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WP 4 Prioritisation and input to the Annual Work Plan

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2. Introduction

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

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

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

Next steps. The current scoping documents will be further updated (month 12) and harmonised in the running of the HBM4EU framework, based on the following input that is expected:

- Improved definition and agreement on the criteria for categorisation (group A,B,C) of the substances in HBM4EU.
- New input of mapping of policy needs from EU policy board
- Input from the inventories and questionnaires within HBM4EU, that will provide information on existing gaps of knowledge.
- Feedback from the work package leaders on ‘research activities to be undertaken’ proposed in the scoping docs.
- Semi-annual reports of the HBM4EU activities within the work packages.

Furthermore it was agreed on the Chemical Group Leader meeting of March 2017 that the reporting of the outcome of HBM4EU activities per substance will be added to the scoping documents. This means that for each of the substance groups, the results of the work done in the different work packages, will be summarized by the respective chemical group leader, and reported in the next scoping docs update.

3. Prioritised substance group: Phthalates & DINCH

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3.1. Background information

3.1.1. Hazardous properties

Phthalates (also named phthalate esters or esters of phthalic acid) and their substitute Hexamoll® DINCH® are a group of plasticizers with a production volume of millions of tons per year. It has been shown that some phthalates cause a variety of adverse effects in humans and in laboratory animals.[1] Some phthalates are endocrine disrupting chemicals, as they have the ability to influence processes in the body which are controlled by hormones. Phthalates with three to seven (or eight) carbon atoms in the backbone of the side chains induce the so-called phthalate syndrome in rats, which covers different reproductive abnormalities in male offspring of rats exposed during pregnancy. The most potent representative is di-*n*-pentyl phthalate (DnPeP), followed by di(2-ethylhexyl) phthalate (DEHP), di-*n*-butyl phthalate (DnBP), di-*iso*-butyl phthalate (DiBP), butylbenzyl phthalate (BBzP), and dicyclohexyl phthalate (DCHP) with a comparable potency. Di-*iso*-nonyl phthalate (DiNP) has a somewhat lower potency to act as an endocrine disruptor.[2] It must be assumed, that similar adverse effects are also caused in humans (for more information see 2.4). It is important to note that mixtures of the above named phthalates have direct additive effects, which is important when it comes to risk assessment.[3]

3.1.2. Exposure characteristics

Phthalates like DEHP, DiNP, di-*iso*-decyl phthalate (DiDP) or di-2-propylheptyl phthalate (DPHP), made of alcohols with long alkyl chains are mainly used in polyvinyl chloride (PVC) plastics. The ones with shorter chains (or aryl rings) like DnBP, DiBP, BBzP, diethyl phthalate (DEP) or dimethyl phthalate (DMP) are also used in personal care products, textile industry, pesticides, lubricants and adhesives.[4] Since they are not chemically bound to the (plastic) materials, they can leach, migrate or evaporate into indoor air and atmosphere, foodstuff or other materials and so are of ubiquitous presence in the environment.[5] This is why plasticizers can be taken up by ingestion, inhalation and dermal contact, while the main source of exposure is via food originating from contamination and food contact materials.[6] Inhalation, exposure via ingestion of house dust by children and dermal contact (especially for the short chain phthalates) contribute to the overall exposure to a minor degree. Phthalate metabolites are present in every urine sample investigated. Levels found in children at least in Germany have in the past been so high that an impact on health could no longer be excluded with sufficient probability. In regard to occupational exposure there is only limited data on the exposure of workers to different phthalates in the plastic industry. Also, phthalate use in the industry has changed dramatically during the past decade due to regulatory restrictions, which means, that the exposure to old, well known phthalates (DEHP, DnBP etc.) in the industry has decreased.[4, 7] However, the workers may be significantly exposed to newer phthalates like DiNP and DPHP or substitutes like DINCH®.
Nevertheless, one can assume that people in Europe will be exposed to restricted phthalates in the future e.g. due to imports of plastic products.

3.1.3. Technical aspects

In the course of human biomonitoring of phthalates, the concentration of the degradation products (metabolites) are commonly analyzed in urine. Therefore it is important to have comprehensive knowledge on the metabolism of the respective compound.

3.1.4. Policy relevance

Due to the classification as reproductive toxicants category 1B under Annex VI to the Classification Labelling and Packaging (CLP) regulation DEHP, DnBP, DiBP, and BBzP are substances of very high concern (Annex XIV EC 1907/2006) and subjected to authorization under REACH. Furthermore DnPeP, DiPP, DHNUP, DnHP and DMEP (also see 2.2) are on the Candidate List of substances of very high concern for Authorisation (i.e. SVHC candidates) due to the same toxicological properties. The use of DEHP, DnBP, BBzP is restricted in all toys and childcare articles with a concentration limit of 0.1% by entry 51 of Annex XVII to REACH. In addition, DiNP, di-*n*-octyl phthalate (DnOP), 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. Current efforts for a further restriction of DEHP, DnBP, DiBP, and BBzP have been initiated by ECHA in the form of an Annex XV restriction dossier in April 2016.

For some of the phthalates human biomonitoring assessment values, namely Biomonitoring equivalents (BE) or HBM I values, have been derived – these are concentrations of biomarkers (metabolites) in urine, which reflect an acceptable chronic exposure, since the basic assumption is an equilibrium between external exposure and internal burden.[8] BE values have been derived for the Category A phthalates and HBM I values are available for DEHP, DPHP and DINCH.

3.2. Categorisation of substances

Table 1: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C substances (categorization see above)

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	DEHP	Di(2-ethylhexyl) phthalate	117-81-7	REACH Annex XIV; Annex XVII, Entry 51
	BBzP	Butyl benzyl phthalate	85-68-7	REACH Annex XIV; Annex XVII, Entry 51
	DnBP	Di-n-butyl phthalate	84-74-2	REACH Annex XIV; Annex XVII, Entry 51
	DiBP	Diisobutyl phthalate	84-69-5	REACH Annex XIV
	DiNP	Diisononyl phthalate	28553-12-0 / 68515-48-0	REACH Annex XVII, Entry 52; proposed for harmonised classification as Repr. 1B by DE
	DEP	Diethyl phthalate	84-66-2	CoRAP list
B	DiDP	Diisodecyl phthalate	26761-40-0 / 68515-49-1	REACH Annex XVII, Entry 52
	DnOP	Di-n-octyl phthalate	117-84-0	REACH Annex XVII, Entry 52
	DMP	Dimethyl phthalate	131-11-3	-
B	DnPeP	Di-n-pentyl phthalate	131-18-0	REACH Annex XIV

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
	DCHP	Dicyclohexyl phthalate	84-61-7	CoRAP list; currently under Substance Evaluation for potential ED properties
	DPHP	Di(2-propylheptyl) phthalate	53306-54-0	CoRAP list; currently under Substance Evaluation for potential ED properties
	Hexamoll®DINCH®	Diisononyl cyclohexane-1,2-dicarboxylate	166412-78-8	-
C	DiPP	Di-isopentyl phthalate	605-50-5	REACH Annex XIV
	DHNUP	Di-C7-11-(linear and branched)-alkyl phthalate	68515-42-4	REACH Annex XIV
	DnHP	Di-n-hexyl phthalate	84-75-3	SVHC candidate
	DMEP	Di(methoxyethyl) phthalate	117-82-8	REACH Annex XIV

3.2.1. Additional information by ECHA:

DnOP (category B): doesn't exist on the EU market. See page 14 of the ECHA review report: https://echa.europa.eu/documents/10162/31b4067e-de40-4044-93e8-9c9ff1960715

DHNUP (category C): It is not registered under REACH. There is almost no information available about this phthalate which suggests is not on the market or only has a very marginal market. E.g. Health Canada 2015: stopped at screening assessment because lack of exposure (https://www.canada.ca/en/health-canada/services/chemical-substances/challenge/batch-6/dhnup.html).

DMEP (category C): It is not REACH registered. We *(ECHA)* evaluate it is unlikely that there is significant use in the EU. Might not be the most appropriate to dedicate resources to.

3.3. Objectives / Policy related questions

1. Which are the most sensitive, reliable and cost effective methods and biomarkers to measure phthalates and DINCH?
2. What is the extent of the current exposure of the EU population to the 16 phthalates (Cat A, B and C) and their substitute DINCH?
3. Do the exposure levels differ significantly between the countries?
4. What are the main sources of exposure and the reasons for differences in exposure (different regulations in different countries) to phthalates and DINCH?
5. Are there different time trends for unregulated and regulated phthalates and DINCH? (Starting with Cat. A substances for which methods can be standardized in AWP 2)
6. How effective have the different mitigation steps and regulations been for phthalates?
7. Was the introduction of the Authorisation obligation under REACH effective enough to protect European citizen? Is there a sufficient decrease of the regulated Cat. A substance levels (GM/median) in the population (general/children?) from year 2007 until today (2017)? (DEHP, DnBP, DiBP, BBzP)
8. Had the restriction under REACH the favourable 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?
9. Is a ban of phthalates necessary or favourable?
10. How can HBM4EU results feed into the regulatory decisions of ECHA and EFSA?

11. 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?
12. Is the exposure to phthalates and their substitutes of health-relevance for the general population and vulnerable groups (inter alia children and pregnant women)? What part of the population has exposure levels exceeding the HBM guidance values - if existing- or TDI)?
13. Does the health relevance depend on age, gender and socio-economic status?
14. Can EU wide accepted HBM guidance values be derived for single substances and for the additively acting phthalates?
15. How can cumulative risks of phthalates and other anti-androgenic substances be assessed for their health relevance? Are their additive effects relevant for regulation?
16. What are knowledge gaps and related research needs for Cat. A substances to answer these questions sufficiently in the following years (Year 2)? Which substances have to be moved to Cat. B (or even C)?

Table 2: Listing of research activities to be carried out to answer the policy questions concerning phthalates & DINCH

Cat.	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
A	**DEHP**	Flanders 2007/08, 2013/14 (13-17 yr.): [9](rp); Germany 2003-06 (3-14 yr.): [10](rp) & 1988-2015 (20-29 yr.): [11]; workers 2012: [12]; Austria 2010-12 (6-15, 18-64, 65-81 yr.): [13]; Denmark 2006-12 (4-9, 5-20 yr., young men, pregnant women): [14]; France 2011 (pregnant women): [15]; Greece 2007/08 (new-borns): [16]; Israel 2011 (20-74 yr.): [17]; Slovakia 2015 (workers): [18]; Democophes: [19]	▸ The available data allow assertions concerning **routes of exposure and exposition in some regions**, but no EU wide statement is possible ▸ Taking into account, that data representative for population only are available from Flanders and Germany, WP10 should determine how many population based data are needed in order to measure the current burden and differences in phthalate levels between the countries (please see also **additional comments** below this table) ▸ Since there are **gaps in data on exposure for eastern Europe**, special attention should be paid on this ▸ **Full time series** are available from Germany – more data on trends in exposure are needed, at least over the last ten years ▸ More **studies on workers** are needed
	DnBP	[9], [10-11], [13], [14], [15], [16], [17], [18], [19b-g]	See DEHP
	DiBP	[10-11], [13], [14], [15], [16], [17], [18], [19b-e, 19g]	See DEHP
	BBzP	[9], [10-11], [13], [14], [15], [16], [17], [19]	See DEHP
	DiNP	[10-11], [12], [13], [14], [15], [16], [17], [19b, e, f]	See DEHP
	DEP	[11]1, [13], [14], [15], [16], [19a-d, 19f, g]	See DEHP; even more data on exposure are needed than for the phthalates which are on the Authorization List
B	**DiDP**	[11]1, workers DE: [12], [13], [14]	▸ No representative data available. Data available are from Austria and Denmark, and a time series from Germany (20-29 yr.) ▸ WP10 should determine **how many population based data are needed** in order to measure the current burden and differences in phthalate levels between the countries ▸ Analytical **method** cannot distinguish between DiDP and DPHP (see also DPHP)
	DnOP	[11]1, [13], [14]	▸ See DiDP
	DnPeP	[11]1, [13], [14]	▸ See DiDP

[1] ESB data available for 2007-2015. For DEHP, DNBP, DiBP, BBzP and DiNP there is a time series available from 1988-2015.

Cat.	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
B	**DMP**	[11]1, [19a]	▸ No representative data or data on workers available. Time series available from Germany (20-29 yr.). ▸ WP10 should determine **how many population based data are needed** in order to measure the current burden and differences in phthalate levels between the countries
	DCHP	[11]1, [13], [19a]	▸ No representative data or data on workers available. Data available are from Austria, plus a time series from Germany (20-29 yr.) ▸ WP10 should determine **how many population based data are needed** in order to measure the current burden and differences in phthalate levels between the countries
	DPHP	Method (for DPHP metabolites only, see DIDP): [20]; Time series: [21]	▸ No representative data or data on workers available. Time series available from Germany (1999-2012, 20-29 yr.). ▸ WP10 should determine **how many population based data are needed** in order to measure the current burden and differences in phthalate levels between the countries
	DINCH	Method: [22]; Exposure: SE, NO, PT, DE [23]; Time series DE: [24]	▸ First data show omnipresent exposure, but far below established health benchmark levels. Nevertheless, rapidly increasing exposures are to be expected, as shown in the time series from Germany. ▸ WP10 should determine **how many population based data are needed** in order to measure the current burden and differences in DINCH levels between the countries
C	**DiPP**		Studies on metabolisation are needed, in order to develop a method (analogies to DnPeP likely).
	DHNUP		See DiPP (analogies to HMW (high molecular weight) phthalates such as DEHP DiNP and DiDP likely)
	DnHP		See DiPP (analogies to DnPeP likely).
	DMEP		See DiPP

rp = representative for the (respective) population

3.3.1. Additional Comments:

a) Since most of the phthalates can be measured with one analytical method, future surveys should make use of this advantage in order to determine the EU wide exposure to these substances.

b) Surveyed data to be analyzed or published (in English)
- Spain: Adult working population, 18-65 years, n = 1880. Nation-wide representativeness. March 2009-July 2010
- Sweden: DEHP, DnBP, BBzP and DEP: Time series on children and population based study from 2010-2011 (Bjermo et al., report in Swedish)
- Belgium: FLEHS3: Data surveyed for DiBP and DEP

c) Data (representative for population) expectable from:
- France: Esteban (running since 2nd half of 2016): DEHP, DnBP, BBzP, DEP, DiNP, DnOP, DMP, DCHP.[25]
- Finland: FinHealth from 2017 on. 6000 samples planned: all Cat A substances and DiNP, DiDP, DnOP, DCHP, DPHP
- Germany: GerES V (children): 2015-2017, all Cat A and B substances

d) Information for Pillar 3:
- Like it was mentioned in the Background Information some phthalates (3 to 8 carbon atoms in the backbone of the side chain) have or are suspected to have anti-androgenic properties and as such induce developmental and reproductive malfunctions in rodent studies (phthalate syndrome). Those disturbances include malformations of the epididymis, vas deferens, seminal vesicles, prostate, external genitalia (hypospadias), and cryptorchidism (undescended testes) as well as retention of nipples/areolae (sexually dimorphic structures in rodents) and demasculinization of the perineum, resulting in reduced anogenital distance (AGD). Those effects can be ascribed to a disturbance of fetal testicular Leydig function, which results in significant reduction of testosterone levels.[2] Also the production of insulin like factor 3 in Leydig cells is disturbed by phthalates, which also causes anti-androgenic effects.
  Those effects are similar to the ones subsumed under the human testicular dysgenesis syndrome. However, there are no resilient data on humans, which is why epidemiological studies should try to prove the associations between a phthalate burden and adverse health effects.[26] Data from birth cohorts would probably meet some of the requirements, since the discussion on whether the health impacts can be traced back to in utero exposure or to exposure during childhood could be furthered. Among other endocrine effects in adults (differing for male and female individuals), phthalates are furthermore associated with respiratory problems and effects on blood pressure. For Category C phthalates a first step should be an assessment concerning the relevancy (are the people in Europe exposed or not?), before starting research activities in pillar 3 on those substances.
- Cumulative assessment
  Since a lot of relevant phthalates have similar toxicological profiles, a cumulative assessment is important in order not to underestimate risks. A decision is needed on which substances of the phthalate group should be included in such an additive approach. Basis for this should be similar adverse effects (function that is disrupted) and not only the mode of action.
  Further information by JRC: https://ec.europa.eu/jrc/en/publication/review-case-studies-human-and-environmental-risk-assessment-chemical-mixtures

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4. Prioritised substance group: Bisphenols

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4.1. Background Information

4.1.1. Hazardous properties

There is a large literature on the toxicity of bisphenol A including at low doses [reviewed in WHO and UNEP (2012), Gore et al. (2015), and Vandenberg (2014)]. Studies have indicated that it could be associated with increased risk for:

- Fetal development: miscarriages, decreased birth weight at term,
- Reproductive and sexual dysfunctions,
- Breast and prostate cancer or at least significant breast tissue remodelling. Studies have indicated that those effects were associated with gestational and neonatal exposure [Seachrist et al. (2016)].
- Altered immune system activity,
- Obesity and metabolic dysfunctions and diabetes in adults,
- Cardiovascular disease in adults
- Cognitive and behavioural development in young children.

Despite the wealth of studies, there are still controversies concerning the toxic effects of BPA. Those are related to some lack of reproducibility of the experimental studies possibly due to different designs. Different types of studies should be distinguished. Several studies (both experimental and human) have focused on perinatal exposure using different doses including low doses and monitoring a variety of outcomes [FitzGerald and Wilks (2014)]. In human there are several cohort studies associating perinatal exposure and child development. In addition, there are cross-sectional studies where associations were found between BPA exposure and metabolic and cardiovascular diseases. The latter studies have established association but cannot reveal a causal link between BPA and a toxic outcome. In conclusion, there is a real concern that BPA exposure could be linked to a variety of health outcomes in human, with different level of evidence depending on the outcome and the exposure period. Other Bisphenols have been less studied [Rochester and Bolden (2015)].

BPA elicits a variety of endocrine disrupting effects targeting steroid hormones as well as thyroid hormones. Several studies have explored the mechanisms of endocrine disruption. Initial studies have indicated an interaction with the nuclear ER alpha estrogen receptor with a relatively low affinity. Further studies have indicated an interaction with other receptors such ERbeta, ERRgamma and GPR32. An unresolved question is which of those receptors is involved in the low dose fetal effects of BPA.

4.1.2. Exposure characteristics

BPA is used in certain plastics, epoxy resins and thermal papers and is among the highest volume of chemicals produced world-wide. There is evidence that contamination can occur through

different routes, including food, water, air and skin (particularly in occupational exposure of cashiers). BPA has a relatively short half-life (hours); it is conjugated and believed to be inactive in that form, but there is concern that it may be locally deconjugated at the tissue level. There is a clear advantage in measuring free and conjugated forms both to address the possibility of external contamination during the assay and to better assess the active form of the substance.

There is solid evidence that a large majority of the human population is exposed to BPA. Many biomonitoring studies are available for bisphenol A (BPA) but the majority of the studies have a single measurement of exposure. These studies are useful in estimating the exposure to BPA in a particular population and follow time trends but not for risk assessment. Studies with multiple biological samples (usually pregnancy cohorts) have shown that BPA has poor Intraclass Correlation Coefficient (ICC) and therefore a single biological measurement can cause exposure misclassification. Further, there is a lack of consensus on how to deal with multiple samples in estimating the correct exposure. In addition, not all countries in Europe have biomonitoring data available on BPA. In DEMOCOPHES2, seventeen European countries participated, but BPA was added for a group of only 6 countries. BPA is analyzed in very few European birth cohorts in Germany, Norway, Spain and France [Casas et al. (2013)].

4.1.3. Policy relevance

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 materials and articles intended to come into contact with food [Commission Regulation (EU) No 10/2011], and the only EU restriction is for BPA in baby bottles [Commission Directive 2011/8/EU]. The EU is considering additional regulation of BPA in coatings and varnishes such as for the use of coatings in metal packaging and varnishes on screw caps. Additional measures have been taken in several countries. For example, France banned BPA in all food contact materials [French Law No 2012-1442], other countries like Denmark, Belgium and Sweden, banned it in those materials intended for children under 3.

Since 2017 BPA is on the Candidate List of substances of very high concern for Authorisation (SVHC candidates) as it is classified toxic for reproduction. Currently, France is preparing a dossier for the identification of BPA as a human ED-SVHC substance, and Germany for the identification as an environmental ED-SVHC substance.

There are also controversies between different agencies concerning the most protective Total Daily Intake (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 and Bolden (2015), Auerbach et al. (2016)]. Other bisphenol compounds are also manufactured and little is known about their toxicity and diffusion at this stage.

2 Demonstration Of A Study To Coordinate And Perform Human Biomonitoring On A European Scale – DEMOCOPHES (2010) http://www.eu-hbm.info/democophes

4.1.4. Technical aspects

Although BPA (and to a much lesser extent BPS and BPF) have been assayed in several human biomonitoring studies there is a need to harmonize procedures for sample handling, storage and analytical methodologies. Assays for conjugated and free substances should also be harmonized. The same holds true for other bisphenols.

Furthermore, external contamination during sample collection, handling and analysis is an important criteria during the evaluation of studies to be considered both for assigning reference values (HBM values) and risk assessment. For BPF and BPS, there are few biomonitoring studies available (see below) but there is a lack of literature for other bisphenols [Chen et al. (2016)].

4.1.5. Societal concern

In several countries and probably world-wide, BPA has been considered as the typical endocrine disruptor. In many cases, the societal concern towards EDCs is highly connected to the bisphenol case and to the campaigns to regulate BPA. Therefore there is a lot of expectations in this field. It is important to fill the gaps and to attempt to address the uncertainties, because the bisphenol case appears to be emblematic of the EDC. It is also associated with the Di-ethylstilbestrol scandal which is well known by the EU population. Similarly to Di-ethylstilbestrol, BPA is considered as a threat for pregnant women, the fetus and young children. Whatever we achieve with bisphenols will actually be useful for all EDCs and for the role of public authorities in protecting pregnant women and the next generations.

