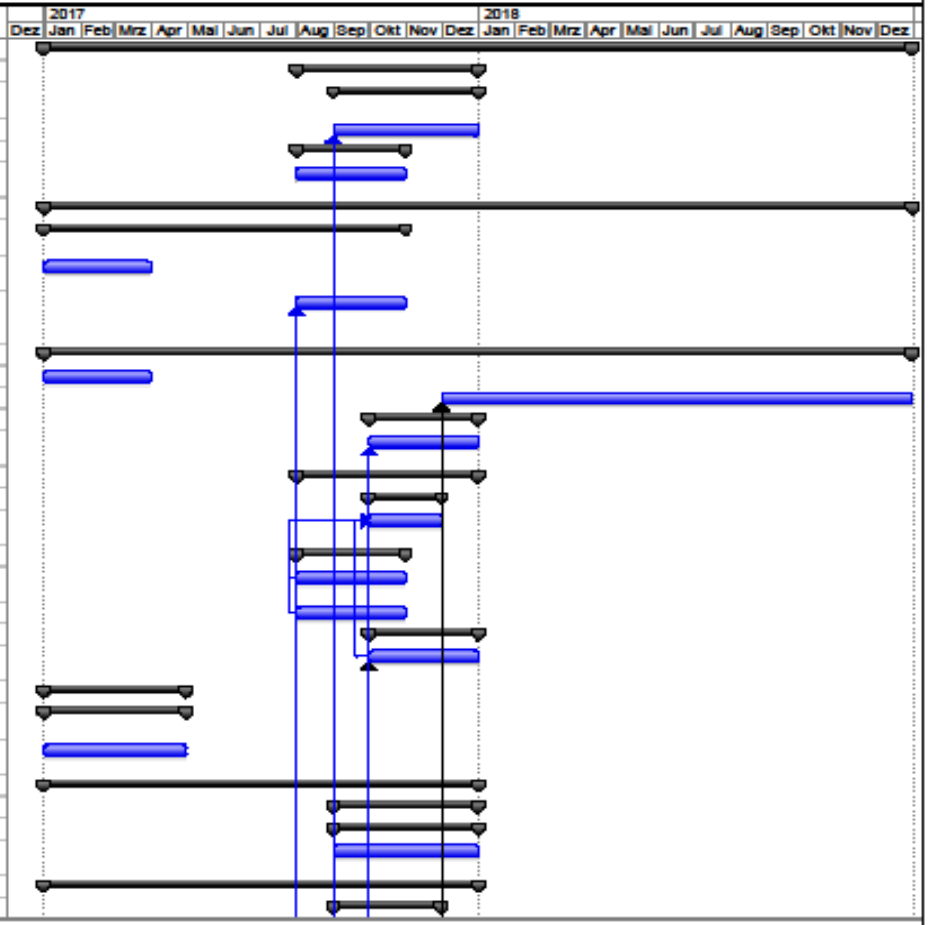
Integration of chemical screening data and toxicological data (yr 2-5). Development of a method for prioritisation of screening for unknown features (yr 2-5). This will build on approaches that are being developed in several centers and also in the U.S.A (ToxCast).

ANNEX: GANTT CHARTS (old)

Gantt Chart Phthaltes and DINCH

First Year Phthalates

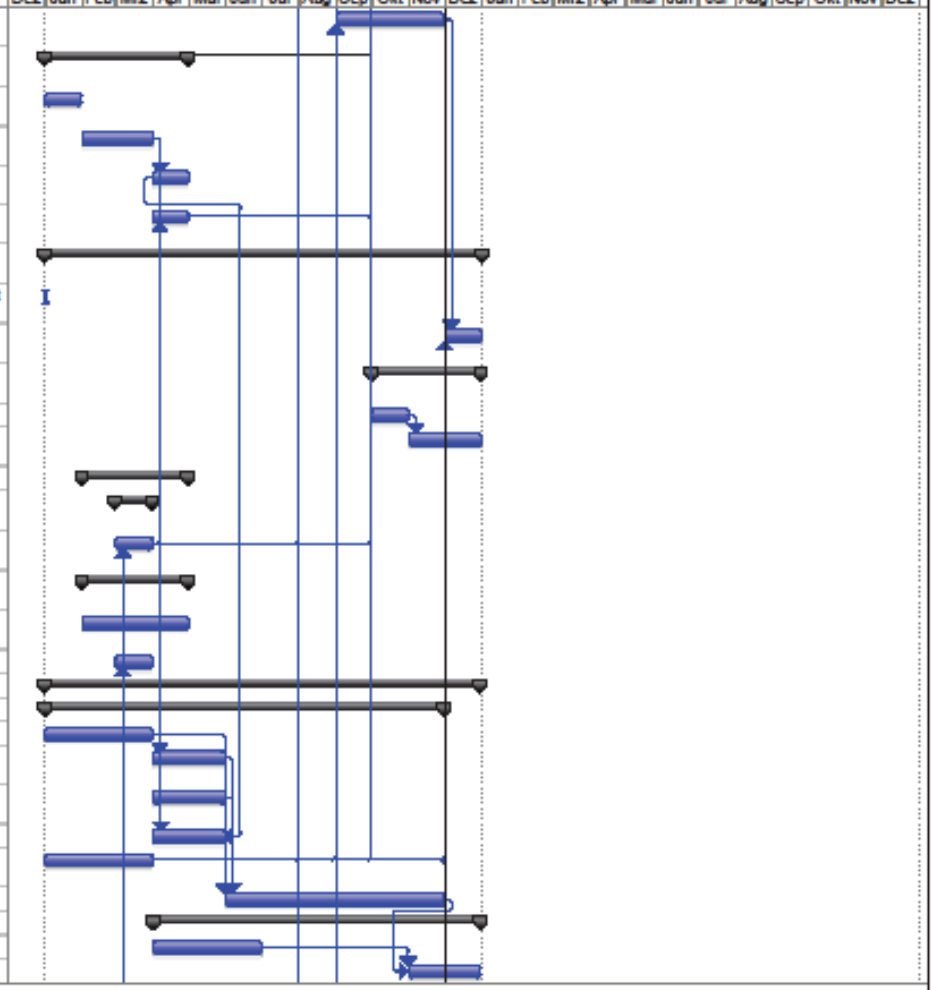
Nr.	Task name	Month
1	**2. Science to Policy**	
2	**2.1 Pillar Coordination**	
3	**2.1.1 Coordination between Work Packages and with other Pillars**	**4 M**
4	Deliverable 2.1.1.1.Annual Work Plan for Year 2	4 M
5	**2.1.3 Coordinate Pillar information for knowledge hub**	**3 M**
6	Deliverable 2.1.3.1.Ethical and legal document for EU-wide sharing of data, knowledge, research outcomes	3 M
7	**2.2 Prioritization**	
8	**2.2.1 Collect information needs from policy makers/SFAB/focus groups**	**3 M**
9	Deliverable 2.2.1.1 Inventory of relevant actors and policies to come for non-regulated phthalates	3 M
10	Deliverable 2.2.1.2 Inventory of current needs, gaps, cost estimates for additional measurements and analytical gaps for Cat A-C substances	3 M
11	**2.2.2 Develop a prioritization strategy**	
12	Deliverable 2.2.2.1 Accepted list of decision criteria	3 M
13	Deliverable 2.2.2.2 Proposal of priority substances for first 5 years	13 M
14	**2.2.3 Scoping in collaboration with Pillar 3 + Pillar 4**	
15	Deliverable 2.2.3.2 Draft project descriptions for Cat. B&C substances	3 M
16	**2.3 Policy Translation of Results**	
17	**2.3.1 Develop and consolidate EU HBM guidance values**	
18	Deliverable 2.3.1.1 Develop EU-wide HBM guidance values for Cat A substances	2 M
19	**2.3.2. HBM data in risk assessment strategies**	
20	Deliverable 2.3.2.1. HBM data in burden of disease estimate of phthalates	3 M
21	Deliverable 2.3.2.2. HBM data in health impact analysis of phthalates	3 M
22	**2.3.3. Identify indicators useful for policy making**	
23	Deliverable 2.3.3.1. Identify exposure indicators for phthalate exposure and alternatives (DINCH); early warning indicators	3 M
24	**2.4. Sustainability and capacity building**	
25	**2.4.3. Explore accessibility of other funding mechanisms & resources for national capacity building**	
26	Deliverable 2.4.3.1. Inventory of financing mechanisms from national, regional, EU or international origin	4 M
27	**3. HBM-Platform**	
28	**3.1. Pillar Coordination**	
29	**3.1.4. Dissemination and Communication**	
30	Deliverable 3.1.4.1. Guidelines for Dissemination & Communication ; Materials and Framework (Adapt from COPHES/DEMOCOPHES)	4 M
31	**3.2. Preparatory Phase**	
32	**3.2.1. Develop basic survey design**	