4.2. Categorisation of Substances

Table 3: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C substances (see above)

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	BPA	4,4'-isopropylidenediphenol	80-05-7	REACH Annex V; Annex XVII, Entry 66 PACT list entry 13/04/2017: Hazard assessment. Scope: ED. OSH Legislation: Consumer uses, Article service life, Widespread uses by professional workers, Formulation or re-packing, Uses at industrial sites, Manufacture, Signs at work, CAD, Young workers, Pregnant or breastfeeding workers. Environmental legislation: Classified Seveso Waste Directive Annex III Professional and consumer legislation: Cosmetics (EC) No 1223/2009 Annex II; Toy safety Directive Appendix C
B	BPS	4,4'-sulphonyldiphenol	80-09-1	CoRAP list PACT list entry 01/04/2015: Hazard assessment. Scope: ED. OSH Legislation: Article service life, Formulation or re-packing, Uses at industrial sites, Manufacture.
	BPF	4,4'-methylenediphenol	620-92-8	REACH Annex III Inventory PACT list entry 01/10/2015: RMOA. Scope: ED. Under development OSH Legislation: CAD
C	BPB	4,4'-(1-methylpropylidene) bisphenol	77-40-7	REACH Annex III Inventory PACT list entry 07/03/2017: RMOA. Scope: ED. Under development OSH Legislation: CAD
	BPAF	4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene] diphenol	1478-61-1	REACH Annex III Inventory PACT list entry 01/10/2015: RMOA. Scope: ED. Under development OSH Legislation: CAD Environmental legislation: Classified Seveso

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
C	BPAP	4,4'-(1-Phenylethylidene)bisphenol	1571-75-1	REACH Annex III Inventory OSH Legislation: CAD Environmental legislation: Classified Seveso Waste Directive Annex III
	BPBP	2,2-bis(2-hydroxy-5-biphenylyl)propane	24038-68-4	-
	BPC	4,4'-isopropylidenedi-o-cresol	79-97-0	REACH Annex III Inventory
	BPCI2	4,4'-(dichlorovinylidene) diphenol	14868-03-2	REACH Annex III Inventory OSH Legislation: CAD
	BPE	4,4′-Ethylidenebisphenol	2081-08-5	-
	BPPH	4,4'-Dihydroxytetraphenyl-methane	1844-01-5	-
	BPM	4,4'-(1,3-phenylene-bis(1-methylethylidene))bis-phenol	13595-25-0	CoRAP list PACT list entry 02/02/2017: Hazard assessment. Not ED. OSH Legislation: Article service life, Uses at industrial sites, Manufacture, Signs at work, CAD, Pregnant or breastfeeding workers. Environmental legislation: Classified Seveso Waste Directive Annex III
	BPP	4,4'-(1,4-Phenylenediisopropylidene) bisphenol	2167-51-3	REACH Annex III Inventory OSH Legislation: CAD
	BIS2	Bis(2-hydroxyphenyl)methane	2467-09-9	-
C	DHDPE	p,p'-oxybisphenol	1965-09-9	REACH Pre-Registration process OSH Legislation: CAD, Young workers. Waste Directive Annex III

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
	BPFL	9,9-Bis(4-hydroxyphenyl)fluorene	3236-71-3	REACH Registration Dossier OSH Legislation: CAD Environmental legislation: Classified Seveso Waste Directive Annex III
	BPZ	4,4'-cyclohexylidenebisphenol	843-55-0	REACH Annex III Inventory OSH Legislation: CAD, Pregnant or breastfeeding workers. Environmental legislation: Classified Seveso
	BP4,4’	Biphenyl-4,4'-diol	92-88-6	REACH Registration Dossier OSH Legislation: Widespread uses by professional workers, Uses at industrial sites, CAD, Young workers. Environmental legislation: Classified Seveso Waste Directive Annex III Professional and consumer legislation: Plastic contact with food (EU) No 10/2011 Annex I

4.3. Objectives / Policy-related questions

There are several critical questions concerning bisphenols that need to be resolved. The first is whether different regulations in different countries lead to different internal exposure values and whether the increasingly frequent use of substituents has led to increased exposure and to the presence of mixtures of bisphenols in humans. The second is identify safety values taking into consideration the accumulating knowledge on Bisphenol toxicity particularly at low doses. A third question is whether substitutes are safer than BPA considering their hazardous properties and current and expected exposure to those compounds.

Specific objectives are:

1. To identify existing analytical methods allowing to monitor in human matrices BPA, BPS, BPF and possibly other bisphenols, as well as the necessary gaps to be fulfilled in terms of method development/validation.
2. To urgently harmonize procedures for sample handling, storage and analytical methodologies for BPA, BPS and BPF to minimize external contamination. Encourage European countries to participate in inter-laboratory comparisons.
3. To map already available biomonitoring data in Europe to find out which countries lack this kind of data and to evaluate the quality of the available data such that design of future biomonitoring studies can be improved accordingly.
4. To use already available biomonitoring data to answer questions like: What are the minimum number of samples required per individual to estimate the correct exposure to BPA? How to deal with multiple samples in estimating the correct exposure?
5. To follow the time and spatial trends for Bisphenols: what is the current exposure of the EU population to BPA, BPS and BPF and possibly other bisphenols? What are the reference values for EU population?
6. To determine whether different regulatory controls across EU MS lead to different exposures.
7. To determine whether current or expected exposure 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 BPA substitutes? Is there a gender difference in relation to health risks? What are the most exposed subgroups? What is the evidence for low-dose effects? Are AOP for those compounds similar to those of BPA?
8. To identify effect biomarkers associated to bisphenol exposure and to determine whether those effect markers are common to all bisphenol compounds
9. To identify exposure pathways for bisphenols and toxicokinetic characteristics of those compounds
10. To determine the effect of combined exposures to substance mixtures within the bisphenol family and with other families and whether this should impact health guidance (in food contamination, cosmetics, other plasticizers, etc.).
11. To derive EU-wide health based guidance values for BPA and other bisphenols. How can this feed into an assessment of the Tolerable Daily Intake (TDI) for BPA of 4 µg/kg/day as set by the European Food Safety Authority (EFSA)?
12. To determine age and gender specific health effects of BPA.
13. To find out whether BPA occupational exposure of cashiers is a health concern. To feed into the Commission decision on whether to ban BPA in till receipts, as recommended by ECHA's Committee for Socio-Economic Analysis (SEAC).
14. As longer term goal, it will be important to eliminate legacy BPA from material cycles (i.e. waste till receipt rolls) when implementing a circular economy in order to protect human health

4.4. Research activities to be undertaken

Table 4: Listing of research activities to be carried out to answer the policy questions concerning bisphenols

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
BPA	**Germany** 1995-2009, (20-29 yr.- urine & plasma): **[Koch et al. (2012)]** & 2003-2006 (GerES IV), (3-14 yr.- urine): **[Becker et al. (2009)]** (*rp*); **Belgium, Flanders** 2007-2012 (14–15 yr.): **[Geens et al. (2014)]** (*rp*) & 2011-2012 (DEMOCOPHES), (6-12yr., mothers, pregnant women- urine): **[Covaci et al. (2015) and 3XG (2013)]** & 2012-2015 (FLEHS 3), (50-65 yr.-urine): **[Steunpunt Milieu en Gezondheid (2015)]**; **Norway** 2012, (food): **[Sakhi et al. (2014)]**; **Greece** 2009-2011, (mother-child pairs: 2yr., pregnant women- urine): **[Myridakis et al. (Oct. 2015)]** & 2011-2014, (children <18yr., adults- hair): **[Tzatzarakis et al. (2015)]** & 2012 (2.5-87 yr. X̄=49yr.- urine) **[Asimakopoulos et al. (Feb. 2014)]** & 2014, (adult males, anonymous individuals- urine, serum)- analytical method: **[Myridakis et al. (Feb 2015), Asimakopoulos and Thomaidis (2015) and Asimakopouloset al. (Jan. (2014)]** & 2014 (Developing foetus, neonates, infants, children and adults- plasma, urine) -continuous lifetime model: **[Saringiannis et al. (2014)]**; **Austria** 2008-2011, (mother- children pairs: 6-11yr., 25-50 yr.-urine): **[Hohenblum et al. (2012)]** & 2010-2012, (6-15 yr., 18-64 yr., 65-79 yr.- urine): **[Hartmann et al. (2016)]**; **Sweden** 2008-2009 (food, young women-serum): **[Gyllenhammar et al. (2012)]** & 2010-2011, (18-80 yr.-urine): **[Bjermo et al. (2013)]** & 2010-2013, (17-19 yrs.-urine)-time series:**[Jönsson et al. (2014)]** & 2011-2012 (DEMOCOPHES) (mother-child pairs: 6-11yr.,<45yr.-urine): **[Larsson et al. (2014)]** 1996-2011, (first-time mothers-blood serum): **[Gyllenhammar et al (2012) Tidstrend 1996-2011]** **Czech republic** 2015, (35.8±4.7 yr.-plasma, seminal plasma) analytical method: **[Vitku et al. (2015)]** & 2000-2006, (canned foodstuffs, migration)-analytical method: **[Poustka et al. (2007)]** & 1999-2000 (water samples & river sediments): **[Stachel et al. (2003)]**; **France** 2011, 2013 (Blood, urine, amniotic liquid, tissue extracts) - analytical method: **[Lacroix et al. (2011), Viguie et al. (2013) and Gayrard et al. (2013)]** & 2013-2016, (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]** & 2003-2006, EDEN cohort (pregnant women-urine): **[Philippat et al. (2014)]** & 2011 ELFE cohort (pregnant women on delivery-urine) **[Dereumeaux et al. (March 2016) and Dereumeaux et al. (Dec. 2016)]**.	***Ongoing in different WPs***

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
BPS	**Belgium, Flanders** 2012-2015 (FLEHS 3), (50-65 yr.-urine): **[Steunpunt Milieu en Gezondheid (2015)]** method development; **Sweden** 1996-2011, (first-time mothers-blood serum): **[Gyllenhammar et al (2012) Tidstrend 1996-2011]**; **France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPF	**Sweden** 1996-2011, (first-time mothers-blood serum): **[Gyllenhammar et al (2012) Tidstrend 1996-2011]**; **Czech republic** 2000-2006, (canned foodstuffs, migration)-analytical method: **[Poustka et al. (2007)]** & 1999-2000 (water samples & river sediments): **[Stachel et al. (2003)]**; **France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPB	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPAF	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPBP	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPC	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPCl2	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPE	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPPH	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPM	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPP	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BIS2	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
DHDPE	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
BPFL	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BPZ	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***
BP4,4'	**France** 2013-2016 (Mother-premature infants-human breast milk): **[Deceuninck et al. (2015)]**;	***Ongoing in different WPs***

rp = representative for the (respective) population

First activities needed to rapidly answer policy question:

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.

Moreover, 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 first focus on the safety and actual exposure of the EU population to 2 substituents of BPA: BPS and BPF. This initial work will develop along the following subtasks:

- 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. First a validated analytical method is urgently needed as mentioned in the objectives. Thus, it should be evaluated whether the collected biomonitoring data will provide information on current exposures in EU. Larger and more representative studies could be conducted in the future, but we can already fund the analysis 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, high quality national studies, studies including several samples per individual to account for intra-individual variability, studies with available or planned health outcomes. Studies should be focused on women of child bearing age, children and adolescents. 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. The linkage with effect biomarkers could be explored in human samples as well as mixture effects. This project is relevant to task 13.1, 14.3 and 15.3.

Such studies should be planned in the first half of the initiative and could be carried either within the WP activities or through an internal call.

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5. Prioritised substance group: Per- and polyfluoroalkyl substances (PFASs)

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5.1. Background Information

5.1.1. 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 extremely persistent, bioaccumulative and toxic. Many have been detected globally in the environment, biota, food items, and in humans (OECD, 2015). It has been recognised more recently that shorter chain PFAS, increasingly used as alternatives are also very persistent and thus very mobile in the environment, presumably leading to ground water contamination in future. To date many known and unknown alternatives of the so far regulated PFASs are used worldwide leading to environmental contamination und increasing human body burdens.

5.1.2. Hazardous properties:

PFASs bind to proteins and partition to phospholipids. The elimination kinetics are highly species dependent, with humans showing the longest half-lives of up to e.g. 8.5 years for PFHxS. A recent publication reports an estimated elimination range of 10.1 to 56.4 years – median 15.3 years for Cl-PFESA (Shi et al., 2016). The CLP human health hazard classifications of the different substances are depicted in table 1. Substances which are best-known, PFOS and PFOA, are classified as carcinogenic (Carc. 2, suspected human carcinogens), toxic for reproduction (Repr. 1B, presumed human reproductive toxicants; Lact., may cause harm to breast-fed children), toxic to specific target organs (STOT RE 1, specific target organ toxicity – repeated exposure) and acute toxic (Acute Tox. 3-4) for different exposure routes. PFOS and PFOA belong to the so called long-chain perfluorinated compounds, which refers to perfluorocarboxylic acids with carbon chain lengths of 8 and higher, including perfluorooctanoic acid (PFOA); perfluoroalkyl sulfonates with carbon chain lengths of 6 and higher, including perfluorohexane sulfonic acid (PFHxS) and perfluorooctane sulfonate (PFOS); and precursors of these substances that may be produced or may be present in products.

Several long-chain compounds beside PFOS and PFOA have also been identified as toxic to reproduction; further endpoints concern carcinogenicity, liver toxicity, neurotoxicity and immunotoxicity. Whether numerous other non-regulated PFASs show similar toxicity is currently less well established. In many cases data availability is poor and therefore no classification is possible. However, persistence is assumed to concerns largely all PFASs by reason of the extreme strength and stability of the carbon-fluorine bonds.

For PFOS and PFOA adverse effects on thyroid metabolism and lipid metabolism have been reported in a multitude of epidemiological studies suggesting endocrine disrupting potential.

Additional concerns include increased risk of miscarriage, reduced birth weight, increased weight in adult life, 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).

Grandjean and Clapp (2015) documented carcinogenicity, immunotoxicity and developmental toxicity of PFOA and highlighted the endocrine disrupting effects. A recent publication describes prenatal exposure to perfluoroalkyl substances and reduction in anogenital distance in girls at 3 months of age in a Danish mother-child cohort (Lind et al. 2017).

Since PFOS and PFOA can still be measured in highest concentrations in biota and in humans, exerting similar toxic effects along with and similar to a range of long-chain PFASs measured in blood, together with a range of unidentified PFASs the possibility of mixture effects is very high.

5.1.3. Policy relevance

Current regulatory actions within the European Union and elsewhere mainly concern PFOS and its derivatives (POP regulation, Commission Regulation (EU) No 757/2010) and PFOA (upcoming EU restriction of PFOA and PFOA-related substances; PFOA and PFOA-related substances are currently under review as global POPs under the UNEP-Stockholm Convention). Certain per- and polyfluorinated substances can be degraded to persistent perfluorinated substances like PFOS or PFOA under environmental conditions or in humans and are therefore precursors. OECD (2007) lists e.g. 165 PFOS and related substances including derivatives and polymers of perfluorooctane sulfonate, perfluorooctane sulfonamide and perfluorooctane sulfonyl chemicals. Additional identities of PFOS- and PFOA-related substances can be found in ECHA (2014), Buck et al. (2011), Environment & Health Canada (2012), OECD (2011) or U.S. EPA (2006). With the current and upcoming regulations on PFOS and PFOA also these precursor substances are subject to the EU restrictions.

Another restriction proposal for long-chain PFCAs is currently under development covering perfluorononan-1-oic acid (PFNA), nonadecafluorodecanoic acid (PFDA), henicosafluoroundecanoic acid (PFUnDA), tricosafluorododecanoic acid (PFDoDA), pentacosafluorotridecanoic acid (PFTrDA), heptacosafluorotetradecanoic acid (PFTDA), including their salts and precursors. Several long-chain PFASs are on the Candidate List of substances of very high concern (SVHC) under REACH: nonadecafluorodecanoic acid (PFDA) and its sodium and ammonium salts (Reprotox. (57c) and PBT (57d)), nonadecafluorodecanoic acid, decanoic acid, nonadecafluoro-, sodium salt, ammonium nonadecafluorodecanoate, perfluorononan-1-oic-acid and its sodium and ammonium salts (Reprotox (57c)), perfluorononan-1-oic-acid, sodium salts of perfluorononan-1-oic-acid, ammonium salts of perfluorononan-1-oic-acid, ammonium pentadecafluorooctanoate (APFO) (Reprotox. (57c) and PBT (57d)), henicosafluoroundecanoic acid (C11-PFCA) (vPvB (57e)), and heptacosafluorotetradecanoic acid (C14-PFCA) (vPvB (57e)). Other widely used substances are still under substance evaluation or are foreseen to be regulated under REACH, such as PFSAs (PFHxS, PFBS), ADONA, 6:2 FTMA and several short-chain PFCAs (C_4-C_7). For Cat A-C substances, regulatory actions are depicted in table 1.

Further (regulatory) activities, which have been highlighted as necessary but not yet sufficiently covered, should address fluoropolymers and fluoroethers, including monitoring to support the ongoing regulatory work (Pelthola-Thies, 2017). According to KEMI (2015) less than 2 percent of the 3,000 on the global market available PFAS are registered under REACH.

The current workplan for regulatory activities of PFASs under REACH/CLP proposed by ECHA is a group–wise as well as an arrow head approach. Aim is to identify the precursors of the respective "arrow head" substance which is the terminal degradation product that is object of the regulatory action which should cover the precursors – and group of precursors already identified.

According to ECHA is additional work at a more generic level needed considering the high amount of precursor types. Further information on PFASs from imported articles is needed as well as work on fluoropolymers and fluoroethers to clarify if those can be perceived as PFASs precursors (Pelthola-Thies 2017).

PFASs are also relevant within the remit of the European Food Safety Authority (EFSA): as food contact materials, food flavourings on one hand and food contaminants on the other. Recently, EFSA has been asked to prepare an opinion on the human health risks of the presence of PFASs in food. Results are expected mid-2017; preliminary results suggest that from the 27 substances under investigation refined chronic dietary exposure estimates can only be calculated for 11 substances. To date, it is not known for which compounds sufficient documentation, including reliable modelling results, will be available to derive health-based guidance values (Johanson 2017). Various PFASs are used as food contact materials, and also as flavouring in food, e.g. one of the flavourings currently approved unter Regulation No 1334/2008 is a polyfluorinated organic chemical (FL16.119, N-(2-methylcyclohexyl)-2,3,4,5,6-pentafluorobenzamide).

There are voluntary agreements with industry in Canada or the USA to phase out PFASs C8 chemistry like the U.S. EPA Stewardship Programme3.

PFASs have been recognized as an issue for concern under SAICM (Strategic International Approach to International Chemicals Management)4. The OECD has established a web portal in order to facilitate information exchange among stakeholders5.

5.1.4. Exposure characteristics

Trends in production volume/environmental concentrations

A minor part of the family of PFASs are perfluoroalkyl acids (PFAA), perfluoroalkylcarboxylic acids (PFCA), perfluoroalkane sulfonic acids (PFSA), compounds derived from perfluoroalkane sulfonyl fluoride (PASF), fluorotelomer (FT)-based compounds and per- and polyfluoroalkylether (PFPE)-based compounds. Another presumably major part are polymers (fluoropolymers (FPs), side-chain fluorinated polymers and perfluorpolyethers (PFPEs)) (OECD 2013). According to KEMI (2017) there are 2,817 PFASs on the market. For only 15 % of them adequate data are available; whereas for 40% data are missing (KEMI 2017). Many fluorinated substances enter the EU through the import of articles (e.g. textiles) and for the most part these are not monitored (KEMI 2015) providing an indirect exposure source. The lack of data concerns identification, use and exposure beside from toxicity and ecotoxicity. Among the new chemical groups, fluoro silicones, perfluoro polyethers and perfluoro alkanes are under discussion. Recent uses comprise surfactants, repellents, uses in textile and leather-, paper and electronic industry, cosmetics, pesticides, lubricants, pharmaceuticals and printing (Fischer, 2017). For the large group of polymers no data are available at all, as polymers are not covered within REACH.

3 https://www.epa.gov/assessing-and-managing-chemicals-under-tsca

4 http://www.saicm.org/EmergingPolicyIssues/Perfluorinatednbsp;Chemicals/tabid/5478/language/en-US/Default.aspx

5 http://www.oecd.org/ehs/pfc/#Purpose_of_Web_Portal

However, there are concerns from the scientific point of view that at least some groups of polymers may also be degraded into persistent PFASs. For example fluorinated side-chains can be lost through ageing and environmental conditions.

Environmental behaviour: half-lives in environment/ transport
Perfluoroalkyl and perfluoroether moieties of PFASs are highly persistent under environmental conditions. All PFASs ultimately degrade into highly persistent end products. PFASs are ubiquitously detected in the environment. Whereas most data are available for the small group of long-chain PFASs, non-reversible environmental exposure has to be considered for a by far larger group.

There are also concerns about short-chain PFASs, which are less bioaccumulative but very persistent and mobile contaminants found in drinking water and food, including vegetables.

Human-related exposure sources and uses, human exposure routes
Humans can be exposed directly (via diet, drinking water, consumer products etc.) and indirectly through transformation of «precursor substances» such as polyfluoroalkyl phosphate esters (PAPs), fluorotelomer alcohols (FTOHs), fluorotelomer iodides (FTIs), and fluorotelomer acrylate monomers (FTAcs). These fluorotelomer-based substances biotransform to yield PFCAs, yet also form bioactive intermediate metabolites, which have been observed to be more toxic than their corresponding PFCAs (e.g. Rand et al. 2017).The precursor contribution to PFASs daily exposures was recently estimated for a high exposure scenario to contribute up to >50% to individual PFCAs like PFOA or PFDA, whereas it is considerable lower up to 10% for e.g. PFOS for a low exposure scenario (Gebbink et al. 2015).

Human biomonitoring (HBM) data availability
Human exposures to PFASs have been reported in numerous studies in Europe and worldwide. Most of these studies were focused on blood or breast milk concentrations of PFOS and PFOA, while others also included PFBS, PFHxS, PFDS, PFBA, PFPeA, PFHxA, PFHpA, PFNA, PFDA, PFUdA, PFDoA, PFTrDA, PFTeDA, FOSA, MeFOSA, N-EtFOSA, N-EtFOSAA and diPAP. On the other hand, human exposure to e.g. 8:2 diPAP, 6:2 diPAP, 8:2 PAP, 6:2 PAP, PFDPA, PFOPA, PFHxPA or ADONA has been addressed to a small extent only; the majority of new fluorinated compounds that enter the market as replacements has not been measured in human matrices yet. Concerning PFOS the effectiveness evaluation under the UNEP Stockholm Convention concluded that for human matrices from Western Europe, Canada, Australia and Asia-Pacific countries levels seem gradually declining. Although PFOS is measured at low concentrations in human breast milk and is better detected in human blood, there are good correlations between the measurement results in these two matrices (UNEP, 2016).

Several studies investigated time trends of PFAS exposure in European countries. According to Axmon (2014) investigating plasma samples from 1987 -2007 in Sweden there was a peak in PFOS and PFOA blood concentrations around 2000 and increasing PFHxS, PFNA, PFDA and PFUnDA concentrations within the whole period (Axmon et al. 2014). Also Glynn reported increasing concentrations of PFBS, PFHxS, PFNA and PFDA in Swedish breast milk samples between 1996 and 2010 (Glynn et al., 2012). This is also in line with the study from Gebbink who reported increasing trends in pooled serum samples from Sweden for PFHxS, PFNA, PFDA, PFUnDA, PFODA and PFTrDA (Gebbink et al.2015). Analyses of serum samples from Norway from 1979 to 2007 documented decreasing concentrations of PFOS and PFOA from 2001 onwards, whereas PFNA, PFDA, PFUnDA were increasing, for PfHxS and PfHpS no trend could be observed (Nost et al. 2014). In Denmark seven PFASs (PfHXS, PfHpS, PFOS, PFOA, PfNA, PfDA, PfUnDA) decreased in the period 2008 – 2013 (Bjerregaard-Olsen et al. 2016). Schröter-

Kermani reported decreasing concentrations from 2001 onwards for PFOS, from 2008 for PFOA and from 2005 for PfHxS and stable concentrations for PFNA in samples from Germany from 1982 to 2010 (Schröter-Kermani et al. 2013). Also Yeung et al. (2013) observed decreasing concentrations for PFOA after 2000, and increasing concentrations for PFNA, PFDA and PFUnDA, no significant trend was observed for PFHXS and 8:2 di-PAPs (Yeung et al. 2013).

There are major knowledge gaps on alternatives currently used by industry; these knowledge gaps concern production volumes, use, fate and behaviour, and toxicity (Danish EPA 2013, Wang et al. 2013, 2016, 2017). Known fluorinated alternatives can be categorized into two groups, namely [i] shorter-chain homologues of long-chain PFAAs and their precursors and [ii] functionalized perfluoropolyethers (PFPEs), in particular perfluoroether carboxylic and sulfonic acids (PFECAs and PFESAs) (Wang et al. 2015). Perfluoroalkyl phosphonic and phosphinic acids are also used as alternatives in certain applications. PFPAs are likely to be persistent and long-range transportable, whereas PFPiAs may be transformed to PFPAs and possibly PFCAs in the environment and in biota (Wang et al. 2016).

In environmental samples fluorotelomer-based substances were identified as the most relevant precursors of PFCAs based on the frequency of detection and the concentration of FTOHs, biotransformation intermediates (e.g. FTUCAs and FTCAs) and persistent biotransformation products (e.g. x:3 acids and PFCAs) (UBA, 2016).

Health based guidance values available for HBM data

In the REACH restriction dossier on PFOA internal DNELS6 were derived based on different endpoints in animal and human studies. The respective values derived for the general population were in the range of 0.3 ng/ml and 277 ng/ml (ECHA 2014). The Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) has finally derived a DNEL of 800 ng/ml for the general population, arguing that a DNEL cannot be reliably derived from some effects that may be more sensitive than the animal data currently used in the risk characterisation (ECHA 2015). The German Human Biomonitoring Commission has published a re-assessment of the HBM values of PFOS and PFOA in 2016. The HBM I value represents the concentration of a substance in human biological material below which no risk for adverse health effects over life time is expected (HBM Commission 2014). The respective HBM I values are 2 ng PFOA/ml and 5 ng PFOS/ml blood plasma (HBM Commission 2016). The HBM Commission has decided to use the existing POD ranges of 1 to 10 ng/ml as a basis and selected 2 ng/ml comprising the HBM I value for PFOA, pointing to the consistency of results from animal and epidemiological studies.

Within the scientific community discussions on the most sensitive health endpoints are still ongoing, effects on immune system and on cholesterol levels might occur at even lower exposure concentrations. Results of the ongoing EFSA assessment are expected in autumn 2017.

6 DNEL: Derived No Effect Level:

5.1.5. Technical aspects

Biomarkers available for parent compounds or metabolites in human matrices, and main characteristics of analytical methods (quantitative, semi-quantitative…)

Analytical targets for the analysis in biomonitoring studies can include the parent compound, its metabolite(s) and transformation product(s) or other chemical products formed in the body or the environment. Known PFASs were mostly analysed by high performance liquid chromatography coupled with tadem mass-spectrometry (HPLC-MS/MS). FTOH and FTOH precursors (FTMAC and PAPs) and their metabolites can be measured by targeted methods, by low or high resolution mass spectrometry. Methods for possibly cationic PFAS (such as betaines used e.g. in firefighting foams) can be analysed using specific methods used for environmental matrices. Analyses of FTMAC require derivatisation, followed by gas chromatography coupled with mass-spectrometry (GC-MS) analysis (Trier, pers. comm. 2017, Fields 2012). In recent years, several studies on total fluorine (TF), inorganic fluorine (IF), exactable organic fluorine (EOF) and specific known PFASs in environmental and blood samples were conducted. Usually, TF, IF and EOF were fractionated and measured by combustion ion chromatography (CIC). It has been shown that PFOS was still the dominant PFAS contributing up to 90% to known PFASs in 30 blood samples sampled in three Chinese cities in 2004. PFOS, PFHxS, PFOSA, PFDoDA, PFUnDA, PFDA, PFNA, PFOA, PFHpA, PFHxA contributed 33 to 85% to total EOF (Yeung et al. 2008). In 2016 Yeung and Mabury investigated blood samples from China and Germany to identify concentrations of EOF and 52 specific PFASs including including PFSAs, PFCAs, PFPAs, PFPiAs, FTSAa, PAPs, FTCAs/FTUCAs, di-SAmPAPs, FASAs, FOSAA and N-alkyl-FOSAAs. PFSAs represented the majority of EOF with decreasing contribution: 70% in 1982, 60% in 2003, 25% in 2009. Mass balance analysis between EOF, which provides an estimate of all fluorinated substances, and known quantifiable PFASs in human blood samples have shown the presence of unidentified organofluorides up to 80%. These findings suggest that other PFASs (e.g. precursor or intermediate compounds) might be significantly important (Yeung and Mabury 2016). A detailed description of the study results can be found elsewhere (Miyake et al. 2007a, Yeung et al. 2008, 2009, Yeung and Mabury 2016)

However, these methods may not allow distinguishing between PFASs exposure and fluorine based medication. This concern is particularly related to the fact that many pharmaceuticals may contain fluorinated moieties to make them more persistent in human bodies (Wang, pers. Comm. 2017).

In best of our knowledge, it is not feasible and reasonable to measure all relevant PFAA precursors due to a lack of an overview on which precursors are being produced and used and to which ones humans are exposed to at the moment. Considering that most precursors would be transformed into acids in human body, it would be an interesting approach to measure the “total oxidisable precursors” in human matrices. The “total oxidisable precursors” methods have been used to reflect the total exposure to PFAAs and PFAA precursors in a number of environmental samples. Due to its nature of radical reactions with a large, complex mixture, the methods may not easily or never be standardised and the results may not be reproducible. However, it might be a semi-quantitative indicator to demonstrate PFAAs exposure stemming from the variety of precursors (Wang, pers. Comm. 2017).

Further analytical methods to simultaneously analyse as many PFASs as possible should be developed (Wang et al. 2016).

5.1.6. Societal concern

PFASs are widely used in society and be as a whole group a cause for concern. Individual PFASs or their degradation products are extremely persistent in the environment and for some it was proven to be very mobile, bioaccumulative and toxic, whereas for several others there is only some indication as scientific proof is lacking at present. Nevertheless, many PFAS, including fluorinated alternatives to long-chain PFASs, can be ubiquitously detected in the biotic and abiotic environment, wildlife and humans, even in remote regions such as the Arctic since several years. Recently, in several countries PFASs have been found in ground and drinking water (KEMI 2017). Currently there are several contamination cases known in different countries (e.g. Germany, Sweden, Italy, and Netherlands). It can be assumed that also in the majority of the European and associated countries PFASs contamination in certain areas is a so far unidentified issue. In early 2017, an news alert has been published in *Science for Environment Policy* titled “Europe's rivers ‘highly contaminated’ with long-chain perfluoroalkyl acids”, stating that all large European rivers are highly contaminated with perfluoroalkyl acids and further, that European environmental quality standards for PFOS are exceeded in all of them (EC 2017). Furthermore, there is a strong indication that PFASs are increasingly used in chemical products, processes and articles, and that they are more and more detected in various environmental matrices. The knowledge about their specific uses and therefore the sources of emissions as well as hazard and risk is poor for many of the substances in this group (KE~~R~~MI 2017). Especially very limited knowledge in the public domain on the structures, properties, uses and toxicological profiles of fluorinated alternatives is available. The levels of some fluorinated alternatives or their degradation products, such as perfluorobutane sulfonic acid (PFBS) or perfluorobutanoic acid (PFBA), have been shown to be rising in the environment and human tissues in recent years in Europe (Scheringer et al. 2014). Fluorotelomer market size estimations predict increasing demands globally as well as a rise in the consumption as shown by Global Market Insights (2016). The number of approved patents in the US with “perfluor” in the patent text has raised to more than 400 per month (Fischer, 2017).

One of the major societal concerns is the irreversibility of contamination, together with endocrine disrupting effects, carcinogenicity, toxicity to reproduction, effects on immune system and on lipid metabolism for a broad range of PFAS. According to the EEA, PFASs contamination has the potential of a planetary boundary threat (Trier 2017).

5.2. Categorisation of Substances

*For **category A** compounds: many studies were recently conducted. Data may be sufficient to provide an overall picture across Europe, interpretation of health risks is possible and we expect to answer important policy-related research questions within the first two years of the project. For **category B** substances: spatial gaps within Europe, have been identified. For **category C** substances: very little or no data or toxicological/health effect information is available.*

Based on the huge amount of available PFAS on the market and the knowledge gaps on identity, toxicity and uses (of the alternatives) the listing of chemicals in category C is a first attempt to identify possibly relevant substances that contribute to the overall PFAS burden in humans. For substance selection the following issues were considered: availability of substance identity and literature, building blocks or alternative processing aid in polymer manufacturing, use as food contact material, alternatives to long-chain PFAS and degradation products/intermediates. Due to the variety of PFAS classes and structures it is clear that category C is on open ended substance list and should regularly be updated.

Table 5: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C substances (see above)

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
A	PFBA	perfluoro-n-butanoic acid	375-22-4	206-786-3	NH, Other HH,	Annex III REACH (susp P)	PFCA highlighted by ECHA Norman 2015
	PFPeA	perfluoro-n-pentanoic acid	2706-90-3	220-300-7	NH, Other HH	Annex III REACH (susp P, susp. skin irritant)	PFCA highlighted by ECHA Norman 2015
	PFHxA	perfluoro-n-hexanoic acid	307-24-4	206-196-6	NH, Other HH	PACT7: PBT Germany	PFCA highlighted by ECHA Norman 2015
	PFHpA	perfluoro-n-heptanoic acid	375-85-9	206-798-9	NH, Other HH	Annex III REACH (susp P, susp B, susp actox, susp C)	PFCA highlighted by ECHA Norman 2011
	PFNA	perfluoro-n-nonanoic acid	375-95-1	206-801-3	H, Carc.2, Lact., SOT RE1, Repr. 1B, other HH	SVHC: CMR, PBT Restriction proposal (drafting phase)	PFCA, comparable high toxicity, upcoming restriction Norman 2011
	PFDA	perfluoro-n-decanoic acid	335-76-2	206-400-3	NH, STOT SE3, other HH	SVHC: CMR, PBT Restriction proposal (drafting phase)	PFCA upcoming restriction Norman, 2011
	PFU(n)dA	perfluoro-n-undecanoic acid	2058-94-8	218-165-4	NH, STOT SE3, other HH	SVHC: vPvB, Restriction proposal (drafting phase)	PFCA upcoming restriction

7 PACT: Public Activities Coordination Tool https://echa.europa.eu/de/addressing-chemicals-of-concern/substances-of-potential-concern/pact

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	PFDoA	perfluoro-n-dodecanoic acid	307-55-1	206-203-2	NH, STOT SE3, other HH	SVHC: vPvB, Restriction proposal (drafting phase)	PFCA upcoming restriction
	FTrDA	perfluoro-n-tridecanoic acid	376-06-7	276-745-2	-	SVHC: vPvB, Restriction proposal (drafting phase)	PFCA upcoming restriction
	PFTeDA	perfluoro-n-tetradecanoic acid	376-06-7	206-803-4	NH, other HH	SVHC: vPvB, Restriction proposal (drafting phase)	PFCA upcoming restriction Norman 2011
A	PFOA	Perfluorooctanoic acid	335-67-1	206-397-9	H, Carc.2, SOT RE1, Repr.1B, other HH	SVHC: PBT EU Restriction accepted, POP nomination for the Stockholm Convention (review phase)	PFCA upcoming restriction
	PFBS	perfluoro-1-butanesulfonate	375-73-5	206-793-1	NH, Other HH	SVHC, PACT: PBT: Norway	PFSA; highlighted by ECHA, ground water contaminant (PFBS and related substances)
	PFDS	perfluoro-1-decanesulfonate	335-77-3	206-401-9	-	Annex III REACH (susp P, susp B, susp actox.,susp C)	PFSA
	PFHxS	perfluoro-1-hexanesulfonate	355-46-4	206-587-1	-	SVHC8: vPvB, PACT	PFSA, longest half live in humans med.8.5-30 years Norman, 2015
A	PFHpS	perfluoro-heptanesulfonate	60270-55-5	262-135-3	NH, STOT SE3, other HH	Annex III REACH (susp P, susp B, susp actox, susp C, susp R)	PFSA, restricted

8SVHC: Substances of Very High Concern, cf. https://echa.europa.eu/de/candidate-list-table

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	PFOS	Perfluorooctane sulphonate	1763-23-1	217-179-8	H, Carc.2, Lact., SOT RE1, Repr. 1B, other HH	Regulation (EC) No 757/2010 (POP Regulation), PIC Regulation9	PFSA, restricted
B	FOSA, PFOSA	Perfluoroctylsulfonamide; Perfluorooctanesulfonic acid amide or 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-1-octanesulfonamide (IUPAC)	754-91-6	212-046-0	NH, STOT SE3, other HH	Annex III REACH (susp P, susp B,.susp C) PFOS-related substance	FASAs, restricted frequently Norman 2011
	N-MeFOSA	N-methylperfluoro-1 octanesulphonamide 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluoro-N-methyl-1-octanesulfonamide (IUPAC))	31506-32-8	-	NH, STOT SE3, other HH	Annex III REACH (susp P, susp B, susp C) PFOS-related substance, PIC Regulation	FASAs measured in some European studies Norman 2011
	Me-PFOSA-AcOH, Me-FOSAA	N-Methyl-perfluorooctane sulfonamido acetic acid	2355-31-9	-	-	-	FASAAs, transformation product, may be markers of food or consumer exposures; measured in some European studies Norman 2011
B	N-Et-FOSAA, Et-PFOSA-AcOH, Et-FOSAA	N-ethyl-perfluorooctane sulfonamidoacetate or N-ethyl-N-[(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctyl)sulfonyl]-glycine (IUPAC)	2991-50-6	-	-	-	FASAAs, transformation product, may be marker of food or consumer exposures; measured in some European studies Norman 2015

9 PIC, Prior Informed Consent Regulation, https://echa.europa.eu/de/regulations/prior-informed-consent-regulation , 2017-05-23

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	4:2 FTSA	4:2 fluorotelomer sulfonic acid, 3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexanesulfonic acid (IUPAC)	757124-72-4	-	-	-	FTSA, Priority HBM List California10; investigated in Yeung and Mabury (2016), human blood levels in all samples were below LOQ
	6:2 FTSA, H4PFOS, THPFOS	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid, 6:2 fluorotelomer sulfonic acid	27619-97-2	248-580-6	NH, STOT RE2	Annex III REACH (susp P, susp B, susp C)	FTSA, limited toxicity data; found in human blood samples at concentrations of <0.01-0.016 µg/l (Yeung and Mabury, 2016)
	8:2 FTSA	3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecanesulphonic acid, 8:2 fluorotelomer sulfonic acid	39108-34-4	254-295-8	NH, STOT RE2, other HH	Annex III REACH (susp P, susp C)	FTSA, Priority HBM List California ; found in human blood samples at concentrations of <0.01-0.072 µg/l (Yeung and Mabury, 2016)
B	8:2 diPAP	polyfluoroalkyl phosphoric acid diesters, Bis(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl) hydrogen phosphate	678-41-1	211-649-6	-	Annex III REACH (susp P, susp B, susp C, susp R) PFOA-related substance	diPAP, Priority HBM List California; detected in concentrations of 0.015±0.008 µg/l in human blood (Yeung and Mabury, 2016), 0.013±0.05 µg/l in human sera (Lee and Mabury, 2011), 0.013±0.008 µg/l in human plasma (Yeung et al., 2013a, 2013b) Norman 2015

10 *http://biomonitoring.ca.gov/sites/default/files/downloads/PriorityChemicalsList_December2015.pdf*

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	ADONA	Ammonium 4,8-dioxa-3H-perfluorononanoate (ammonium 2,2,3 trifluor-3-(1,1,2,2,3,3-hexafluoro-3-trifluormethoxypropoxy), propionate)	958445-44-8	480-310-4	NH, other HH	CORAP, suspected PBT, vPvB	PFECA, highlighted by ECHA ,Priority HBM List California; alternative to APFO; possible PPARα-antagonist; use in food contact material
	5:3 FTCA 7:3 FTCA	Fluorotelomer carboxylic acids 5:3 Fluorotelomer carboxylic acid 7:3 Fluorotelomer carboxylic acid	-	-	-	-	FTCAs; Fluorotelomer metabolites, detected in blood in ski wax technicians (Nilsson et al. 2013), Priority HBM List California
	6:2 FTUCA 8:2 FTUCA 10:2 FTUCA	Fluorotelomer unsaturated carboxylic acids 6:2 Fluorotelomer unsaturated carboxylic acid 8:2 Fluorotelomer unsaturated carboxylic acid 10:2 Fluorotelomer unsaturated carboxylic acid	70887-88-6 70887-84-2 70887-94-4	-	-	-	FTUCAs; Fluorotelomer metabolites, detected in blood in ski wax technicians (Nilsson et al. 2013), Priority HBM List California
C	PFECA	Perfluoroether carbocylic acids for example: Ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate (GenX)	62037-80-3	700-242-3	NH STOT RE2, other HH	GenX: CoRAP (suspected PBT, vPvB and exposure to environment)	PFECA: highlighted by ECHA Norman 2015

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	PFECA	Perfluoro-1,2-propylene glycol and perfluoro-1,1-ethylene glycol, terminated with chlorohexafluoropropyloxy groups Perfluoro[(2-ethyloxy-ethoxy)acetic acid], ammonium salt	329238-24-6	682-234-970	NH STOT RE1, other HH	-	PFECA; alternatives; structural similarity to PFCAs and PFSAs; resistant, persistent, not easily to metabolise, maybe bioaccumulative;; expected increase in production and use; partially used in food contact materials; restrictions on use according EFSA
	PFECA	perfluoro-1,1-ethylene glycol, terminated with chlorohexafluoropropyloxy groups Perfluoro[(2-ethyloxy-ethoxy)acetic acid], ammonium salt	908020-52-0	700-323-3	NH Repro2, other HH	CORAP susp vPvB, PBT	
C	6:2 FTMAC	Fluorotelomer methacrylates e.g. 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate	2144-53-8	218-407-9	NH: STOT SE 3(2) other HH	PACT, susp endocrine disrupter,PBT, vPvB,	FTMAC ECHA. fully registered subst 100-1000 tonnes, In human blood probably only metabolites detectable (FTOH, FTCA, FTUCAs) Used for polymer production
	6:2 FTAC 8:2 FTAC 10:2 FTAC	Fluorotelomer acrylates e.g. 6:2 Fluorotelomer acrylate 8:2 Fluorotelomer acrylate 10:2 Fluorotelomer acrylate	17527-29-6 27905-45-9 17741-60-5	241-527-8 27905-45-9 -	NH: STOT RE 2 (liver, teeth), other HH NH: STOT SE 3 -	Included in CoRAP - -	FTAC, CAS 27905-45-9 is a PFOA-related compound, Used for polymer production, Priority HBM List California, in human blood probably only metabolites detectable
	PTFE	Teflon: Polytetrafluoroethylene	9002-84-0	618-337-2	NH: STOT SE3	Annex III: susp P,C,M,R	FP; produce toxic products if

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	PVDF	1,1 Difloroethene (PVDF)	24937-79-9	607-458-6	NH STOT SE 3, o.HH	Annex III: Susp P, M	overheated. Production of ultrafine particles by degradation (PTFE); lung inflammation (PTFE); toxic monomers
	PVF	Polyvinyl fluorine (PVF)	24981-14-4	-	-	-	
	TFE	Tetrafluoroethylene (TFE)	116-14-3	204-126-9	NH: Carc. 1B	TFE: PACT (CMR)	
	HPF	Hexafluoropropylene (HFP)	116-15-4	204-127-4	NH: STOT SE 2(3), STOT RE2 other HH	HFP: CoRAP (high tonnage, suspected C and R)	
	PFODA	Perfluorostearic acid; Perfluorooctadecanoic acid	16517-11-6	240-582-5	NH, other HH (skin Corr. 1B)	Annex III: susp C, susp R	PFCA Priority HBM List California
C	PfHxDA	Perfluoropalmitic acid, Perfluoro-n-hexadecanoic acid or 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-Hentriacontafluorohexadecanoic acid (IUPAC)	67905-19-5	267-638-1	NH, other HH (skin Corr. 1B)	Annex III: susp P,B,C	PFCA Priority HBM List California
		Fluorotelomer carboxylic acids					
	6:2 FTCA	6:2 Fluorotelomer carboxylic acid,	53826-12-3	-	-	-	FTACs, Fluorotelomer metabolites; Priority HBM List California
	8:2 FTCA	8:2 Fluorotelomer carboxylic acid	27854-31-5	-	-	-	
	10:2 FTCA	10:2 Fluorotelomer carboxylic acid	53826-13-4	-	-	-	
	FBSA	Perflurobutane sulfonamide	30334-69-1	-	-	-	Alternative to PFOS, transformation product, recently detected in biota (fish), Cu et al. (2016)