Seite 1

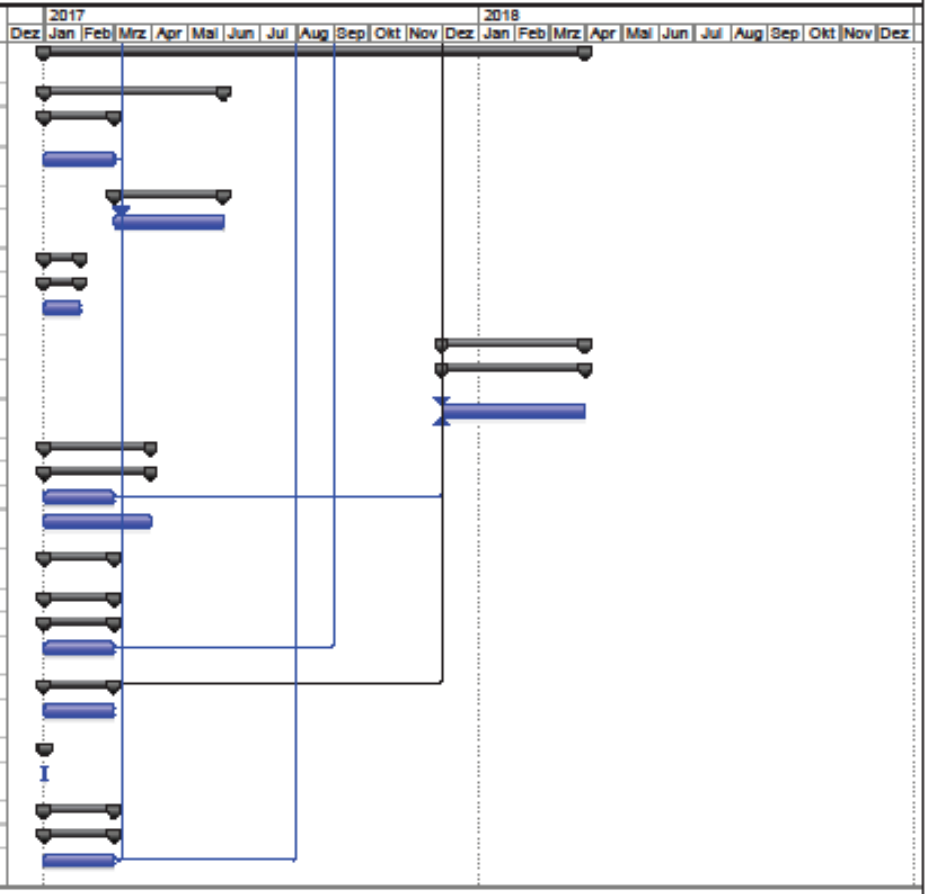
First Year Phthalates

Nr.	Task name	Month
33	Deliverable 3.2.1.1. Guidelines for substance specific survey design /recruitment&sampling strategy if needed	3 M
34	**3.2.2. Identify most appropriate biomarkers & matrioes and researoh needs for new analytioal methods**	
35	Deliverable 3.2.2.1. Inventory of available biomarkers for Cat A-C substances	1 M
36	Deliverable 3.2.2.2. Valitated list of criteria to prioritize biomarkers & urine sampling &comparability of results	2 M
37	Deliverable 3.2.2.3. Prioritized list of biomarkers & matrices for Cat. A-B substances	1 M
38	Deliverable 3.2.2.4. Inventory of countries with analytical gaps for Cat. A-C	1 M
39	**3.2.3. Prepare Questionnaires in ooordination with health/oooupational surveys**	
40	Deliverable 3.2.3.1.Inventory of health/occupational surveys were phthalites&DINCH can be included	Before start
41	Deliverable 3.2.3.2. Tailored Questionnaire adjusted for phthalates & DINCH (adopted from COPHES/DEMOCOPHES)	1 M
42	**3.2.4 Development of strategy for exohange of human samples**	
43	Deliverable 3.2.4.1. Strategy Plan	1 M
44	Deliverable 3.2.4.2. SOP for exchanging & storage, coding, preserving if needed	2 M
45	**3.4. Laboratory Analysis & Quality Assurance**	
46	**3.4.1.Establishment of Network of Referenoe HBM Laboratories for developing new methods**	
47	Deliverable 3.4.1.1. Inventory of accreditated labs able to measure Cat. A-C substances	1 M
48	**3.4.2. Establishment of Network of Referenoe HBM Laboratories to perform Quality Control Programs**	
49	Deliverable 3.4.2.1. Development of QS/QA procedure (adapt from COPHES/DEMOCOPHES; EQUAS)	3 M
50	Deliverable 3.4.2.2. Inventory of labs able to perform QS/QA	1 M
51	**3.5. Data Management**	
52	**3.5.1. Develop a statistioal analysis plan**	
53	Deliverable 3.5.1.1. Statistical Analysis Plan for Meta-analysis	3 M
54	Deliverable 3.5.1.2. SOP for metanalysis for Cat. A substance (can be extrapolated to B&C substances)	2 M
55	Deliverable 3.5.1.4. Develop harmonized SOP for statstical analyis, DI estimations for Cat A substances	2 M
56	Deliverable 3.5.1.5. SOP for inclusion criteria for meta-analysis	2 M
57	Deliverable 3.5.1.6. Mapping of exisiting data in EU & identifying data gaps of countries	3 M
58	Deliverable 3.5.1.7. Actual Meta-analysis / statistical analysis	6 M
59	**3.5.3. EU referenoe values**	
60	Deliverables 3.5.3.1. Standardized scheme for derivation of reference	3 M
61	Deliverables 3.5.3.2. EU reference values for Category A substances	2 M