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	N-EtFOSE	N-ethyl-perfluorooctane sulphonamidoethanol; N-Ethyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide or N-Ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-1-octanesulfonamide (IUPAC)	1691-99-2	216-887-4	-	Annex III REACH (susp P, susp B, susp actox.,susp C, susp R) PFOS-related substance, PIC Regulation	FASAs, detected in indoor dust and air samples (cf. compilation in Gebbink et al. 2015) quickly and extensively metabolized to PFOSA with an eliminationhalf-lifeof16–20h
C	N-MeFOSE	N-methyl perfluorooctanesulfonamidoethanol or 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-N-methyloctane-1-sulfonamide (IUPAC)	24448-09-7	246-262-1	-	PFOS-related substance, PIC Regulation	FASAs, detected in indoor dust and air samples (cf. compilation in Gebbink et al. 2015)
	N-EtFOSA, SULFLURAMID	N-ethylperfluoro-1-octanesulphonamide or N-Ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonamide (IUPAC)	4151-50-2	223-980-3	NH, other HH	Annex III REACH (susp P, susp B, susp actox.,susp C) PFOS-related substance, PIC Regulation	FASAs; not detectable in human samples (plasma and whole blood, n=60 resp.) of Chinese adults as reported in Jin et al. (2016) and not detectable in human blood samples reported in Miyake et al. (2007b) detected in indoor dust and air samples (cf. compilation in Gebbink et al. 2015)
	PFAIs	Heptadecafluoro-1-iodooctane, 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-8-iodooctane (IUPAC)	507-63-1	208-079-5	NH: STOT SE3, other HH	Annex III: susp P,B, C PFOA-related substance	PFAIs; starting material for fluorotelomer-based products, rapid transformation in air, relevant for occupational exposure

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	HFPO	hexafluoropropylene oxide	220182-27-4	620-665-6	NH, other HH	-	FP highlighted by ECHA
	-	Perfluoroctyl silanes	-	-	-	-	PFS
C	PFCHS -	Cyclic PFSA e.g Cyclohexanesulfonic acid undecafluoro-, potassium salt Cyclohexanesulfonic acid, nonafluorobis(trifluoromethyl)-, potassium salt Perfluoro-4-ethylcyclohexane sulfonate	 3107-18-4 68156-01-4 335-24-0	221-465-8	-	Annex III: susp P,C	Cyclic PFSA, dissociate in water/body fluids to release potassium cations, lack of effects data11, CAS 335-24-0 detected in biota (Letcher et al. 2015)
	6:2 PAP	6:2 polyfluoroalkyl phosphoric acid monoesters	57678-01-0	611-565-3	-	-	monoPAP, Priority HBM List California
	6:2 diPAP	6:2 polyfluoroalkyl phosphoric acid diesters	57677-95-9	-	-	-	diPAP, Priority HBM List California
	6:2/8:2 diPAP	6:2/8:2 polyfluoroalkyl phosphoric acid diesters	943913-15-3	-	-	PFOA-related substance	diPAP, Priority HBM List California
	8:2 monoPAP	8:2 polyfluoroalkyl phosphoric acid monoester	57678-03-2	-	-	PFOA-related substance	monoPAP
	PFHxPA	Perfluorohexylphosphonic acid	40143-76-8	-	-	-	PFPAs, high environmental exposure Priority HBM List California

11 https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=2019

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	PFOPA	Perfluorooctylphosphonic acid, 2-(Perfluorohexyl) ethyl]phosphonic acid	252237-40-4	-	NH, STOT SE3, other HH	-	PFPAs, high environmental exposure Priority HBM List California
C	PFDPA	Perfluorodecylphosphonic acid	52299-26-0	-	-	-	PFPAs Priority HBM List California
	C4/C4 PFPiA	Bis(nonafluorobutyl)phosphinic acid	52299-25-9	700-183-3	toxic if swallowed, causes serious eye damage	CoRAP	PFPiAs
	C6/C6 PFPiA	Bis(perfluorohexyl)phosphinic acid	40143-77-9	-	-	-	PFPiAs
	C6/C8 PFPiA	Bis(perfluorohexyloctyl)phosphinic acid	610800-34-5				PFPiAs ,Priority HBM List California
	C8/C8 PFPiA	Bis(perfluorooctyl)phosphinic acid	40143-79-1	-	-	-	PFPiAs
	C8/C10 PFPiA	Bis(perfluorooctyldecyl)phosphinic acid	500776-81-8	-	-	-	PFPiAs
	8:2 FTOH	8:2 fluorotelomer alcohol	678-39-7	211-648-0	CLH proposal:: Repro 1B	PFOA-related substance	EAA consultant Norman 2011
	8:2 FTSA	8:2 fluorotelomer sulfonic acid (8:2 FTSA) (CAS:, EC: 254-295-8)	39108-34-4	254-295-8	NH. STOT SE 2 other HH	Annex III: susp P, suspC	EAA consultant Norman 2011
	-	Trimethoxy(1H,1H,2H,2H-heptadecafluorodecyl)silane	83048-65-1	617-434-7	NH: other HH	-	EAA consultant Norman 2015
	FL16.119	N-(2-methylcyclohexyl)-2,3,4,5,6-pentafluorobenzamide	1003050-32-5	-	NH:other HH	-	PFCADs

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	EC No.	Classification H/NH CMR, STOT, Other HH	Regulation	PFASs subtype Comments/
	Denum SH	Poly[oxy(1,1,2,2,3,3-hexafluoro-1,3-propanediyl)],a-(2-carboxy-1,1,2,2-tetrafluoroethyl)-w-(1,1,2,2,3,3,3-heptafluoropropoxy)-	120895-92-3	-	-	-	PFECA
	Krytox	Krytox-H	60164-51-4	-	-	-	PFECA
C	Fomblin Z-DIAC,	Fomblin Z-DIAC, bis(pentafluorophenyl) ester	97462-40-1	-	-	-	PFECA
		C3; C15-C20					PFCA
		C3, C15-C20					PFSA

H: harmonised; NH: not harmonised; other HH: other health hazards

Annex III to the REACH regulation: inventory compiled by ECHA, showing indications for concern (based on publicly available (experimental) data and QSAR models)

PFCAs: Perfluorinated carboxylic acids

PFSAs : Perfluoroalkyl sulfonic acids

FASAAs: Perfluoroalkanesulfonamidoacetic acids

PFPAs: Perfluorinated phosphonic acids

PFPiAs: Perfluorinated phosphinic acids

monoPAPs: Polyfluoroalkyl phosphoric acid monoesters

diPAPs: Polyfluoroalkyl phosphoric acid diesters

FTSAS: Fluorotelomermercaptoalkylamido sulfonate

FTSAs: Fluorotelomer sulfonic acids

FTCAs: Fluorotelomer carboxylic acids

FTUCAs: Fluorotelomer unsaturated carboxylic acids

di-SAmPAP: Perfluorooctanesulfonamidoethanol (EtFOSE)-based polyfluoroalkyl phosphate ester

FASAs: Perfluoroalkanesulfonamides (R = H, Methyl, Ethyl)

PASF: Perfluoroalkanesulfonylfluoride

FOSAAs: Perfluoroalkanesulfonamidoacetic acids ; (R = H; N-alkyl FOSAAs, R = Methyl, Ethyl.)

PFAIs: Perfluoroalkyliodides

FTIs: Fluorotelomeriodides

FP: fluoropolymer

PFPEs: Perfluoropolyethers

PFESAs: Per-and polyfluorethersulfonic acids

PFECAs: Per-and polyfluorethercarboxylic acids

PFECAs: Per-and poly-fluorinated polyether-based fluorinated surfactants

PFS: perfluorinated Silanes

PFCADs : perfluorinated carboxylic acid derivatives)

5.3. Objectives / Policy-related questions

1. What is the current exposure of the EU population to PFASs and do they exceed Guidance values (reference and HBM values), where available?
2. Are there differences in exposure of the EU population to regulated and non-regulated PFASs?
3. Has restriction of PFOS according to the POP Regulation led to a reduction in exposure, especially for children?
4. Is exposure driven by diet, consumer exposure, occupation or environmental contamination?
5. Which areas and environmental media in Europe are contaminated with PFASs?
6. How can this feed into an assessment of the TDI for PFOS and PFOA set by EFSA?
7. What is the impact of a pending 2016 ECHA decision to restrict the manufacturing, marketing and use of PFOA under REACH?
8. Is it important to eliminate legacy PFASs from material cycles (i.e. waste electronic equipment) when implementing a circular economy in order to protect human health?
9. Can differences in PFASs profiles be observed in different population groups and time periods?
10. What are the PFASs levels and health effects in vulnerable population groups?
11. How can mixture effects of environmental and human PFASs mixtures present to date be estimated?
12. How can PFAS substances of relevance for human exposure and health be identified having in mind that more than 3000 substances are at the market?
13. How can identification and assessment (including data on (potential) adverse effects on human health and the environment) of alternatives currently hampered by CBI (Confidential Business Information) be facilitated?

5.4. Research activities to be undertaken

Table 6: Listing of research activities to be carried out to answer the policy questions

Policy question	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
1	**CAT A substances**	Alternatives to PFOS (e.g. PfHXS, PFBS) are detected more frequently and in increasing concentrations	Proceed with collecting, combining, harmonizing and comparing existing exposure data on PFASs WP10
	PFOS and PFOA	There are ongoing discussions on the appropriate Point of Departure for derivation of DNELs respective HBM values for PFOS and PFOA; values differ among orders of magnitude	Compare PFOA exposure values with the newly derived HBM values from the German HBM Commission and the upcoming EFSA health guideline values, develop HBM4EU values for PFOS and PFOA WP5
	CAT A substances	Within year one (2017) assessment of the so far conducted PFASs studies will make it possible to answer this question, at least for some of the substances. For others targeted studies should be performed.	Based on the results a detailed data gap analysis should be performed, taking the respective human health related endpoints into consideration in order to address the question if health based guidelines are met or not. In order to specifically address health endpoints where currently insufficient data are available study protocols should include measurement of transaminases, cholesterol, immune parameters and thyroid hormones. Mixture effects should be considered, taking the similar mode of action for certain substances into consideration. Uncertainty regarding the total PFASs exposure has to be considered. WP5, 8,9,10,15

Policy question	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
2	**CAT A and B probably C substances**	Within the first year assessment differences in exposure will be documented. To date PFOS and PFOA are most probably still the substances occurring in the highest concentrations in serum in Europe and elsewhere, however concentrations of alternatives – e.g. long chain compounds (such as PFNA and PfHXS) or short chain PFAS (such as PFBS, PFBA) are increasing.	New targeted studies identifying a multitude of PFASs in human blood and urine including newly developed methods such as TOF or oxidisable fractions should be planned and performed, in order to be able to quantify also the so far unidentified compounds. Analyses should be further complemented by measurement of transaminases, cholesterol, immune parameters and thyroid hormones. Development of TOF and oxidisabel fraction methods should be validated and harmonised in order to integrate them in planned and ongoing studies WP8,9
3	**PFOS**	The effectiveness evaluation under the UNEP Stockholm Convention concluded that for human matrices from Western Europe, Canada, Australia and Asia-Pacific countries levels seem gradually declining. It will most probably turn out that data on PFAS exposure in children is currently underrepresented; most studies performed within Europe are from adult populations with the exceptions of birth cohorts.	Exposure of children to PFASs should be investigated, complemented by measurement of transaminases, cholesterol, immune parameters and thyroid hormones. WP8,9,

Policy question	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
4	**Cat A substances**	Long chain PFASs exposure is presumed to be via diet; contribution of food additives and flavourings is so far not sufficiently investigated. Also knowledge on the exposure to short chain PFASs via diet (e.g. crops and vegetables) and drinking water is scarce. Further, information on exposure via various consumer product has to be considered.	All new studies performed within HBM4EU targeting PFASs should include detailed questionnaires based on current knowledge on exposure pathways. Therefore a PFASs related questionnaire should be developed. WP8,9
5	**Cat A and B substances**	Currently there are several hot spots known in different countries (e.g. Germany, Sweden, Italy, Netherlands). It can be assumed that hot spots exist also in the majority of the European and associated countries.	A questionnaire should be developed based on the knowledge existing from known cases (e.g. reason for contamination, facility, substances related to the respective case, production or use volume, area contaminated). The questionnaire could be sent out to NHCPs in order to get an overview on other known or suspected cases.
6	**Cat A Substances**	The EFSA opinion will be published in 2017 (foreseen according to mandate for 31.07.2017). As working group members are involved in HBM4EU, information exchange can be expected.	The detailed EFSA assessment shall be used within HBM4EU for defining data gaps and refining research questions. Based on previous information exchange and discussion among HBM4EU partners it is clear that there are several questions on human health that have to date not been sufficiently addressed due to relatively small size of many previous studies. Combining several comparable studies will allow for more robust assessment of health outcomes in terms or broader exposure range and examination of rare health outcomes which individual studies have been underpowered to address (including low birth weight, pregnancy complications. WP 13

Policy question	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
7	**PFOA and related substances**	The restriction is expected to lead to declining levels of PFOA	The identification, assessment and monitoring of alternatives is of importance. WP4, 5
8	**Cat A Substances**	According to experts in different fields it is anticipated to eliminate legacy PFASs from waste streams.	It is not clear weather this question can be tackled within HBM4EU; Studies near landfields could clarify if PFASs exposure occurs. WP 8,9
9	**Cat A and B substances**		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 10, 12
10	**Cat A and B substances**	As PFASs exposure pattern are changing current exposure of vulnerable populations needs to be investigated.	Current exposure levels in vulnerable populations need to be investigated, preferable with methods, which allow identifying Cat A and B substances as well as the total PFASs burden. WP8,9
	Cat A substances		Development of PFASs related AOPs by addressing critical endpoints in humans such as effects on liver and thyroid, developmental toxicity, immunotoxicity and non carcinogenic toxicogenicity, WP13

Policy question	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
11	**Mixture of substances**		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, immunotoxicity reproductive, developmental and carcinogenic effects, WP15
12	**Cat B and C substances**	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?	Identification of compounds to be prioritized for further information on exposure and/or toxicity to be measured in HBM studies WP4,5

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6. Prioritised substance group: Flame retardants (FR)

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6.1. Background Information

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

Since the 1970s, the primary FR compounds used were the polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane[12] (HBCDD). However, due to concerns regarding the persistence, toxicity and bioaccumulative potential, these compounds have been added to the Stockholm Convention on Persistent Organic Pollutants (www.pops.int), including the most recent addition of deca-BDE (also called BDE-209, referring to the PBDE with 10 bromines) in 2017. Yet, although these compounds are regulated under the Stockholm Convention and through other regulatory mechanisms, the need for FRs has not decreased and this has led to a broadening of the market for FR compounds, with a wide range of replacement compounds used globally. These replacement compounds are typically brominated, chlorinated and organophosphate compounds, some of which are mentioned below. In the following document, OPE (organophosphate esters), refers to the organophosphate-based FRs, while NBFR (novel brominated flame retardant) refers to the brominated replacements for PBDEs and HBCDD.

6.1.1. Hazardous Properties

PBDEs and HBCDDs have been identified to have a range of adverse health effects, including potential neurotoxic, endocrine, and carcinogenic effects.[inter alia ,1–3] The toxicity of tetrabromobisphenol A (TBBPA) is also well-studied and it has been identified to have a range of potential hazardous properties.[4–7] Early evidence suggests that a number of the replacement FRs may have similar health concerns,[8–10] and moreover, insufficient evidence exists to evaluate toxicity for many of these new FRs. The toxicity and human exposure of selected FRs has been investigated in individual studies, and aquatic toxicity has received significant attention, but there remain large gaps in toxicity studies of directly applicability to human populations.

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

Bis(2-ethylhexyl)tetrabromophthalate (BEH-TEBP) and 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) have been identified as potentially bioaccumulative.[11] Decabromodiphenyl ethane (DBDPE) is structurally similar to BDE-209 and hypothesized to have similar toxicity. Triphenyl phosphate (TPHP) is identified by ECHA as very toxic to aquatic life, has been found to affect oestrogen receptor binding activities in zebrafish,[12] and may be associated with altered hormone levels and decreased semen quality in men.[13] Tris-2-chloroethyl phosphate (TCEP) was also found to affect oestrogen receptor binding activities in zebrafish,[12] may affect neurodevelopment, with multiple mechanisms of toxicity,[8] and is a possible reproductive toxin.[14] TCIPP may also affect neurodevelopment[8] and is potentially carcinogenic.[14] Tris(1,3-dichloropropyl)phosphate (TDCIPP) may be associated with altered hormone levels and decreased semen quality in men,[13] may affect neurodevelopment, with multiple mechanisms of toxicity,[8] and also may be carcinogenic.[14]

6.1.2. Exposure Characteristics

Human exposure to FRs can occur through a variety exposure pathways, via inhalation, ingestion (either through food or ingestion of indoor dusts, as FRs migrate from products and materials into the indoor and outdoor environment) and dermal exposure, including through direct contact with flame-retarded consumer products.[15] In addition to use as FRs, a number of these compounds (particularly the phosphorus-based FRs) also act as plasticizers,[14] and thus are also added to synthetic materials for this purpose. The exposure pathways differ based on the compound properties and FR use. For example, while adult exposure to some FRs is primarily through diet, for babies and toddlers, due to the hand-to-mouth behaviour and mouthing of toys, the primary exposure pathway is through ingestion of house dust.[16]

Many flame retardants exist in mixtures, e.g., the technical mixtures of the PBDEs, and Firemaster 550, which contains triphenyl phosphate (TPHP), isopropylated triphenyl phosphate isomers (ip-TPP), 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)- 2,3,4,5-tetrabromophthalate (BEH-TEBP). In terms of toxicity, the PBDEs have received attention as mixtures and as individual compounds,[17] and there is evidence of Firemaster 550 as an endocrine disrupting compound and obesogen.[9] However, there is generally little attention given to the toxic effects of the typical mixtures of FRs occurring indoors and to which humans are exposed. Thus, the issue of mixture toxicity is highly relevant to FRs, and remains a large data gap within the toxicological knowledge on FRs.

Highly lipophilic FRs, particularly those with higher persistence, such as the PBDEs, can be detected in parent compound form in human matrices, most commonly in human serum[18–20] and breast milk.[21,22] In contrast, some NBFRs and many OPEs are metabolized in the body, and more commonly used biomarkers of exposure are metabolites detected in urine.[23,24] However, many of the metabolites are uncertain, and metabolic pathways are only characterized for a limited number of FRs.[25–30] Biomarkers for many FRs of emerging concern are unknown. Target matrices for biomonitoring for the emerging FRs can be inferred from physicochemical properties of the molecules, considering their structural similarity to better quantified compounds, and/or relying on chemical modelling techniques, but there is a lack of practical measurement data for many compounds. Many biomonitoring studies report high detection frequencies of FR biomarkers in human matrices, but there is little systematic assessment of temporal or spatial trends. PBDEs are one of the few compounds where generalization of trends and distributions has been made from biomarkers. Quantification of a rapidly increasing temporal trend of PBDEs in maternal milk in Sweden[31,32] lead to initial concerns regarding human exposure to PBDEs and first regulatory actions.

In general, human exposure to PBDEs is lower in Europe than in North America,[33] while evidence from indoor dust and chemical usage suggests higher human exposure to HBCDDs in Europe than in North America based on identified correlations between dust and serum concentrations.[34,35] The strong interpretations of exposure trends from PBDEs suggest that sufficient biomarker data for other FRs, once obtained, will enable similar improvements in understanding of FR exposure and effects in the European population.

6.1.3. Policy Relevance

A small number of FRs are regulated/restricted both within the EU as well as at the international level. PBDEs and HBCDD are restricted under the Stockholm Convention on Persistent Organic Pollutants, and now have limited use. Additionally, many replacement/alternative FRs are under REACH evaluation, however there are currently no restrictions or regulations for a number of FR compounds. Given the existing regulations on flame retardants both at the international (e.g., Stockholm Convention) and European level (e.g., REACH), HBM4EU can contribute by providing information on the effect of legislative restrictions and bans on concentrations in the European human population, particularly with respect to establishing baseline exposure concentrations for current-use flame retardants. Evaluating and comparing temporal trends for banned/restricted vs. current-use FRs will also allow us to determine if current regulations are effective across the EU, and if the emerging FRs are showing signs of accumulation in the environment or within the European population. For the majority of FRs there are no established safety limits, health-based reference values or guidance values, and limited knowledge of usage volumes due to manufacturer confidentiality. HBM4EU provides a platform to identify geographic patterns and time trends of exposure from existing data sets and to identify and rectify where major gaps exist through additional targeted investigation. This will allow regulatory agencies to identify any FRs that may be of concern and to make informed decisions.

Of concern is the relative lack of information regarding the use, exposure pathways and toxicity of many of these compounds. The European Food Safety Authority (EFSA) identified 17 brominated FRs which are currently in use and with detectable levels in environmental and/or human matrices, and a further ten brominated FRs that have concentrations >0.1% in consumer products and materials, but lack any information on human and environmental levels or even occurrence at all.[36] 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 (e.g., quantitative structure–activity relationship models), and estimates rather than direct evidence. This makes it difficult for regulatory bodies and legislative agencies to make informed decisions. Furthermore, the broad suite of known FRs covers a wide range of physicochemical properties, meaning that in most cases each individual FR must be independently studied to understand emission, exposure and toxicity, Conclusively, it can be said that large data gaps exist for a wide number of FRs.