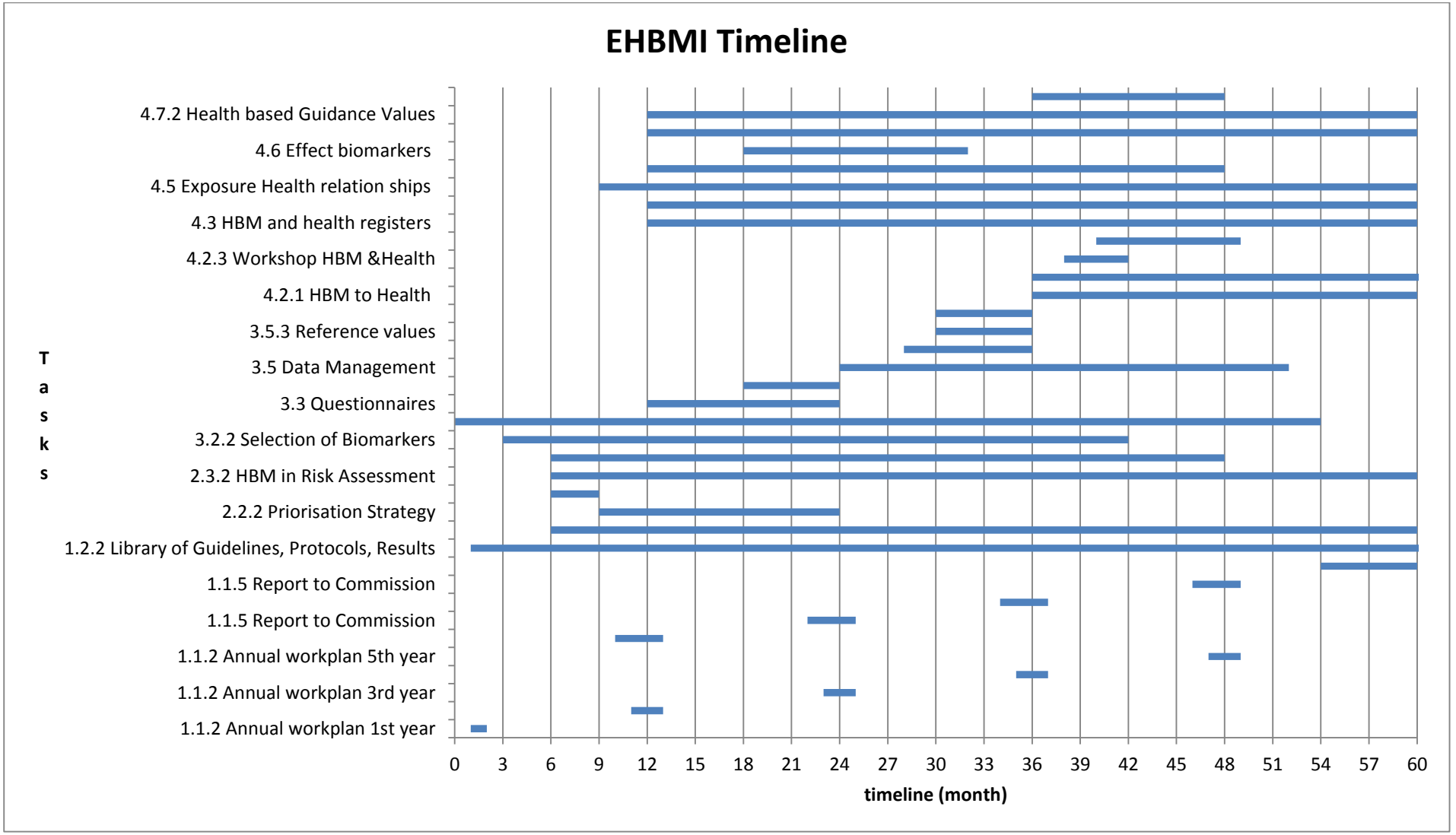


First Year Phthalates

Nr.		Task name	Month
62		**Pillar 4**	
63		**4.2 Linking HBM with health surveys/population studies**	
64		**4.2.1. Feasibility of linking HBM programmes to health surveys/population studies**	
65		Deliverable 4.2.1.1 List of HES and EPI studies that could be of use to link health outcomes with exposure data	2 M
66		**4.2.2. SOPs and Guidelines**	
67		Deliverable 4.2.2.1 SOPs and Guidelines for linking EPI/Health studies with exposure data	3 M
68		**4.3. HBM and health registries**	
69		**4.3.1. Linking HBM to administrative registries**	
70		Deliverable 4.3.1.1. list of relevant registries with available biosamples	1 M
71		**4.4. From HBM to exposure**	
72		**4.4.2. Reverse dosimetry approaches to estimate exposure from HBM**	
73		Deliverable 4.4.2.1. Determine exposure levels from HBM and compare to available TDI using toxicokinetic models	4 M
74		**4.7 From HBM to human health risk**	
75		**4.7.1. Identifying mixture health effects and relevant mixtures**	
76		Deliverable 4.7.1.1. List of mixtures to be considered	2 M
77		Deliverable 4.7.2.1. Report on current data and gaps in knowledge	3 M
78		**Pillar 5**	
79		**5.2 National Priorities**	
80		**5.2.1 Mapping information needs from policy makers**	
81		Deliverable 5.2.1.1. Identify policies at national level that benefit from use of HBM for Cat A-C substances	2 M
82		**5.2.2. Implement national prioritization strategy**	
83		Deliverable 5.2.2.1. Proposal for priority substances for first 5 years	2 M
84		**5.3. National Policy translation of results**	
85		5.3.1. Establish Review Committee for deriving reference & guidance values	
86		**5.5. National sustainibility and capacity building**	
87		**5.5.2. Evaluate training needs**	
88		Deliverable 5.5.2.1. Inventory of analytical&statistical needs for measuring phthalates and DINCH per country	2 M

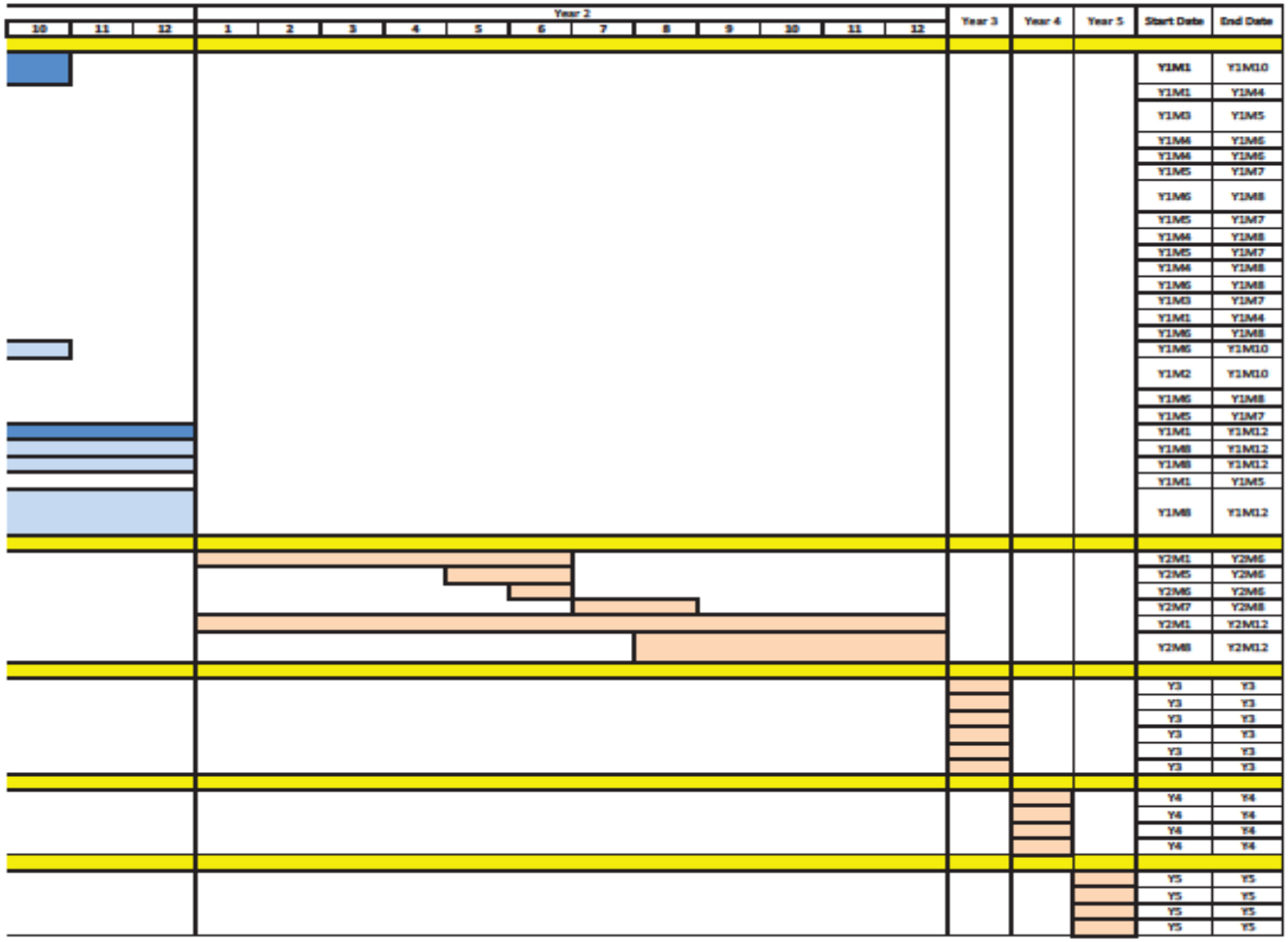


Gantt Chart Per-/polyfluorinated compounds



Gantt Chart Flame Retardants

Task	Type of Action	Year 1								
		1	2	3	4	5	6	7	8	9
Year 1										
Development of inventory and analysis of existing data	**Data mining, interpretation, statistical analysis**									
What current information is available regarding human exposure to FRs, both past and current?	Data mining									
How do we catagorize existing data for use.. i.e. is a mean value sufficient or do we need raw data, is how data processed important in fitness.	Data interpretation									
How well does the information cover the European population, spatially and temporally?	GIS and statistical analysis									
What are current human levels of legacy FRs (e.g., PBDE and HBCD)?	Data mining									
How do these compare to any historical records?	Statistical analysis									
Is the current legislative framework and proposed actions leading to a significant decline inrestricted compounds and is this uniform across the EU?	Data Mining, Statistical analysis									
How do the levels of legacy FRs compare to levels of new/emerging FRs?	Data interpretation									
Is any temporal or spatial trend observed?	Data interpretation									
Can we relate this to use patterns and/or production volume?	Statistical analysis									
What are the population groups most at risk?	Data interpretation									
What compounds should be prioritized for further information regarding exposure and/or toxicity?	Data interpretation									
How can use and risk information be combined to identify and prioritize knowledge gaps for further study?	Modelling									
Overview of available biomonitoring and exposure data on FR relevant to the European population	Data mining									