6.1.4. Societal Aspects

FRs are widely used in consumer products and building materials, in particular in electronics, textiles and furnishings, automobiles and other vehicles, building insulation, flooring, appliances and ducting, and studies have identified a range of FRs in all of these product groups [37–42]. The amounts of and types of FRs vary widely even within product groupings, and can be found at up to percentage levels in consumer products, but typically are in the µg/g range.

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

The FRs that have received the most attention, both scientifically and in terms of regulation and restriction are PBDEs, HBCDD and tetrabromobisphenol A (TBBPA). However, despite this attention, publically available information on production and/or usage volumes is still limited.

PBDEs: In 2001, global use of the three PBDE technical mixtures was as follows: 7500 tonnes of pentaBDE, 3790 t of octaBDE, and 56150 t of decaBDE.[43] European use at this time was 150 t of pentaBDE, 610 t of octaBDE, and 7600 t of decaBDE,[43] however, as noted above, more PBDEs may have been in actual use due to import of products manufactured in other regions. There should be no production of pentaBDE and octaBDE after 2004 due to voluntary phase-out by production companies followed by subsequent listing in the Stockholm Convention. For decaBDE, global use was 7300 t in 2008.[44] There should be no production/use of deca-BDE in Europe after 2008. DecaBDE has been accepted for inclusion on the Stockholm Convention in May 2017. Currently, ECHA identifies that decaBDE is imported into the European Economic Area in amounts of 1000 to 10000 t per year.

HBCDD: In 2001, global use was 16700 t, and the majority of use, 9500 t, was in Europe.[43] In 2015, global use was similar: 16750 t, but the use within Europe was significantly less, at 2800 t.[45] Due to Stockholm Convention restrictions on HBCDD, there should be no new use by signatory countries excepting in expanded polystyrene and extruded polystyrene used as building insulation.[46] Currently, the ECHA identifies that HBCDD is manufactured and/or imported into the European Economic Area in amounts of 10000 to 100000 t per year.

TBBPA: In 2001, global use of TBBPA was 119700 and of this, European use was 11600 t.[43] By 2008 global use had increased to 230000 tonnes per year.[44] Currently, ECHA identifies that TBBPA is manufactured and/or imported into the European Economic Area in amounts of 1000 to 10000 t per year.

There is even more limited information for other FRs, despite the general perception that they are being used in increasingly higher amounts as replacements for PBDEs and HBCDD. ECHA usage information for selected Category B FRs is given in Table1:

Table 7: The mass of FRs in use in the EU per year based upon ECHA and REACH estimates accessed in March 2017.

Compound	Manufacture and/or import amount (tonnes/year)
Bis(2-ethylhexyl) tetrabromophthalate (BEH-TEBP)	100-1000 t/y
Decabromodiphenylethane (DBDPE)	10000-100000 t/y
Triphenyl phosphate (TPHP)	1000-10000 t/y
Tri(2-butoxyethyl) phosphate (TBOEP)	1000-10000 t/y
Tris(1,3-dichloropropyl)phosphate (TDCIPP)	1000-10000 t/y
2-ethylhexyl diphenyl phosphate (EHDPP)	1000-10000 t/y

Category A substances have identified toxicity to humans and/or environmental systems, and have been regulated/restricted in view of this. However, many Category B substances are also of concern due to potential toxicity and high environmental concentrations with increasing temporal trends, particularly in the indoor environment[47,48] and consumer products,[37,38] yet no production and/or usage information is publicly available. In particular, this applies for 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB), 1,2-bis(2,4,6-tribromophenoxy)-ethane (BTBPE), Dechlorane Plus (DDC-CO), tris-2-chloroethyl phosphate (TCEP) and tris(1-chloro-2-propyl) phosphate (TCIPP).

Many of the alternative/replacement FRs have no available biomonitoring data, or only 1 or 2 reports. European biomonitoring data is wholly absent for many FRs (including the majority of Category C compounds), and when it exists, is often limited to Northern Europe (Scandinavian countries, Germany, Netherlands, Belgium). Biomonitoring data for Southern and Eastern Europe is a crucial data gap for almost all FRs. However, despite the lack of biomonitoring data, the majority of the FRs are consistently detected in indoor matrices, in particular, in residential dust at high levels,[42,47–59,24,60–62] which suggests potential human exposure by ingestion of dust and dermal contact with surface dusts. Notably, the concentrations of the organophosphate FRs are order of magnitude higher than many other compounds in residential dust, suggesting high potential for ingestion and dermal exposure, particularly for children.

6.2. Categorisation of Substances

The FRs of interest to HBM4EU have been categorized according to the availability of data relevant to the project research questions. ***Category A*** *compounds are those for which many studies were recently conducted and HBM and toxicity/epidemiological data may be sufficient to provide an overall picture across Europe, interpretation of health risks is possible and we expect to answer important policy-related research questions within the first two years of the project.* ***Category B*** *substances have spatial gaps in data within Europe, while* ***category C*** *substances have very little or no data or toxicological/health effect information available.*

Table 8: Substances included in the substance group, listed according to availability of human biomonitoring data, in category A, B, C substances (see above)

Cat.	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
A	tetraBDE	Tetrabromodiphenyl ether	5436-43-1	Stockholm Convention
	pentaBDE	Pentabromodiphenyl ether	60348-60-9	Stockholm Convention
	hexaBDE	Hexabromodiphenyl ether	36355-01-8	Stockholm Convention
	heptaBDE	Heptabromodiphenyl ether	189084-67-1	Stockholm Convention
	HBCDD	Hexabromocyclododecane	3194-55-6, 25637-99-4	Stockholm Convention
	mirex	Perchloropentacyclodecane	2385-85-5	Stockholm Convention
	BDE-209	2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether	1163-19-5	Stockholm Convention
	TBBPA	Tetrabromobisphenol A	79-94-7	
B	BEH-TEBP	Bis(2-ethylhexyl)tetrabromo-phthalate	26040-51-7	
	EH-TBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate	183658-27-7	
	BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane	37853-59-1	
	DBDPE	Decabromodiphenylethane	84852-53-9	
	DBE-DBCH	Tetrabromoethylcyclohexane	3322-93-8	
	DBHCTD	Hexachlorocyclopentenyl-dibromocyclooctane	51936-55-1	
	HBB	Hexabromobenzene	87-83-2	
	OBTMPI	Octabromotrimethyphenyl indane	1084889-51-9, 1025956-65-3,893843-07-7, 155613-93-7	
	PBB-Acr	Pentabromobenzyl acrylate	59947-55-1	
	PBT	Pentabromotoluene	87-83-2	
	TBCO	1,2,5,6-tetrabromocyclooctane	3194-57-8	
	TBX	2,3,5,6-tetrabromo-p-xylene	23488-38-2	
	PBEB	Pentabromoethylbenzene	85-22-3	
	DDC-CO	Dechlorane Plus	135821-03-9	
B	TDBPP	Tris(2,3-dibromopropyl) phosphate	126-72-7	

Cat.	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
	TPHP	Triphenyl phosphate	115-86-6	
	TMPP	Tricresyl phosphate	1330-78-5	
	TBOEP	Tri(2-butoxyethyl) phosphate	78-51-3	
	TCEP	Tris-2-chloroethyl phosphate (TCEP	115-96-8	
	TCIPP	Tris(1-chloro-2-propyl) phosphate	13674-84-5	
	TDCIPP	Tris(1,3-dichloropropyl)phosphate	13674-87-8	
	TEP	Triethyl phosphate	78-40-0	
	TNBP	Tri-n-butyl phosphate	126-73-8	
	TIBP	Tri-iso-butyl phosphate	126-71-6	
	TEHP	Tris(2-ethylhexyl) phosphate	78-42-2	
	EHDPP	2-ethylhexyl diphenyl phosphate	1241-94-7	
	TnPP	Tri-n-propyl-phosphate (TnPP	513-08-6	
	DCP	Cresyl diphenyl phosphate	26444-49-5	
	V6	2,2-bis(chloromethyl)trimethylenebis[bis(2-chloroethyl) phosphate]	38051-10-4	
C	HEEHP-TEBP	2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromophthalate	20566-35-2	
	4'-PeBPO-BDE208	Pentabromophenoxy-nonabromodiphenyl ether	58965-66-5	
	TBNPA	Tribromoneopentyl alcohol	1522-92-5	
	HBCYD	Hexabromocyclodecane	25495-98-1	
	DBNPG	Dibromoneopentylglycol	3296-90-0	
	DBS	Dibromostyrene	31780-26-4	
	TDBP-TAZTO	Tris(2,3-dibromopropyl)isocyanurate	52434-90-9	
	BDBP-TAZTO	1,3-bis(2,3-dibromopropyl)-5-(2-propen-1-yl)-1,3,5-triazine-2,4,5(1H,3H,5H)-trione	75795-16-3	
	DBP-TAZTO	1-(2,3-dibromopropyl)-3,5-diallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (CAS-No:)	57829-89-7	
C	TTBP-TAZ	2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine (CAS-No:)	25713-60-4	
	EBTEBPI	N,N'-ethylenebis(tetrabromophthalimide)	32588-76-4	

Cat.	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
	BPA-BDPP	Bisphenol A bis(diphenylphosphate)	5945-33-5	
	RBDPP	Resorcinol bis(diphenylphosphate)	125997-21-9	
	2,4,6-TBP	2,4,6-tribromophenol	118-79-6	
	PBP	Pentabromophenol	608-71-9	
	DBP	2,4-dibromophenol	615-58-7	
	Dec 602	Dechlorane 602 (1,2,3,4,6,7,8,9,10,10,11,11-Dodecachloro-1,4,4a,5a,6,9,9a,9b-octahydro-1,4:6,9 dimethanodibenzofuran)	31107-44-5	
	Dec 603	Dechlorane 603 (1,2,3,4,5,6,7,8,12,12,13,13-Dodecachloro-1,4,4a,5,8,8a,9,9a,10,10a-decahydro-1,4:5,8:9,10-trimethanoanthracene)	13560-92-4	
	HCTBPH/Dec 604	Dechlorane 604 (1,2,3,4,7,7-hexachloro-5-(2,3,4,5-tetrabromophenyl)-bicyclo[2.2.1]hept-2-ene)	34571-16-9	
	TTBNPP	Tris(tribromoneopentyl) phosphate	19186-97-1	
	ip-TPP	Isopropyl triphenyl phosphate	68937-41-7	
		Melamine polyphosphate	20208-95-1	
		Diethylphosphinic acid	813-76-3	

Table 9: Prioritised FRs. The above table lists 60 FRs of interest to HBM4EU. However, in order to sufficiently address each compound, Year 1 of HBM4EU is focusing on a subset of 18 of these compounds, selected based on known human exposure and toxic effects or reported high levels in environments/matrices linked with human exposure (e.g., residential dust) or recent reports of high environmental levels or detection in consumer products at high levels. The prioritized list is below.

Cat.	Abbreviation	Name
A	HBCDD	Hexabromocyclododecane
	BDE-209	2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether
	TBBPA	Tetrabromobisphenol A
B	BEH-TEBP	Bis(2-ethylhexyl)tetrabromophthalate
	EH-TBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate
	BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane
	DBDPE	Decabromodiphenylethane
	DDC-CO	Dechlorane Plus
	TPHP	Triphenyl phosphate
	TBOEP	Tri(2-butoxyethyl) phosphate
	TCEP	Tris-2-chloroethyl phosphate
	TCIPP	Tris(1-chloro-2-propyl) phosphate
	TDCIPP	Tris(1,3-dichloropropyl)phosphate
	EHDPP	2-ethylhexyl diphenyl phosphate
	V6	2,2-bis(chloromethyl)trimethylenebis[bis(2-chloroethyl) phosphate]
C	BPA-BDPP	Bisphenol A bis(diphenylphosphate)
	RBDPP	Resorcinol bis(diphenylphosphate)
	Dec 602	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)

6.3. Objectives / Policy-related questions

The following are the major questions to be addressed for FRs:

1. What current information is available regarding human exposure to FRs, both past and present? In particular, what is the availability of information for the 18 priority substances. How well does the information cover the European population, spatially and temporally? Are sensitive populations, such as infants and children, covered by the existing exposure data?
2. 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?
3. Are existing analytical methods appropriate and sufficient to quantify the FRs and/or associated metabolites in human matrices? What method improvements are needed and what laboratories/regions have analytical capacity for measurement of human matrices for FRs, particularly the category B FRs?
4. What are current human levels of legacy/regulated FRs (e.g., PBDE and HBCDD)? How do these compare to any historical records? Is the current legislative framework and proposed actions leading to a significant decline in restricted compounds and is this uniform across the EU?
5. 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?
6. What are the population groups most at risk?
7. What additional FRs (beyond the initial 18 priority 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?
8. Has the compound been identified in environmental or other matrices such that human health may be at risk, e.g., in indoor dusts, consumer products, indoor air, food? Can modelling techniques be used to estimate exposure via these external pathways?

6.4. Research activities to be undertaken

Primarily, the initial focus will be on analysis and synthesize of existing data regarding biomonitoring and exposure for priority FRs and identification of additional compounds based on production and use.

The list of FRs is extensive, and not fixed, as new FRs are identified in human and environmental matrices on a regular basis. Therefore, flexibility must be maintained in the list of relevant and priority compounds. However, of the current list of 60 FRs, 18 individual compounds have been identified as those with highest priority. These 18 compounds are prioritized based on (1) known high use and levels in human matrices in conjunction with current regulatory action (e.g., HBCDD, decaBDE), (2) repeated detection in environmental matrices at high levels, known use, and limited information on human exposure and toxicity (e.g., BEH-TEBP, EH-TBB, BTBPE), or (3) recent new identification in environmental matrices, but limited other data (e.g., V6). The prioritized FRs are: HBCDD, BDE-209, BEH-TEBP, EH-TBB, BTBPE, DBDPE, DDC-CO, TBBPA, TPHP, TBOEP, TCEP, TCIPP, TDCIPP, EHDPP, BPA-BDPP, RBDPP, Dec 602, V6 (given in full in section 3).

Table 10: Listing of research activities to be carried out to answer the policy questions summed up in chapter 6.

Substance	Available HBM knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
PBDEs	**Biomonitoring data for PBDEs in a range of human matrices (primarily serum, maternal milk):** Sweden: ▸ Breast milk20,31,63–65,22,66–71 ▸ Blood63,72,73 ▸ Serum71,74–76 ▸ Plasma77,78 ▸ Adipose tissue79,80 ▸ Ingestion intake65 ▸ Liver tissue79 ▸ Feces81 Norway: ▸ Blood82,83 ▸ Plasma84 ▸ Serum85,86 ▸ Breast milk87–90	Gaps: ▸ Biomonitoring data for Southern and Central/Eastern Europe ▸ Coherence and synthesis in data Activities: ▸ Synthesis and/or meta-analysis of existing HBM data to identify time trends in exposure and possible regional differences. Inform on whether current regulatory structure can effectively lead to decreases in human exposure ▸ Statistical evaluation of average concentrations, time trends and potential variance between population subgroups both regional and at risk (meta-analysis).
	Germany: ▸ Diet91 ▸ Blood92,93 France: ▸ Serum18,94,95 ▸ Breast milk94,96 ▸ Cord blood94,95 ▸ Adipose tissue97 ▸ Adipose tissue94	

Substance	Available HBM knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
	Denmark: ▸ Placental tissue98 ▸ Breast milk96 ▸ Cord blood99 ▸ Plasma99 Finland: ▸ Adipose tissue100 ▸ Placenta101 ▸ Breast milk96,101 Belgium: ▸ Breast milk102–104 ▸ Adipose tissue105 ▸ Cord blood104,106 ▸ Serum104,106 Netherlands: ▸ Breast milk107 ▸ Serum and cord blood serum108–111 Spain ▸ Adipose tissue, Spain112 ▸ Serum, Spain113–116 ▸ Breast milk114 ▸ Colostrum117 ▸ Placentas114 ▸ Cord serum114–116	

Substance	Available HBM knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
	Other countries: ▸ Hair, Poland118 ▸ Blood, Austria119 ▸ Adipose tissue, Czechia120,121 ▸ Breast milk, Czechia122,123 ▸ Modelled exposure assessment, Europe124 ▸ Breast milk, Italy125 ▸ UK, dietary exposure126 ▸ Breast milk, Greece127 ▸ Serum, Greece19	
HBCDD	**Biomonitoring data for HBCDDs in a range of human matrices (primarily serum, maternal milk):** Belgium: ▸ Breast milk102–104 ▸ Serum104,106,35 ▸ Modelled exposure35 ▸ Cord blood104,106 Norway: ▸ Breast milk87–90 ▸ Serum86,128 ▸ Dietary exposure35 Netherlands: ▸ Cord serum108–110 ▸ Serum109,110	Gaps: ▸ Biomonitoring data for Southern and Central/Eastern Europe ▸ Coherence and synthesis in data Activities: ▸ Synthesis and/or meta-analysis of existing HBM data needed to identify time trends in exposure and possible regional differences. Inform on whether current regulatory structure can effectively lead to decreases in human exposure ▸ Statistical evaluation of average concentrations, time trends and potential variance between population subgroups both regional and at risk (meta-analysis).

Substance	Available HBM knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
	France: ▸ Breast milk94,96 ▸ Serum94 ▸ Cord blood94 ▸ Adipose tissue94	
	Other countries: ▸ Dust ingestion exposure, UK129 ▸ Breast milk, Denmark96 ▸ Breast milk, Finland96 ▸ Breast milk, Sweden22,66,69,71 ▸ Serum, Sweden71,74 ▸ Hair (method)130 ▸ Germany, serum93 ▸ Adipose tissue, Czechia121 ▸ Breast milk, Czechia122 ▸ Breast milk, Spain131 ▸ Serum, Greece19	

Substance	Available HBM knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
Cat. B substances	Inventory of available human exposure data for Cat. B substances: Dechlorane Plus, serum, France[18] Dechlorane Plus, serum, Germany[132] Dechloranes, BFRs, serum, Norway OPEs, hair, Norway[133] OPEs, urine (metabolites), Norway[23] OPEs, urine (metabolites), Germany[24] NBFRs, hand wipes, Sweden[134] OPEs, inhalation and dermal occupational exposure, Finland[135] OPEs, dietary intake, Sweden[136] OPEs and BFRs, dietary intake, Norway[137] OPEs, Norway, human exposure[138] TPP, urine (metabolites), Sweden[139] NBFRs, Methods for analysis of serum[140] NBFRs – methods for breast milk[107] NBFRs – Breast milk, Netherlands[107] NBFRs, feces, Sweden[81] NBFRs, serum, Sweden[74] BTBPE, DBDPE, EH-TBB, BEH-TEBP, TBBPA-DBPE – human exposure estimate via dust ingestion, UK, Belgium[141] TBBPA – inhalation and dermal occupational exposure, Finland[135]	Synthesis of existing data regarding biomonitoring and exposure for all target FR – evaluation of data gaps for regions and compounds. Assessment of HBM data quality – appropriateness of monitored matrices for target compounds FR metabolite data – identification of urine metabolites, especially for OPEs Evaluation of published toxicity data (scientific literature) to identify which compounds have currently available information of relevance to typical human exposure levels Development of SOPs for determination of compounds in target human matrices Screening of existing HBM projects or biobank archives for Cat. B substances with lack of HBM data. Particular data gap for Southern and Eastern Europe

Substance	Available HBM knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
	TBBPA – estimated total human exposure, Greece and Romania[142] TBBPA, serum, Belgium[106,143] TBBPA, breast milk, Czechia[122] TBBPA, France: ▸ Breast milk94 ▸ Serum94 ▸ Cord blood94 ▸ Adipose tissue94	
Cat. C substances	Inventory of available human, environmental, usage and toxicological data for Cat. C substances HCDBCO – identification in air and dust[144], detection in breast milk and serum (Canada)[145] Dechloranes – detection in breast milk and serum (Canada)[145] Dechloranes, serum, France[18] Dechloranes – dietary intake, Belgium[146] TTBP-TAZ – detection in consumer products and dust[147] RDP – detection in consumer products[41] BPA-BDPP – detection in consumer products[41] V6 – detected in consumer products and dust from USA[148]; foam baby products, USA[40]; urine (ND) and nails, Norway[149] TBC – identified in river water and biota, China[150]	Screen (semi-quantitative) for presence of compounds in human and/or environmental matrices, using existing biobank archives where possible Develop validated methods to improve quantification for compounds that are consistently identified or listed as high concern based on gathered toxicity information

Other knowledge:

- OPE metabolites in urine, German Environmental Specimen Bank
- OPE metabolites in urine, Environment Agency of Austria
- PBDEs in breast milk, Environment Agency of Austria
- PBDEs, HBCDD, NBFRs in selected human matrices, Czech national biomonitoring, Czech Institute of Public Health

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
- 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
- Evaluation of HBM data (linking with exposure estimates/reference doses through PBPK modeling and/or TDI 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 exposure levels based on biomonitoring and toxicity evaluation)
- 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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7. Prioritised substance group: Cadmium (Cd) and Hexavalent Chromium (Cr VI)

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7.1. Background Information

7.1.1. Hazardous properties:

Cadmium

Cadmium is a potentially toxic metal that ranks 7th on the priority list of hazardous substances of US Agency for Toxic Substances and Disease Registry's (ATSDR). International Agency for Research on Cancer (IARC) has classified cadmium as a human carcinogen (Group 1B). Chronic occupational exposures (~45 years) to Cd in the air at concentrations of 5-10 µgCd/m^3 could lead to renal tubular damage in some of exposed workers and exposure to higher levels of 100 µgCd/m^3 may result in obstructive lung disease (Nordberg et al., 2015). Experimental studies showed that Cd can induce lung and prostate cancer in laboratory animals and some epidemiological studies have also found increased rates of cancer in the same and some other organs (Nordberg et al., 2015).