Identification of data and analytical gaps according to substance, region and/or population	Data interpretation									
EU-wide reference values	Modelling and statistical analysis									
Toxicological evaluation of HBM data (comparison with assessment values and/or TDI values) and HBM guidance values for those still missing	Data interpretation and modelling									
Mapping of the spatial and temporal variation across the EU to identify variability in exposure and risk.	GIS models and statistical evaluation									
Identify existing SOPs for FRs and can these be validated for use in EHBMI?	Data mining and interpretation									
Year 2 planning	Data interpretation and evaluation									
Identify from year 1 the compounds that may be moved between the 3 catagories based on final data mining	Data interpretation and evaluation									
Identify compounds of low information that have limited production and use in the EU -assign a low importance/relevance	Data interpretation and evaluation									
Identify toxicity testing methods that should be used to characterize risk of compounds where information is limited	Meeting, discussion									
Indicate compounds that require more indepth HBM and the scope and range required i.e. can we use existing biobanks for preliminary data, can we request current biomonitoring assign samples for such analysis as required, do we need to plan a targeted camapign.	Data interpretation and evaluation									
Year 2										
Laboratory development of analytical method(s) for FRs within one institution	Laboratory work									
Identify detection limits based on estimated concentrations in the EU population, develop SOP for estimated sample volume, etc.	Laboratory work									
Dissemination of method and training to ensure countries with the capability can reproduce the method	Training									
Interlaboratory validation of method across the EU groups	Laboratory work									
Toxicity testing	Laboratory work									
Plan sample collection or distribution of biobank samples needed for additional study, determine which laboratroies will handle samples, etc.	Laboratory work									
Year 3										
Sample collection	Sampling									
Laboratory analysis	Laboratory work									
Data dissemination	Data interpretation and evaluation									
Progress meetings, further training	Meeting, discussion									
Identification of further needs	Data interpretation and evaluation									
Planning for final data needs	Planning									
Year 4										
Final period of laboratory analysis	Laboratory work									
Data homogenization, comparability evaluation	Data interpretation and evaluation									
Information validation and synergy	Data interpretation and evaluation									
Prioritization of compounds that require action based on risk	Data interpretation and evaluation									
Year 5										
Data synthesis	Data interpretation and evaluation									
Prioritization of compounds that require action based on risk	Data interpretation and evaluation									
Project reporting	Meeting, discussion									
Data dissemination, stakeholder meetings	Meeting, discussion									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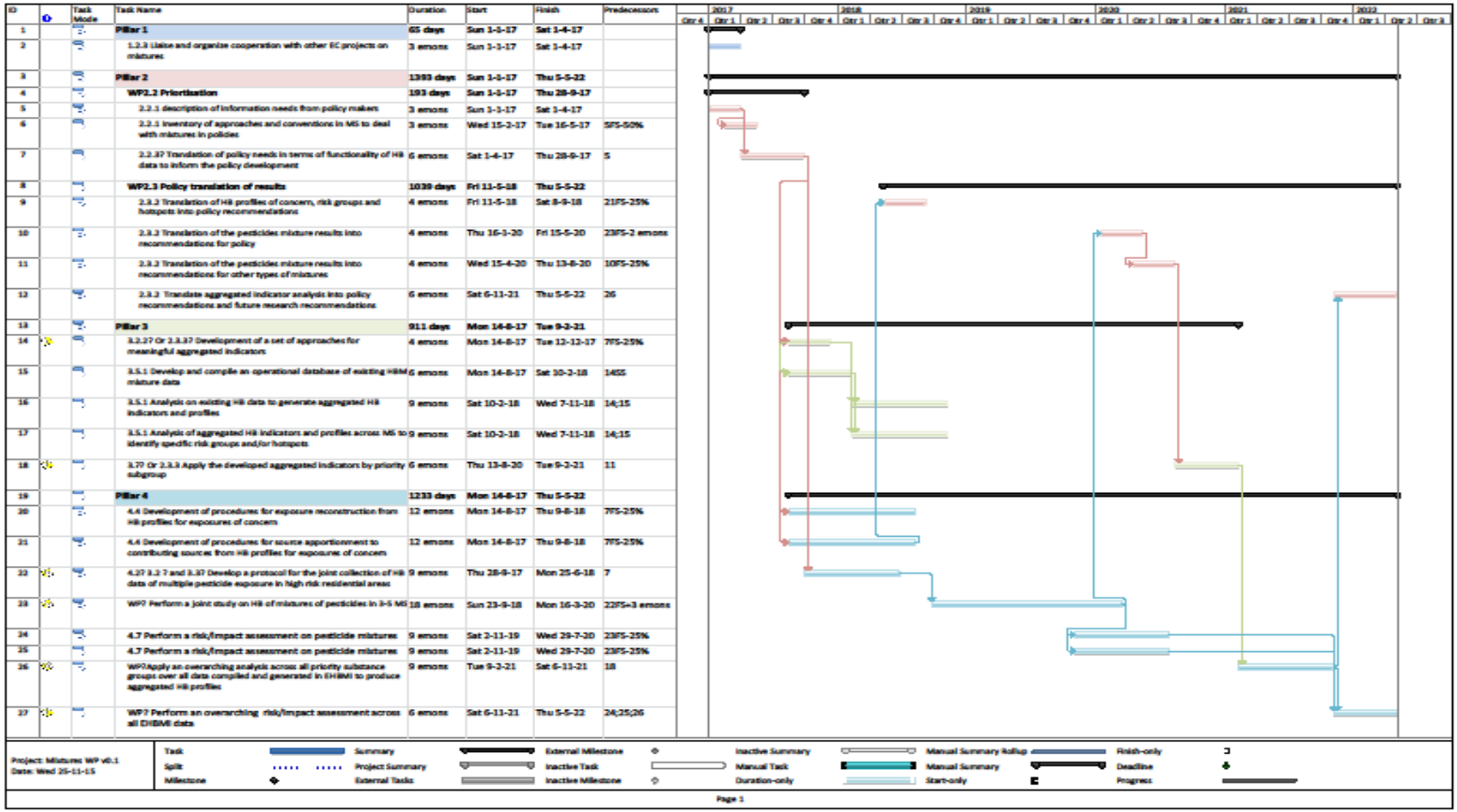
Gantt Charts Mixtures



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[ii] http://publications.jrc.ec.europa.eu/repository/handle/JRC97522

[iii] Ministry of Infrastructure and the Environment (2014). Explicitly dealing with safety' (in Dutch) Bewust Omgaan met Veiligheid, Rode Draden; Een proeve van een IenM-breed afwegingskader veiligheid. 's Gravenhagen, Ministry of Infrastructure and the Environment.