Kidneys, as a major location of Cd accumulation, are primary organ of adverse metal effects that occur at general population after lifelong exposure resulting in urine concentrations of 4 µg Cd/g creatinine. The same level of exposure in more sensitive groups (pregnant and postmenopausal women, elderly) can also lead to bone effects such as osteoporosis and increased risk of fractures. Cadmium adverse effects at lower environmental exposures (<1 µg Cd/g creatinine) - related to bone diseases, effects on kidney functions, effects on endocrine system, reproduction and development ect. - have been recently seriously questioned (Åkesson et al., 2014; Nordberg et al., 2015; Apostoli and Catalani 2015; Bernard, 2016).

However, Cd co-exposure and effects in mixtures of chemicals has not been addressed sufficiently. Most experimental and human studies are dealing with exposure to a single element while real environmental exposure is generally characterised by many substances in unpredictive combinations or exposure conditions and by essential metal status (Apostoli and Catalani 2015, Nordberg 2015).

Hexavalent Chromium

Chromium can exist in oxidation states ranging from -2 to +6, but is most frequently found in the environment in the trivalent (+3) and hexavalent (+6) oxidation states. The +3 and +6 forms are the most important as the +2, +4, and +5 forms are unstable and are rapidly converted to +3, which in turn is oxidized to +6 (Towill et al. 1978). Hexavalent form - Cr(VI) - is more toxic than trivalent form - Cr(III) for its high oxidizing potential - and easily penetrates biological membranes.

Hexavalent chromium was classified by IARC as a human carcinogen (Group 1) associated with increased lung cancer risk among workers in certain industries and also cancer of the nose and nasal sinuses.

In EU the estimated number of Cr(VI)-exposed workers in 2012 was ~786,000, with the largest numbers exposed to welding (IARC, 2012). In the EU CLP Regulation (EC) No 1272/2008 they are classified as genotoxic (Muta. 1B) and as carcinogen (Carc. 1B or 1A).

Also the dermal exposure to Cr(VI) compounds can cause skin irritation, ulceration, sensitization, and allergic contact dermatitis (NIOSH, 2002). The toxicity of Cr(VI) in humans has been reviewed extensively (ATSDR, 2012; Costa and Klein, 2006; U.S. EPA 1998). After absorption, mainly via inhalation for workers and/or via ingestion for the general population, Cr(VI) readily penetrates cell membranes. The details of Cr(VI) toxic activity assumed that genotoxicity, including a wide variety of effects such as DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations, cell transformation, and dominant lethal mutations, may be due to the reduced forms of intracellular origin formed by the reduction of Cr(VI) to Cr(III) (Stearns et al., 1995). The main protection mechanism against Cr(VI) activity in the lungs and the stomach is the extracellular reduction of Cr(VI) to Cr(III) by a NADPH-dependent mechanism involving ascorbate (De Flora et al., 2000). Animal trials show that glutathion plays an important role in Cr(VI) reduction in erythrocytes, also showing certain reduction activity in the lungs (Suzuki and Fukuda, 1990).

7.1.2. Exposure characteristics:

Natural and anthropogenic sources of Cd (European Chemical Agency, 2013; Nordberg et al., 2015)*:*

Cadmium levels in the environment vary widely and are a consequence of both natural (erosion of parent rocks, volcanic eruptions, forest fires; 10-50 %) and anthropogenic sources (used in : plastics as colour pigment and stabilizer, automobile radiators, alkaline batteries, mining activities, fertilizers, sewage sludge, inappropriate waste disposal; 50-90%). During the twentieth century the world consumption of Cd has increased continuously to a global supply of 22,000 metric tons (International Cadmium Association, 2002) and it has remained at this level since 2000. Cadmium is normally transported between the three main environmental compartments:

- Air

Levels of Cd in the ambient air are usually low, whereas indoor air levels can be higher due to cigarette smoking (1 - 2 µg of Cd/ cigarette) and poor ventilation. The document of air quality criteria by World Health Organisation (WHO, 2000) indicates levels of Cd in Europe of 1-10 ngCd/m^3 for urban areas and 0.1 – 0.5 ngCd/m^3 for rural areas. In more remote areas values of 10 – 100 times lower have been reported and around some Cd-emitting industries the levels could approached 200-600 ngCd/m^3.

- Water

Cadmium concentration of natural surface water and groundwater is usually <1µgCd/L. Drinking water in general does not exceed concentrations of 5 µgCd/ L, but could be contaminated in some occasions due to the Cd impurities of galvanized pipes, water heaters/coolers or by leakage of Cd into groundwater from dumped Cd oxide sludge.

- Soil

In nonpolluted areas Cd concentrations are below 1mgCd/kg of soil. Levels in soil can be increased by either waterborne or airborne Cd. Most of agricultural soils contamination occurs by the use of phosphate fertilizers leading in elevated levels of Cd in crops. In Sweden, the levels of fertilizers have been regulated, but a small increase is still occurring, depending on the region and type of farming.

Natural and anthropogenic sources of Cr(VI) and Cr(VI) compounds

The occurrence of Cr(VI) is rare naturally. Most of Cr(VI) compounds are man-made (products or by-products) and human-caused Cr(VI) contamination is a result of large industrial emissions (mainly from metallurgical, chemical, and refractory brick industries). Major uses of Cr(VI) compounds include metal plating, manufacture of pigments and dyes, corrosion inhibitors, chemical synthesis, refractory production, leather tanning, and wood preservation (Blade et al., 2007). Due to a lack of internal supply and to demand from the steel industry, the EU has been an importer of Cr ores. The main sources for EU imports in 2006 were South Africa (approximately 80%). Within the EU, Finland was the main producer of Cr in 2006, producing over 99% of the total EU Cr production (219,500 tonnes). A report on a critical raw material profile by the European Commision in 2014 reveal that the forecast average annual demand for Cr growth of 3%-4.5% *per year* (EC Report, 2014, Report on Critical raw materials for the EU (http://ec.europa.eu/DocsRoom/documents/10010/attachments/1/translations).

Mobilisation of Cr occurs among the following environmental compartments:

- Air

In rural areas Cr concentration above 10 ng/m^3 was uncommon whereas in urban areas it was two to four times higher than regional background concentrations (WHO, 2003; OEHHA, 2011). Air Cr concentrations in urban European areas were found to span 4-70 ng/m3, while in industrial European settings were in the range 5-200 ng/m3 (WHO, 2000). As a result of smoking, Cr concentrations in indoor air (≈ 1000 ng/m3) may be 10-400 times greater than outdoor concentrations (WHO, 2003).

- Water

Surface runoff, deposition from air, and release of municipal and industrial waste waters are sources of Cr in surface waters. The Cr(VI) species can persist in aquatic media as water-soluble complexes, but in presence of organic matter (or other reducing agents) it undergoes to reduction to Cr(III). Although total Cr may be reach levels greater than 50 µg/L, in general it is detected at concentrations in the order of few tens of µg/L or lower. In rainwater, Cr concentrations on average fall in the range 0.2-1 µg/L, some part of which may be accounted for by Cr(VI). Total Cr concentrations in groundwater and water from drinking water sources/supplies may range from < 1 µg/L up to a few µg/L. The presence of Cr(VI) in drinking water and/or its precursors is often consequence of anthropogenic contamination by industrial activity, with levels up to 53 µg/L in the case of Thiva-Tanagra-Malakasa basin (Eastern Sterea Hellas, Greece). Finally, as water treatment facilities use strong oxidants to potabilise water, in drinking water Cr may easily be present in the hexavalent state (WHO, 2003; EFSA 2104).

- Soil

Chromium levels in soils can vary up to three orders of magnitude, reflecting the composition of the parent rock from which the soils were formed and/or local anthropogenic sources (WHO, 2000). Estimated total Cr concentrations in agricultural European soils found that total Cr is quite abundant. From this study, 2.7% of soils were above the threshold value (100 mg/kg) and 1.1% above the guideline value (300 mg/kg) set by the Finnish Ministry of Environment and about 2 million ha of agricultural land - with special emphasis for Piemonte, Lorraine-Alsace, Western-Macedonia and Central Greece - were considered at an ecological and health risk (Toth et al., 2016).

Other sources of exposure to Cr(VI) need to be considered for general population, including the release chromium, with Cr(VI) as the predominant species, from orthopedic implants made from stainless steel and cobalt-chromium alloys. Dermal exposure through leather articles and cosmetics, and oral exposure of children through toys have been reported..

Human exposure route and Human biomonitoring (HBM) data availability for Cd

General population is exposed to Cd primarily through diet and drinking water (5-10 % of ingested Cd is absorbed), and tobacco smoke (10-50 % of inhaled Cd is absorbed). The mean exposure of adults in Europe and North America through food is 10-20 μg Cd/day, which results in average urinary excretion of 0.5-1.0 μg Cd/day and blood concentrations of 0.5-1.0 μgCd/L for non-smokers (twice as high in smokers) (Nordberg et al., 2015).

At the European level the biomarkers are collected in national HBM programs (German Environmental Survey, GerES; The Flemish Environment and Health Study, FLEHS; French Nutrition and Health Survey, ENNS; Czech Republic HBM, CZ-HBM; Slovenian National HBM; etc.) and international projects (Public health impact of long-term, low-level mixed element exposure in susceptible population strata, PHIME and DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale, COPHES/DEMOCOPHES).

Health-based reference values for cadmium in urine are 1 µg/L (µg/g creatinine; HBM I) and 4 µg/L (µg/g creatinine; HBM II) for adults, and 0.5 µg/L (µg/g creatinine; HBM I) and 2 µg/L (µg/g creatinine; HBM II) for children, as set by the German Human Biomonitoring Commission (Schulz et al., 2011). In blood, reference value is below 1 µg/L for adults (Wilhelm et al., 2004).

Human exposure route and Human biomonitoring (HBM) data availability for Cr(VI)

Breathing contaminated workplace air is the main source in occupational setting. For the general population exposure to Cr occurs primarily by ingestion of Cr-contaminated soil, food, and water, but also through inhalation of ambient air. Cigarette smoking is another important source of Cr exposure, including the hexavalent state. When talking about total Cr, it is accepted that the contribution of drinking water to the total exposure is substantial only when levels are above 25 µg/L (WHO, 2003). However, the EFSA Panel on Contaminants in the Food Chain noted that the contribution of drinking water to total Cr refers to Cr(VI), whereas in food the trivalent form Cr(III) is the major form. Mean chronic exposure assessment for Cr(VI) across European dietary surveys through the consumption of drinking water ranged from 0.7 ng/kg b.w. per day to 159.1 ng/kg b.w. per day (EFSA, 2014).

Biological monitoring of exposure to Cr(VI) compounds is a practice in occupational settings. In workers, the distribution of inhaled Cr(VI) permits the biological monitoring of Cr in urine, whole blood, plasma, and blood cells. Relevant biological monitoring guidance values for occupational exposure to Cr have been reported on a national basis, but not at EU level. The Spanish authorities set a biological limit value (BLV) for total Cr concentration of10 µg/L in urine measured during a shift and 25 µg/L at the end of the workweek (INSHT, 2016). In the UK, a biological monitoring guidance value (BMGV) of 10 µmol/mol creatinine in post shift urine was established (HSE, 2011). In Germany, in order to help interpretation of occupational biomonitoring results, DFG did set a BAR (Biologischer Arbeitsstoff-Referenzwert) for the general not occupationally exposed population of working age of 0.6 µg/L urine for Cr(VI) compounds (inhalable fraction) (DFG, 2012). DFG further established the DFG-EKA values (biological exposure equivalents for carcinogenic substances) for Cr(VI) that set the range of total Cr in urine (form 10 µg/L to 40 µg/L) and in erythrocye fraction of whole-blood (form 9 µg/L to 35 µg/L) if soluble alkaline chromate of a certain concentration and/or hexavalent welding fumes (only for urine) were inhaled over a work shift (DFG, 2015).

No HBM survey have been performed at EU level on Cr(VI) exposure of the general population. Few human biomonitoring data come from individuals accidentally or intentionally ingesting Cr(VI) compounds.

7.1.3. Policy relevance

Cadmium

Since cadmium is listed in Regulation (EC) No 1272/2008 as human carcinogen, (Carc. 1B) and due to his increasing evidence of toxicity, both national and international agencies have sought to regulate its exposure. The WHO (2004) guidelines for drinking water quality has been revised from 5 to 3 µgCd/L and WHO (2000) guidelines for ambient air 5 ngCd/L. The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2012) has recommended an intake from food of 25 µg/kg bw/month (Nordberg et al., 2015). 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 and contains the most recent maximum levels for Cd in foodstuffs. These levels continue to be reviewed by the Commission. An updated scientific basis is therefore of great importance.

Hexavalent Chromium

In the case of Cr(VI) compounds an oral minimal risk level (MRL) of 0.005 mg/kg b.w. *per day* was derived for intermediate (15-364 days) exposure based on haematological effects in rats, while reported in a chronic drinking water study (> 1 year) an oral MRL of 0.001 mg/kg b.w*. per day* was derived selecting as critical effect non-neoplastic lesions of the duodenum (ATSDR, 2012). The WHO derived an oral tolerable daily intake (TDI) for non-cancer effects of 0.9 µg CrVI/kg b.w. *per day* taking into account the data relative to outcome observed in female mice after exposure to sodium dichromate dehydrate in drinking-water (WHO/IPCS, 2013). In a recent document, EFSA provided information on benchmark doses, margin of exposure (MOE) and TDI for the European population (EFSA, 2014).

To date no EU regulation regarding maximum levels of total Cr in food has been established.

A maximum value of 50 µg Cr/L for total Cr both in water intended for human consumption and in natural mineral waters are reported by the Council Directive 98/83/EC and the Commission Directive 2003/40/EC, but no level is available specifically for Cr(VI).

In air, the EU proposed a new limit for the hazardous Cr(VI) is 25 µg/m^3, a level of exposure that will have huge effects on the workers as well as anybody living close to facilities where it is used

(http://europa.eu/rapid/press-release_MEMO-16-1655_en.htm). On a national level, many countries experienced a considerably lower level of exposure to Cr(VI): France (1 µg/m^3) as well as Sweden, Lithuania and Denmark (5 µg/m^3), for example. In addition, the Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit (PEL) of 5 µg/m^3 and an action level (AL) of 2.5 µg/m^3; both values represent the time weighted average exposure for Cr(VI) for a typical 8 hour work shift.

Hexavalent Cr is included in the revised Annex XIV to the EU REACH Regulation; inclusion in this Annex means that in order to continue to use chromium trioxide and other hexavalent chromium compounds after 21 September 2017, an authorisation will be required.

In addition, since 1 May 2015 a restriction on Cr(VI) in leather is in place (EU Regulation 301/2014) and applicable at EU level (limit of 3 ppm). That threshold is expected to be 80 % effective in reducing the occurrence of new Cr(VI)-related allergic dermatitis cases due to Cr(VI) in leather articles.

Moreover, current migration limits for Cr(VI) are laid down in the Toy Safety Directive 2009/48/EC for ensuring the safety of toys. The current migration limits for Cr(VI) from toys are: 0.2 mg/kg toy for scraped-off toy materials, 0.02 mg/kg toy material for dry (powder-like or pliable) toy materials and 0.005 mg/kg toy material for liquid or sticky toy materials, respectively.

Regarding cosmetics, because of its allergenic character, the presence of Cr(VI) is prohibited in cosmetics by a German cosmetics regulation and also by the corresponding new EU Cosmetics Directive 76/768/EEC; the only allowable green colorants are those based on the trivalent form of Cr (chromium hydroxide green ($Cr_2O(OH)_4$) and chromium oxide green (Cr_2O_3)).

7.1.4. Technical aspects (Nordberg et al., 2015, Bernard et al 2016)

Biomarkers related to low environmental cadmium exposure that are currently commonly used are levels of:

- Cd in urine is usualy accepted as biomarker of body burden reflecting long term accumulation, but such definition is limited to occupational or really excessive exposures. At low environmental situations urine Cd levels are influenced by several factors including physiological varations related to normal (age, circadian rhythm) and stress conditions (physical stress, smoking) or silent (undercurrent) pathysiological conditions. All these factors are affecting kidney pathways and coexcretion patterns of renal functional biomarkers and Cd itself. Coexcretion of Cd and proteins adds uncertainity to the relationship between UCd and the body burden of Cd.
- Cd in blood /plasma (in most laboratories chemical analyses are not sensitive enough to permit the accurate measurement of plasma or serum). At low Cd levels blood represents recent and past exposure; they can not be properly distinguished.
- Cd in placenta is used as indicator of Cd exposure during pregnancy
- Cd in cord blood is indicating Cd transfer from maternal blood to cord blood
- Cd in faeces - at low doses comparable with urine excretion)
- Cd in kidney, liver or bone tissues is reflecting Cd accumulation.
- renal function biomarkers in urine such as: albumin (Alb) and Imunoglobulin G (IgG) indicating glomerular kidney damage, and N-acetyl-beta-D-glucosaminidase (NAG), α1-microglobulin (A1M), β2 microglobulin (B2M), retinol-binding protein (RBP), Kidney Injury Molecule-1 (KIM-1), metallothioneins (MTs) indicating tubular kidney damage (Nordberg et al., 2015) – at low levels they rather function as indicators of normal physiological processes, so they are unrepresentative for Cd risk assessment at low levels.

The most common methods for Cd determination in human matrices are inductively coupled plasma mass spectrometry (ICP-MS), atomic absorption spectrophotometry (AAS) and atomic fluorescence (AAF). For the in vivo determination of Cd in tissues method of X-ray fluorescence is used. For the determination of renal function biomarkers in urine the standard nephelometric immunochemical method is used, which is less accurate than the measurement of Cd levels in urine or blood. Therefore, determination of renal function biomarkers in relation to Cd exposure and health risk assessment is more reliable at high Cd exposures (> 4 μgCd/ml).

Biomarkers related to Cr(VI) exposure are, currently, the followings:

An important consideration in biological testing for Cr(VI) is the reduction of Cr(VI) to Cr(III) throughout the body. Basically, inhalation is the primary route of concern for occupational Cr(VI) exposure. Inhaled Cr(VI) enters the respiratory system, where it may remain, be reduced, or enter the bloodstream. Cr(VI) may be reduced to Cr(III) in the lungs or plasma and excreted as Cr(III) in the urine. Cr(VI) that is not reduced in the plasma may enter erythrocytes and lymphocytes. This distribution of absorbed Cr(VI) permits the biological monitoring of Cr in urine, whole blood, plasma, and red blood cells (RBCs) in occupational settings.

- Cr in urine

Urinary Cr levels are a measure of total Cr exposure as Cr(VI) is reduced within the body to Cr(III). The average urinary excretion half-life of Cr(VI) is about 39 h.

- Cr measurements in blood and plasma

Plasma or whole blood Cr levels are indicative of total Cr exposure because Cr(VI) may be reduced to Cr(III) in the plasma. Moreover many variables can affect Cr levels in the blood, including diet, varying rates in gastrointestinal absorption, and individual capacity to reduce Cr(VI).

- Cr measurements in red blood cells (RBCs)

Intracellular Cr levels are indicative of Cr(VI) exposure because Cr(VI) passes through cell membranes, while Cr(III) does not. The Cr concentration inside erythrocytes indicates exposure to Cr(VI) sometime during the approximate 120-day lifespan of the cells. There are two advantages to the monitoring of Cr levels in RBCs versus urine: i), the sampling time may be relatively independent of the time of exposure, and, ii), it permits the determination of Cr(VI), rather than only total chromium, absorption.

Thus, in principle, erythrocyte Cr concentration was recommended for its specificity but limited by its low sensitivity. Plasma Cr concentration was recommended as a sensitive parameter, limited by its lack of specificity.

In the last years also the exhaled breath condensate (EBC) is depicted as a very good biomarker of occupational exposure.

However, the above biomarkers of exposure are not sufficiently validated and a great efforts could be made in this sense. In addition, while biomonitoring of occupationally exposed workers has been used to assess high-level inhalation exposures in the workplace, evaluating low-level environmental exposure to Cr(VI) has to be still addressed.

Moreover, the inter- and intrapersonal variability in background levels of Cr is known to be significant and influenced by food and beverage intake, smoking, exercise, habits. Thus, the role of each factor must be carefully understood.

Overview of the biomoritoring methods is available for total Cr in occupational setting. The DFG proposed two regulatory methods: the first for total Cr in urine, the second for total Cr in whole blood as well as in plasma and in erythrocytes. The analytical determination is done using a standard graphite or a pyrolytically coated graphite tube in combination with electrothermal atomic absorption spectroscopy (EAAS) (detection limit were 0.1 µg /L and 0.5 µg /L) (DFG, 1990). Other analytical techniques for total Cr determination in human matrices is inductively coupled plasma mass spectrometry (ICP-MS).

Because Cr(VI) is largely reduced to Cr(III) in the body, speciation of Cr could not be useful in HBM programmes. However, several methods aiming at direct or indirect measurement of Cr(VI) have been published in literature. They are usually based on some kind of separation of Cr(III) and Cr(VI) (i.e., micro liquid chromatography (µLC) system or ion chromatography), followed by ICP-MS quantification (detection limits ranging from 0.1 to 1.0 µg/L).

However, as far as know, none of these methods have obtained the status of regulatory method yet nor have they undergone a validation.

7.1.5. Societal concern:

The societal concerns regarding cadmium exposure is mostly due to (European Chemical Agency, 2013; Nordberg et al., 2015):

- no decrease in soil Cd concentrations and human background intakes in Europe during recent years in spite of improved regulations and guidelines; in local regions and farms even a slight increase have been observed, particularly in Sweden.
- possible occurrence of adverse effects in susceptible population at present exposure levels
- due to continuous accumulation of cadmium in the body
- uncertainties in health risk assessment and therefore in deriving a safe exposure level,
- 'high societal costs in terms of health care and shortening of life time and a decreased quality of life' (European Chemical Agency, 2013; Nordberg et al., 2015).

The societal concerns regarding Cr(VI) exposure are mostly related to:

- presence of high Cr(VI) concentrations in water, air and soils in many European areas despite the limits provided by European regulations and guidelines;
- presence of high Cr(VI) concentrations in many consumers' products such as leather, toys, cosmetics, despite the limits already in place at European level;
- some populations are at higher risk for exposure to Cr(VI), such as children and occupationally exposed workers in many industries;
- possible occurrence of adverse effects with respect to cancer, reproductive and developmental toxicity, but also skin sensitization and allergy, in exposed and general populations;
- the absence of harmonized HBM reference levels and toxicological derived guidance values for Cr(VI) at European level and the lack of validated analytical tools;
- uncertainties in health risk assessment considering also the inter- and intrapersonal variability of Cr(VI) levels and the influence by food and beverage intake, smoking, exercise, habits;
- high prevalence and incidence of Cr(VI) allergy in the general population and risks of carcinogenic effects, maximize the societal costs in terms of quality of life and health care.

7.2. Categorisation of Substances

Table 11: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C substances .

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	Cd	cadmium	7440-47-3	Regulation (EC) No 1272/2008 as carcinogen egulation (EC) No. 1881/2006 for food
C	Cr(VI)	hexavalent chromium	18540-29-9	revised Annex XIV to the EU REACH Regulation EU Directive on cosmetics 76/768/EWG CLP Regulation (EC) No 1272/2008 as genotoxic (Muta. 1B) and as carcinogen (Carc. 1B or 1A) REACH Regulation (EC) No 1907/2006 for inclusion of substances in the Authorisation List (Annex XIV) Regulation (EU) No 301/2014 in leather articles Directive (EC) No 2009/48 on toy safety Directive (EU) No 1223/2009 on cosmetics

7.3. Objectives / Policy-related questions

Objectives:

1. Synthesize an overview of available biomonitoring and exposure data on Cd and Cr(VI) relevant to the European population
2. Overview of 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.

To improve risk assessment related to Cr(VI) other questions need to be addressed:

1. Provide HBM data of occupationally exposed workers to Cr(VI) to assess high-level inhalation exposures in the workplace
2. Provide HBM data of the general population to evaluate low-level environmental exposures to Cr(VI)
3. Provide information as regards relevance and reliability of Cr(VI) measurements in whole blood, urine and RBCs as a biomonitoring tools
4. Validate the above mentioned biomarkers of exposure to Cr(VI)
5. Develop and harmonize methodological approaches for Cr(VI) in biological matrices in terms of proper sampling, sample handling and analysis, and interpretation of results
6. Understand the role of factors as food and beverage intake, smoking, exercise, habits on HBM data of Cr(VI)
7. Provide information on the quantitative relationship between HBM Cr(VI) concentration and Cr(VI) exposure levels (e.g., in air, water and soil)
8. Provide information on the quantitative relationship between HBM Cr(VI) concentration and dermatological risks and cancer risks
9. Monitor effectiveness of Cr(VI) legislative restrictions reported for water, air, soil, leather articles, cosmetics, toys
10. Identify HBM reference values and toxicologically derived HBM guidance values for Cr(VI)

Policy related questions:

1. What is the current (last 5 years) exposure to Cd and Cr(VI) of the European population?
2. What is the level of exposure, environmentally and occupationally relevant to Cr(VI) in the EU population?
3. Do the exposure to Cd and Cr(VI) 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 existing 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 like a reduction of GM/median concentrations?
8. What are the current HBM methods for Cr(VI)? Which are the appropriate biomarkers for Cr(VI)?

7.4. Research activities to be undertaken

Table 12: Listing of research activities to be carried out to answer the policy questions summed up in previous section.

Substance	Policy question	Knowledge gaps / Activities needed to answer policy question
Cd	Current exposure to Cd of the European population: data available for various European countries	Synthesize available biomonitoring and exposure data on Cd relevant to the European population,
	Does the exposure level differ significantly between countries and between population groups: data available for various European countries	Synthesize available biomonitoring and exposure data on Cd and compare the data between different countries and population groups.
	Is there a significant time trend of Cd levels: data available for various European countries	Synthesize available biomonitoring and exposure data on Cd and compare the data on a time scale.
	What are the groups at risk:	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.*
	Are the overall exposure levels in different population groups above any health-relevant assessment levels: data available for various European countries	Compare the available data with the established health-based reference values (e.g. HBM I and HBM II)
Cr(VI)	What are the HBM methods for Cr(VI)	Identify and harmonize the HBM methods for Cr(VI) within EU countries
	Which are the appropriate biomarkers for Cr(VI)	Identify and harmonize the appropriate biomarkers for Cr(VI) in terms of sensitivity, accuracy, needs, costs, availability, etc.
	Current exposure of the European population	Provide biomonitoring data on Cr(VI) to evaluate the exposure of the EU population
	Does the exposure level differ significantly between countries and between population groups	Provide biomonitoring and exposure data on Cr(VI) and compare the data between different countries and population groups (general population, children, workers)
	Is there a significant time trend of Cr(VI) levels	Provide and compare biomonitoring and exposure data on Cr(VI) on a time scale

Substance	Policy question	Knowledge gaps / Activities needed to answer policy question
Cr(VI)	What are the groups at risk	Identify the key groups at risks considering: *life-style, diet; gender, age; regions with elevated levels in the environment; occupational settings; co-exposure to chemical mixtures.*
	Are the overall exposure levels in different population groups above any health-relevant assessment levels	Derive and harmonize reference values and toxicologically derived HBM guidance values for Cr(VI)

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8. Prioritised substance group: PAHs and air pollutants

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8.1. Background Information

8.1.1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants generated primarily during the incomplete combustion of organic materials (e.g. coal, oil, petrol, and wood). Emissions from anthropogenic activities predominate (automobile emissions and cigarette smoke); nevertheless, some PAHs in the environment originate from natural sources (e.g. open burning, natural losses or seepage of petroleum or coal deposits, and volcanic activities).

8.1.2. Hazardous properties: e.g.

- Carcinogenic or Mutagenic or Reprotoxic [category 1A, 1B, 2]
- Specific Target Organ Toxicity (STOT): Repeated Exposure (RE), Single Exposure(SE)
- Endocrine disruptor (ED) potential [identification: substance of very high concern (SVHC), other?]
- Possibility of mixture effects?

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 Persistent Bioaccumulative Toxic (PBT), very Persistent very Bioaccumulative (vPvB) and carcinogenic properties of the PAHs which are present as constituents in these UVCB substances (substances of Unknown or Variable composition, Complex reaction products or Biological materials, ECHA)

Currently eight PAH congeners (Benzo[a]pyrene (BaP), benzo[e]pyrene (BeP), benzo[a]antracene (BaA), chrysene (CHR), benzo[b]fluoranthene, (BbF), benzo[j]fluoranthene (BjF), benzo[k]fluoranthene (BkF), dibenzo[a,h]antracene (DBAhA)) are classified as known carcinogens in Annex VI of Regulation (EC) 1272/2008 (Classification Labelling and Packaging, CLP regulation). These are legally classified carcinogens of Category 2 (acc. to Dir. 67/548/EEC, the ‘Dangerous Substance Directive’ or ‘DSD’) or Category 1B acc. to the CLP regulation.

Benzo[a]pyrene (BaP) and chrysene (CHR) are also legally classified mutagens (BaP: DSD Cat. 2/CLP Cat. 1B; CHR: DSD Cat. 3/CLP Cat. 2). In addition, BaP is a classified reprotoxicant (DSD Cat. 2/CLP: Cat. 1B). Lack of ‘CMR (Carcinogenic Mutagenic Reprotoxic)’ classification1 for the other PAH congeners may rather be attributed to the comparatively limited database available for these compounds. There are indications that the carcinogenic potency of some further PAH congeners, e.g. some of the dibenzopyrenes, may even be considerably higher than that of the lead compound BaP

The mechanism of toxicity is considered to be interference with the function of cellular membranes as well as with enzyme systems which are associated with the membrane. It has been proved that PAHs can cause carcinogenic and mutagenic effects and are potent immune-suppressants. Effects have been documented on immune system development, humoral immunity and on host resistance [1,2]. PAH-induced carcinogenesis can result when a PAH-DNA adduct forms at a site critical to the regulation of cell differentiation or growth. A mutation occurs during cell replication if the aberration remains unrepaired. Cells affected most significantly by acute PAH exposure appear to be those with rapid replicative turnover, such as those in bone marrow, skin, and lung tissue. Tissues with slower turnover rates, such as liver tissue, are less susceptible. Target organs identified in animal studies with some of the PAHs were the skin, the liver, the hemolymphatic and the respiratory system (22, 23, 24). Many PAHs are aryl hydrocarbon receptor (AhR) ligands and several recent studies have suggested that PAHs or their metabolites may activate estrogen receptors (ER). Activation of ER signaling in endocrine cancer prone tissues, such as breast epithelium, might thus further contribute to their known carcinogenicity (25). PAHs have been shown to exert endocrine and developmental toxicity in experimental animals, including decreased weight of reproductive organs, damage to growing ovarian follicles, decreased fertility, embryonic damage and lethality or developmental defects of testis and spermatogenesis in males (26, 27, 28).

PAHs can be formed both during biological processes and as products of incomplete combustion from either natural combustion sources (forest and brush fires) or man-made combustion sources (automobile emissions and cigarette smoke). Thus,

PAHs are commonly detected in air, soil, and water. Therefore, PAHs are considered ubiquitous in the environment [3,4]. PAHs are highly lipid soluble and thus readily absorbed from the gastrointestinal tract of mammals. They are absorbed through ingestion, inhalation, and dermal contact, according to animal study data. The percentage absorbed varies in these studies for several reasons, including the vehicle (transport medium) in which the PAHs are found [Kawamura et al. 1988]. In general, PAHs not bound to particulate matter may be absorbed in the lungs better than the same dose found on the surface of airborne particulate matter [Cresia et al. 1976; Seto 1993]. They are rapidly distributed in a wide variety of tissues with a marked tendency for localization in body fat. Metabolism of PAHs occurs via the cytochrome P450-mediated mixed function oxidase system with oxidation or hydroxylation as the first step. Because of their lipophilic nature, PAHs can accumulate in breast milk and adipose tissue. However, biliary and urinary excretion of PAHs is relatively efficient because of the wide distribution of enzymes that transform PAHs into polar metabolites.

PAHs are predominantly metabolized in the liver, via CYP enzymes (enzymes in the P-450 mixed-function oxidase system) [Kapitulnik et al. 1977; Keifer et al. 1988; Monteith et al. 1987].

In addition to the liver and kidneys, metabolism of PAHs occurs in the adrenal glands, testes, thyroid, lungs, skin, sebaceous glands, and small intestines [ATSDR 1995].

PAHs are transformed initially to epoxides, which are converted to dihydrodiol derivatives and phenols. Glucuronide and sulfate conjugates of these metabolites are excreted in the bile and urine. Glutathione conjugates are further metabolized to mercapturic acids in the kidney and are excreted in the urine.

The hydroxylated metabolites of the PAHs are excreted in human urine both as free hydroxylated metabolites and as hydroxylated metabolites conjugated to glucuronic acid and sulfate [CDC 2005]. A commonly measured urinary metabolite is 1-hydroxypyrene [Becher and Bjorseth 1983; Granella and Clonfero 1993; Popp 1997; Santella 1993].

Metabolism is a prerequisite for hepatobiliary excretion and elimination through the feces, regardless of route of entry. Excretion half-lives in feces and urine have been reported in animal studies as 22 hours and 28 hours, respectively [Becher and Bjorseth 1983].

Pyrene is commonly found in PAH mixtures, and its urinary metabolite, 1-hydroxypyrene, has been used as an indicator of exposure to PAH chemicals [Becher and Bjorseth 1983; Granella and Clonfero 1993; Popp 1997; Santella et al. 1993, CDC 2005].

Exposure to PAHs is almost always to mixtures that pose a challenge in developing conclusions [Samet 1995]. Several epidemiologic studies have shown increased cancer mortality in workers exposed to PAH mixtures.

8.1.3. Air pollutants

Carbon Monoxide is a colourless, odourless, tasteless gas that is slightly lighter than air. Natural background levels of CO fall in the range of 10-200 ppb. Levels in urban areas are highly variable, depending upon weather conditions and traffic density. 8-hour mean values are generally less than 10 ppm (12 mgm-3) but have been known to be as high as 500 ppm (600 mgm-3).

CO is an intermediate product through which all carbon species must pass when combusted in oxygen (O2). In the presence of an adequate supply of O2 most CO produced during combustion is immediately oxidised to carbon dioxide (CO2). However, this is not the case in spark ignition engines, especially under idling and deceleration conditions. Thus, the major source of atmospheric CO is the spark ignition combustion engine. Smaller contributions come from processes involving the combustion of organic matter, for example in power stations and waste incineration.

The main health effects related to exposure to CO are: headaches, dizziness, slows mental processes, and at high levels can lead to death. CO prevents the normal transport of oxygen by the blood. This can lead to a significant reduction in the supply of oxygen to the heart, particularly in people suffering from heart disease.

SO2 is a colourless gas. It reacts on the surface of a variety of airborne solid particles, is soluble in water and can be oxidised within airborne water droplets.

Annual mean concentrations in most major UK cities are now well below 35 ppb (100 µgm-3) with typical mean values in the range of 5-20 ppb (15-50 µgm-3). Hourly peak values can be 400-750 ppb (1000-2000 µgm-3) on infrequent occasions. Natural background levels are about 2 ppb (5 µgm-3).

The most important sources of SO2 are fossil fuel combustion, smelting, manufacture of sulphuric acid, conversion of wood pulp to paper, incineration of refuse and production of elemental sulphur. Coal burning is the single largest man-made source of SO2 accounting for about 50% of annual global emissions, with oil burning accounting for a further 25-30%.

Even moderate concentrations may result in a decrease in lung function in asthmatics. Tightness in the chest and coughing occur at high levels, and lung function of asthmatics may be impaired to the extent that medical help is required. Sulphur dioxide pollution is considered more harmful when particulate and other pollution concentrations are high.

NOx is a collective term used to refer to two species of oxides of nitrogen: nitric oxide (NO) and nitrogen dioxide (NO2). Annual mean concentrations of NO2 in urban areas are generally in the range 10-45 ppb (20-90 µgm-3). Levels vary significantly throughout the day, with peaks generally occurring twice daily as a consequence of "rush hour" traffic. Maximum daily and one hourly means can be as high as 200 ppb (400 µgm-3) and 600 ppb (1200 µgm-3) respectively.

Globally, quantities of nitrogen oxides produced naturally (by bacterial and volcanic action and lightning) far outweigh anthropogenic (man-made) emissions. Anthropogenic emissions are mainly due to fossil fuel combustion from both stationary sources, i.e. power generation (21%), and mobile sources, i.e. transport (44%). Other atmospheric contributions come from non-combustion processes, for example nitric acid manufacture, welding processes and the use of explosives.

The main health effects associated to exposure to NOx are: shortness of breath or coughing and enhanced risk of respiratory disease. Nitrogen dioxide can irritate the lungs and lower resistance to respiratory infections such as influenza. Continued or frequent exposure to concentrations that are typically much higher than those normally found in the ambient air may cause increased incidence of acute respiratory illness in children.

O3 is the tri-atomic form of molecular oxygen. It is a strong oxidising agent, and hence highly reactive. Background levels of O3 in Europe are usually less than 15 ppb but can be as 100 ppb during summer time photochemical smog episodes. In the UK ozone occurs in higher concentrations during summer than winter, in the south rather than the north and in rural rather than urban areas.

Most O3 in the troposphere (lower atmosphere) is formed indirectly by the action of sunlight on nitrogen dioxide - there are no direct emissions of O3 to the atmosphere. About 10 - 15% of tropospheric O3 is transported from the stratosphere where it is formed by the action of ultraviolet (UV) radiation on O2. In addition to O3, photochemical reactions involving sunlight produce a number of oxidants including peroxyacetyl nitrate (PAN), nitric acid and hydrogen peroxide, as well as secondary aldehydes, formic acid, fine particulates and an array of short lived radicals. As a result of the various reactions that take place, O3 tends to build up downwind of urban centres where most of NOx is emitted from vehicles.

Ozone irritates the airways of the lungs, increasing the symptoms of those suffering from asthma and lung diseases.

Particulate matter is a complex mixture of organic and inorganic substances, present in the atmosphere as both liquids and solids. Coarse particulates can be regarded as those with an aerodynamic diameter greater than 2.5 µm (micrometres), and fine particles less than 2.5 µm. Coarse particles usually contain earth crustal materials and fugitive dust from roads and industries. Fine particles contain the secondarily formed aerosols, combustion particles and re-condensed organic and metallic vapours. The acid component of particulate matter generally occurs as fine particles. A further distinction that can be made is to classify particulates as either primary or secondary, according to their origin. Primary particulates are those emitted directly to the atmosphere while secondary particulates are those formed by reactions involving other pollutants. In the urban context, most secondary particulate matter occurs as sulphates and nitrates formed in reactions involving SO2and NOx.

Reported concentrations vary according to the sampling technique. In urban areas typical annual mean values are 10 - 40 µgm-3 (gravimetric sampling) although short-lived pollution episodes such as Bonfire night can cause particulate concentrations to rise to several hundred µgm-3. Background levels in rural areas range form 0-10 µgm-3.

Particulate matter is emitted from a wide range of sources, the most significant primary sources being road transport (20%), homes (20%), construction, mining and quarrying (13%), industrial combustion plants and processes (10%) and public power generation (10%). Natural sources are less important; these include volcanoes and dust storms. Particulate matter can also be formed by the transformation of gaseous emissions such as oxides of sulphur and nitrogen and VOCs.

Fine particles can be carried deep into the lungs where they can cause inflammation and a worsening of the condition of people with heart and lung diseases. In addition, they may carry surface-absorbed carcinogenic compounds into the lungs.

Benzene is a colourless, clear liquid. It is fairly stable but highly volatile, i.e. it readily evaporates. Ambient concentrations of benzene are typically between 1 - 50 ppb. Levels close to major emission sources can be as high as several hundred ppb. The urban background mean concentration of benzene is 1 to 2 ppb (3 to 6 µgm-3); rural areas average 0.5 to 1 ppb (1.5 to 3 µgm-3). Mean annual concentration can be 5 ppb (15 µgm-3) on urban roadsides.

About 80% of man-made emissions come from petrol-fuelled vehicles. This results from both the benzene content of the fuel and partial combustion of the petrol. A further 5% comes from the handling, distribution and storage of petrol and approximately 1% comes from oil refining. Emissions also come from benzene-producing and handling industries, the burning of wood and other organic material, and the use of benzene as a laboratory reagent

Human exposure to benzene has been associated with a range of acute and long-term adverse health effects and diseases, including cancer and aplastic anaemia. Exposure can occur occupationally and domestically as a result of the ubiquitous use of benzene-containing petroleum products, including motor fuels and solvents. Active and passive exposure to tobacco smoke is also a significant source of exposure. Benzene is highly volatile, and exposure occurs mostly through inhalation

VOCs comprise a very wide range of individual substances, including hydrocarbons, halocarbons and oxygenates. All are organic compounds and of sufficient volatility to exist as vapour in the atmosphere. Methane is an important component of VOCs, its environmental impact principally related to its contribution to global warming and to the production of ozone in the troposphere. Regional effects derive from non-methane VOCs (NMVOCs), such as benzene and toluene.

Most measurements of total VOCs are in terms of their carbon content, without analysis as individual compounds. The major contributor to VOCs is normally methane with a local background concentration of 1.6 ppm. Whilst most other individual compounds (e.g. benzene) are present in urban air at concentrations of a few ppb, or less, total NMVOCs will amount to several hundred ppb concentrations.

Hydrocarbons are emitted from petrol evaporation and incomplete combustion, and from leakage of natural gas from distribution systems. Oxygenates arise in vehicle exhausts and via atmospheric chemical reactions. Evaporation of solvents, used in paints or industrial degreasing processes, cause a release of hydrocarbons, oxygenates and halocarbons to the atmosphere.

Possible chronic health effects include cancer, central nervous system disorders, liver and kidney damage, reproductive disorders, and birth defects

8.1.4. Exposure characteristics

- Trends in production volume/environmental concentrations
- Environmental behaviour: half-life in environment/ transport
- Human related exposure sources and uses
- Human exposure routes
- Human biomonitoring (HBM) data availability
- Health based guidance values available for HBM data

Combustion sources are thought to account for over 90% of the environmental concentrations of PAHs. Major anthropogenic sources of PAHs include residential heating, coal gasification and liquefying plants, carbon black, coal-tar pitch and asphalt production, coke and aluminum production, catalytic cracking towers and related activities in petroleum refineries as well as and motor vehicle exhaust.

The following three types: *pyrogenic*, *petrogenic*, and *biological* are the major PAH sources to the environment. In pyrolysis processes pyrogenic PAHs are formed whenever organic substances are exposed to high temperatures under low oxygen or no oxygen conditions. The destructive distillation of coal into coke and coal tar, or the thermal cracking of petroleum residuals into lighter hydrocarbons are pyrolytic processes that occur intentionally. Meanwhile, other unintentionally processes occur during the incomplete combustion of motor fuels in cars and trucks, the incomplete combustion of wood in forest fires and fireplaces, and the incomplete combustion of fuel oils in heating systems.

The temperatures at which the pyrogenic processes occur are ranging from about (350 °C to more than 1200 °C). Pyrogenic PAHs are generally found in greater concentrations in urban areas and in locations close to major sources of PAHs.

PAHs formed during crude oil maturation and similar processes are called petrogenic. Such petrogenic PAHs are common due to the widespread transportation, storage, and use of crude oil and crude oil products. Some of the major sources of petrogenic PAHs include oceanic and freshwater oil spills, underground and above ground storage tank leaks, and the accumulation of vast numbers of small releases of gasoline, motor oil, and related substances associated with transportation. It is well-known that PAHs can be formed during the incomplete combustion of organic substances. PAHs are also found in petroleum products.

On the other hand, it is not well-known that PAHs can be produced biologically. For example, they can be synthesized by certain plants and bacteria or formed during the degradation of vegetative matter.

PAHs are also found in a multitude of consumer articles. Although they are not produced intentionally for this purpose, they are present in these products due to the use of plasticisers (e.g. extender oils) or carbon black (soot) in the manufacture of rubber or other elastomers.

The atmosphere is the most important means of PAH dispersal, it receives the bulk of the PAH environmental load resulting in PAHs being ubiquitous in the environment.

Once released to the atmosphere, PAHs are found in two separate phases, a vapor phase and a solid phase in which the PAHs are sorbet onto particulate matter [5,6,7]. Hydrophobic organic chemicals with low vapor pressures, such as PAHs, are sorbet to atmospheric particulates more readily than chemicals with higher vapor pressures. The variability in vapor pressures of different PAH compounds cause the individual PAHs to distribute in different concentrations in the vapor [8] and other sorbet phases [9]. Low-molecular-weight PAHs (two and three rings) occur in the atmosphere predominantly in the vapour phase, whereas multi-ringed PAHs (five rings or more) are largely bound to particles. Intermediate-molecular-weight PAHs (four rings) are partitioned between the vapour and particulate phases, depending on the atmospheric temperature (21)

The removal of PAHs from the atmosphere by dry and wet deposition processes are strongly influenced by their gas/particle partitioning. Atmospheric deposition is a major source for PAHs in soil.

Background levels of some representative PAHs in the air are reported to be 0.02-1.2 ng/m^3 in rural areas and 0.15-19.3 ng/m^3 in urban areas. Background levels of PAHs in drinking water range from 4 to 24 ng/L

Humans are exposed to PAH through several routes, namely inhalation of air and re-suspended soil and dust, consumption of food and water, and dermal contact with soil and dust (30). All these sources are relevant to global human exposure

There is no sufficient evidence that exposure to PAHs has declined during the last ten years in Europe. In terms of spatial differentiation, exposure to PAHs is expected to be higher in areas with intense traffic and industrial activity.

Personal lifestyle factors, such as smoking and the use of indoor biomass combustion for heating and cooking, are also important determinants of exposure.

Since PAHs are considered carcinogens, there is no threshold under which exposure is safe. Thus, there are no BE values for PAHs. The maximum levels of benzo(a)pyrene and the sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene are regulated in food stuff according to Commission Regulation (EU) No 835/2011 (31). However, there are no other legal instruments regulating the production and/or use of PAHs.

In the Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons (32), United States EPA recommends using toxicity equivalency factors (TEFs) to convert concentrations of 19 carcinogenic PAHs (cPAHs) to an equivalent concentration of benzo(a)pyrene (B[a]P). In this scheme the TEF for B[a]P is set equal to one.

Urinary levels of PAHs and their respective metabolites are associated with proximity to combustion sources such as municipal solid waste incinerators (33). Levels of 1-hydroxypyrene (1-OHP) (a major urinary PAH metabolite) were found to be higher for smokers (0.14 µg/g creatinine) than for non-smokers (0.08 µg/g creatinine) in the study by Lafontaine et al. (34), but not in the study by Leroyer et al. (35). Proximity to hot spot industrial sites in Germany was found to significantly affect PAH exposure levels with the mean urinary 1-OH-P level of 0.31 µg/g creatinine in the children living close to hot spots compared to 0.15 µg/g creatinine compared to children living far from hot spots (36). In all cases, the 1-OH-P levels were lower than the RV of 0.5 ng/L.

Studies in the Czech Republic (37,38) found that levels of B[a]P-like DNA adducts were similar in the Ostrava and Prague regions, although B[a] P levels in the Ostrava region were more than eight times higher. This was attributed to the more efficient DNA repair capacity in the highly exposed population. The nonlinear association between exposure levels and the formation of DNA-adducts, or the occurrence of oxidative stress, highlights the need to use advanced multi-omics approaches that can help to explain the observed pattern and reveal the mechanisms of interaction between environmental toxicants and human systems, which are modified by genetic make-up and other intrinsic factors.

Exposure to PAHs is affected by proximity to intense combustion sources, such as heavily trafficked roads, municipal waste incinerators and industrial sites. An additional source of PAHs is combustion of solid fuel for space heating. In this regard, special attention ought to be paid to the use of biomass in large urban and metropolitan areas, which, if not controlled, may contribute substantially to the overall PAH exposure of the urban population. Biomass combustion for heating is expected to contribute to indoor exposure as well.

8.1.5. Policy relevance

- Existing regulation (sectoral and inter-sectoral policies)
- Upcoming regulation

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.

The following table summarizes the main legislative references for PAHs.

Legislative reference	Matrix	ML[13] (Y/N)	Compound
Commission Regulation (EC) No 1881/2006 Amended by Commission Regulation (EU) No 835/2011	Food	N[14]	16 EPA PAHs (mentioned as generic carcinogenic PAHs at point 58) Not included in other lists: Acenaphthene, Acenaphthylene, Anthracene, Fluoranthene, Fluorene, Naphthalene, Phenanthrene, Pyrene 15+1 EU PAHs:Benzo[*a*]anthracene, Benzo[*b*]fluoranthene, Benzo[*j*]fluoranthene, Benzo[*k*]fluoranthene, Benzo[*c*]fluorene, Benzo[*ghi*]perylene, Chrysene, Cyclopental[*cd*]pyrene, Dibenzo[*a,h*]anthracene, Dibenzo[*a,e*]pyrene, Dibenzo[*a,h*]pyrene, Dibenzo[*a,i*]pyrene, Dibenzo[*a,l*]pyrene, Indeno[1,2,3-*cd*]pyrene, 5-Methylchrysene
		Y	Benzo[*a*]pyrene plus the sum of the 4 marker PAHs (Benzo[*a*]pyrene, Benzo[*a*]anthracene, Benzo[*b*]fluoranthene and Chrysene)
Commission Regulation (EC) No 333/2007 Amended by Commission Regulation (EU) No 836/2011	Food	N	Benzo[*a*]pyrene Plus Benzo[*a*]anthracene, Benzo[*b*]fluoranthene and Chrysene
Commission Recommendation (2005/108/EC) of 4 Faburary 2005 on the further investigation into the levels of polycyclic aromatic hydrocarbons in certain foods	Food	N	15 SCF PAHs: Benzo[*a*]pyrene , Benzo[*a*]anthracene, Benzo[*b*]fluoranthene, Benzo[*j*]fluoranthene, Benzo[*k*]fluoranthene, Benzo[*c*]fluorene, Benzo[*ghi*]perylene, Chrysene, Cyclopental[*cd*]pyrene, Dibenzo[*a,h*]anthracene, Dibenzo[*a,e*]pyrene, Dibenzo[*a,h*]pyrene, Dibenzo[*a,i*]pyrene, Dibenzo[*a,l*]pyrene, Indeno[1,2,3-*cd*]pyrene, 5-Methylchrysene
Commission Regulation (EC) No 672/2006	Primary Smoke products	N	15 SCF PAHs, Benzo[*a*]pyrene, Benzo[*a*]anthracene
Regulation (EC) No 2065/2003 of the European Parliament and of the Council	Primary Smoke products	Y	Benzo*[a*]pyrene, Benzo[*a*]anthracene

[13] Maximum level (Y=yes; N=no)
[14] Benzo[a]pyrene is considered a marker for PAHs

Legislative reference	Matrix	ML[13] (Y/N)	Compound
Directive 2000/76/EC of the European Parliament and the Council	Emissions from incineration plants	N	PAHs (Mentioned as carcinogenic compounds that might be subject to limitations in Member States' regulations)
Decision No 2455/2001/EC of the European Parliament and rhe Council	Water	N	PAHs (Annex: Identified as priority hazardous substance), Benzo[*a*]pyrene, Benzo[*b*]fluoranthene, Benzo[*ghi*]perylene, Benzo[*k*]fluoranthene, Indeno[1,2,3-*cd*]pyrene

For the air pollutants there is regulation which is based on toxicity data available from these pollutants.

8.1.6. Technical aspects

- Biomarkers available for parent compounds or metabolites in human matrices
- Main characteristics of analytical methods (quantitative, semi-quantitative…)

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

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

To study the exposure to PAHs, urinary mono-hydroxylated PAHs (OH-PAHs), a group of PAH metabolites, are commonly used as biomarkers (39). Among the OH-PAHs, 1-hydroxypyrene (1-PYR) is the most commonly used PAH biomarker in both occupational as well as in the general population from various countries (40).

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.).

8.2. Categorisation of Substances

__Category A__ compounds: many studies were recently conducted. Data may be sufficient to provide an overall picture across Europe, interpretation of health risks is possible and we expect to answer important policy-related research questions within the first two years of the project. For __category B__ substances: spatial gaps within Europe, have been identified. For __category C__ substances: very little or no data or toxicological/health effect information is available.

Table 13: Substances included in the substance group, listed according to availablitity of toxicology and human biomarker data, in category A, B, C substances (see above)

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	NO2	Nitrogen dioxide	10102-44-0	Directive 2008/50/EC
	SO2	Sulphur dioxide	7446-09-5	Directive 2008/50/EC
	O3	Ozone	10028-15-6	Directive 2008/50/EC
	CO	Carbon monoxide	630-08-0	Directive 2008/50/EC
B		Acenaphthene	83-32-9	According to the notifications provided by companies to ECHA in REACH registrations no hazards have been classified.
		Acenaphthylene	208-96-8	
		Antracene	120-12-7	Substance of very high concern (SVHC) and included in the candidate list for authorisation.
	BaA	Benzo(a)anthracene	56-55-3	Entry 50 of Annex XVII to REACH
	BaP	Benzo(a)pyrene	50-32-8	Entry 50 of Annex XVII to REACH
	BbFA	Benzo(b)fluoranthene	205-99-2	Entry 50 of Annex XVII to REACH
	BeP	Benzo(e)pyrene	192-97-2	Entry 50 of Annex XVII to REACH

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
B		Benzo(ghi)perylene	191-24-2	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects.
	BjFA	Benzo(j)fluoranthene	205-82-3	Entry 50 of Annex XVII to REACH
	BkFA	Benzo(k)fluoranthene	207-08-9	Entry 50 of Annex XVII to REACH
		Dibenzo(ah)anthracene	53-70-3	Entry 50 of Annex XVII to REACH
		Fluoranthene	206-44-0	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is harmful if swallowed and causes serious eye irritation
		Fluorene	86-73-7	According to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects. ECHA has no data from registration dossiers on the precautionary measures for using this substance.
		Chrysene/Benzo(a)phenanthrene	218-01-9	Entry 50 of Annex XVII to REACH
		Indeno(123-cd)pyrene	193-39-5	According to the classification provided by companies to ECHA in CLP notifications this substance is suspected of causing cancer.
		Naphthalene	91-20-3	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is harmful if swallowed and is suspected of causing cancer. Substance included in the Community Rolling Action Plan (CoRAP).

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
B		Phenantrene	85-01-8	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects and is harmful if swallowed.
		Pyrene	129-00-0	According to the notifications provided by companies to ECHA in REACH registrations no hazards have been classified.
		1-Methylnapthalene	90-12-0	According to the classification provided by companies to ECHA in CLP notifications this substance may be fatal if swallowed and enters airways, is toxic to aquatic life with long lasting effects and is harmful if swallowed. ECHA has no data from registration dossiers on the precautionary measures for using this substance.
		1-Methylphenanthrene	832-69-9	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is harmful if swallowed and is suspected of causing cancer.
		2,6-Dimethylnapthalene	581-42-0	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects
		2-Methylnapthalene	91-57-6	According to the classification provided by companies to ECHA in CLP notifications this substance is toxic to aquatic life with long lasting effects and is harmful if swallowed. ECHA has no data from registration dossiers on the precautionary measures for using this substance.
		7.12-Dimethylbenz(a)anthracene	57-97-6	According to the classification provided by companies to ECHA in CLP notifications this substance may cause cancer and is harmful if swallowed.

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
B	235TMNPT	2,3,5-trimethylnaphthalene	2245-38-7	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects and is harmful if swallowed
		Benzene	71-43-2	Entry 5 of Annex XVII to REACH
		Toluene	108-88-3	Entry 48 of Annex XVII to REACH
		Ethylbenzene	100-41-4	According to the harmonised classification and labelling (ATP06) approved by the European Union, this substance may be fatal if swallowed and enters airways, is a highly flammable liquid and vapour, is harmful if inhaled and may cause damage to organs through prolonged or repeated exposure.
		Xylene	1330-20-7	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
		o-Xylene	95-47-6	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
		m-Xylene	108-38-3	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).
B		p-Xylene	106-42-3	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is a flammable liquid and vapour, is harmful in contact with skin, is harmful if inhaled and causes skin irritation. Substance included in the Community Rolling Action Plan (CoRAP).

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
		Formaldehyde	50-00-0	ccording to the harmonised classification and labelling (ATP06) approved by the European Union, this substance is toxic if swallowed, is toxic in contact with skin, causes severe skin burns and eye damage, is toxic if inhaled, may cause cancer, is suspected of causing genetic defects and may cause an allergic skin reaction. Substance included in the Community Rolling Action Plan (CoRAP).
		Acetaldehyde	75-07-0	According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance is an extremely flammable liquid and vapour, causes serious eye irritation, is suspected of causing cancer and may cause respiratory irritation.
C		Biologicals (mould, pollen)		
	PM	Particulate matter (PM1)		
	UFP	Ultra-fine particles (UFP)		

8.3. Objectives / Policy-related questions

1. How high is the current (year 2012 or more recent) exposure (both external and internal) of the EU population to data-rich substances?
2. 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?)
3. 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?
4. 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.?
5. 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)?
6. What are the policy or socio-economic drivers that may have significant impacts on the exposure levels of the European population to these substances?
7. What are knowledge gaps and related research needs for data-rich substances to answer the questions above satisfactorily in the following years (Year 3)? Can the identified knowledge gaps be mended based on existing data or by extension of current good HBM practices?

8.4. Research activities to be undertaken

Table 14: Listing of research activities to be carried out to answer the policy questions

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
PAH (parent)	**Current exposure** to PAHs of the European population: data available for various European countries	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs relevant to the European population, Establish reference values for selected PAHs parent metabolites in urine for general population (adults/children, smokers/non-smokers) and for worker's populations (smokers/non-smokers)
PAH (parent)	Does the exposure level **differ significantly between population groups**: data available for various European countries	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs and compare the data between different countries and population groups.
PAH (parent)	Is there a significant **time trend** of PAHs levels: data available for various European countries	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs and compare the data on a time scale.
PAH (parent)	Which are the **groups at risk**?	Identify the key groups at risk considering: gender, age, life-style, diet and genetic background; regions with elevated levels in the environment; occupational settings.
PAH (derivate)	**Current exposure** to PAHs derivate metabolites of the European population: data available for various European countries	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)
PAH (derivate)	Does the exposure level **differ significantly between population groups**: data available for various European countries	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs derivate metabolites and compare the data between different countries and population groups.
PAH (derivate)	Is there a significant **time trend** of PAHs levels: data available for various European	Collect, combine, harmonize and compare existing HBM and exposure data on PAHs

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
	countries	derivate metabolites and compare the data on a time scale.
PAH (derivate)	Which are the **groups at risk**?	Identify the key groups at risk considering: gender, age, life-style, diet and genetic background; regions with elevated levels in the environment; occupational settings.
Benzene		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		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)
VOC		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)

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9. Prioritised substance group: Anilines

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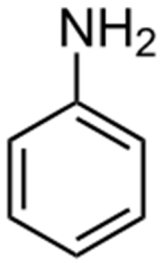
9.1. Background Information

Aniline is the simplest member of the primary 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.



Picture 1: Structure of aniline, the simplest member of the aniline group.

Many aromatic amines may cause methemoglobinemia in humans. Aniline and many of its derivatives are known or suspected human carcinogens. Several aniline derivatives can also cause skin sensitization. Classical members of this family are bladder carcinogens 2-naphtylamine and benzidine, which use has been restricted in EU and there is therefore no exposure to these compounds. Anilines are also formed as degradation products from e.g. azo-colourants, pharmaceuticals and from aromatic isocyanates used for polyurethane polymers, lacquers, foams and adhesives. Search from European Chemicals Agency (ECHA) website from SVHC (substances of very high concern) and registration lists with a search term “aniline” results in more than 2000 search results. Several aniline derivatives can be found also from the candidate list of substances of very high concern (SVHCs) and the list of substances restricted under REACH.

When looking at the aniline substances which are produced or imported in EU areas according to ECHA registration database at amounts above 1000 tonnes per year (tpa) and which have significant health hazards (other than only irritation/corrosion) the following substances can be retrieved:

- aniline, CAS: 62-53-3, harmonized classification in EU; H301, H311, H318, H317, H331, H341, H351, H372, H400
- o-toluidine, CAS: 95-53-4, harmonized classification in EU; H301, H319, H331, H350, H400
- 4,4'-methylenedianiline (4,4'-MDA), CAS: 101-77-9, harmonized classification in EU: H317, H341, H350, H370, H373, H411
- 4,4'-methylenebis[2-chloroaniline] (MOCA), CAS: 101-14-4, Harmonized classification in EU: H302, H350, H400, H410
- p-toluidine, CAS: 106-49-0, harmonized classification in EU: H301, H311, H319, H317, H331, H351, H400
- 1,3-diphenylguanidine, CAS: 102-06-7, harmonized classification in EU; H302, H315, H319, H335, H411, H361f
- p-phenylenediamine, CAS: 106-50-3, harmonized classification in EU; H301, H311, H319, H317, H331, H400, H410

Many anilines have been registered for intermediate use only. These include for example 4-aminoazobenzene, 4-methyl-m-phenylenediamine, 6-methoxy-m-toluidine, 5-nitro-o-toluidine, 4,4'-methylenedi-o-toluidine. Although also these compounds have serious health hazards, they are not considered further because of the limited exposure due to intermediate use. Below, some anilines are discussed in some detail.

9.1.1. MOCA, MDA and diisocyanates

4,4-methylenebis(2-chloroaniline) (MOCA) and 4,4-methylenedianiline (MDA) are currently authorized under REACH. 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. Therefore, biomonitoring is the best method for assessing occupational exposure to them. MDA is also a degradation product and a metabolite of MDI, one of the diisocyanates.

MOCA

MOCA is mainly used as a curing agent of the polyurethane products. It has a low vapour pressure and it is well absorbed through the skin. Therefore biomonitoring is the best method to assess occupational exposure to it. Exposure to MOCA can be biomonitored by measuring MOCA excreted into the urine (free and conjugated MOCA). These methods are well established and used in occupational surveillance of workers. ECHA has recently made a dose-response analysis for the carcinogenicity of MOCA and calculated cancer risk levels for different urinary MOCA levels measured as total urinary MOCA in the end of the work-shift in the end of the work week (ECHA, 2015a). Also the EU Scientific Committee on occupational exposure limits (SCOEL) has recommended a biological guidance value (BGV) for MOCA (SCOEL, 2013). There is one application for authorization for MOCA (ECHA, 2016a). It covers up to 89 sites in EU using MOCA as a curing agent in polyurethane production. Estimated number of exposed workers in EU is, however, only about 200. Authorization has been applied for 12 years. There is, however, no European Commission (EC) decision nor ECHA's Risk Assessment Committee (RAC) and Socio-Economic Analysis Committee (SEAC) recommendation on the authorization available yet.

The applicant has used biomonitoring data to assess the workers' exposure to MOCA. In addition, there are established methods available and published studies, especially from UK, on the biomonitoring of MOCA. Since there are substitutes for MOCA available for the use in polyurethane production, the use of MOCA may cease within becoming years when companies are able to move to the substitutes.

Therefore, MOCA might not be a very relevant candidate for further studies under HBM4EU although biomonitoring of MOCA would still be needed in EU as long as there are authorized uses in the EU. Furthermore, biomonitoring in workers should reveal a decrease over time (monitoring policy effectiveness). The general population is not exposed to MOCA, and the levels of MOCA and its metabolites in the urine of the general population are below the detection limits.

4,4'-MDA

Similarly to MOCA, the production and use of 4,4'-MDA is authorized under REACH. Like MOCA, also 4,4'-MDA is well absorbed through the skin and biomonitoring is the best method to assess occupational exposure to it. There are well established methods for the biomonitoring of MOCA which are based on the analysis of total urinary MDA excretion. The risk assessment committee (RAC) of ECHA has derived a dose-response for the carcinogenicity of MDA and calculated cancer risk levels for different urinary 4,4'-MDA levels measured as total urinary 4,4'-MDA in the end of the work-shift in the end of the work week (ECHA, 2015b). There are only two applications for authorization under REACH. They concern 1) the industrial use of an epoxy resin hardener containing technical MDA aimed at immobilizing spent ion exchange resins in a high containment matrix and 2) the formulation of MDA mixtures for this use. For these uses, there are RAC and SEAC opinions available and a 12 years review period has been proposed for these uses (ECHA, 2017ab). Total number of exposed workers in these uses is 56. The applicant of the authorization provided biomonitoring datasets on the exposure of workers in these uses, and these data were used by RAC in the assessment of excess cancer risk to workers. Due to the limited use (other than intermediate use) and limited number of workers exposed to MDA, exposure to 4,4'-MDA in its use is not a good candidate for further work under HBM4EU.

Diisocyanates

MDA is one of the degradation products and main metabolites of methylene diphenyldiisocyanate (MDI, CAS 101-68-8) MDI is an important respiratory sensitizer. Measurement of urinary MDA can be also used to measure exposure to MDI). Similarly, toluene diamine (2,4-TDA or 2,6-TDA) can be used as a marker for exposure to toluene diisocyanate (TDI, CAS 584-84-9 for 2,4-TDI and 91-08-7 for 2,6-TDI). These diisocyanates are widely used in different applications (e.g. foams, sealants, coatings) throughout the EU, total volume in commerce is 2.5 million tpa (ECHA, 2016b). These diisocyanates (together with non-aromatic hexamethylene diisocyanate, HDI) are causing several thousand new cases of respiratory allergies (mainly asthma) annually in Europe. 4,4'-MDA (and isomers) is also the major cause of non-compliant black nylon kitchen utensils imported from China, and the continuous EC testing requirement under the food contact materials legislation EC 10/2011. The source is likely from recycled polyamide (nylon), and from polyamide containing isocyanate lacquers used to coat the glass fibre reinforcement in the utensils. Aromatic isocyanates are also used in adhesives for laminated flexible plastic food packaging. (Mortensen et al. 2005, Trier et al. 2011). Aromatic Polyurethane polymers are also used in medicinal utensils, e.g. for stomi-bags, as nets operated into patients, in blood bags and tubings, as breast implants from where metabolites have been measured in the patients' blood and sensitisation has occurred.

The use of the diisocyanates MDI, TDI and HDI has been recently proposed to be restricted in EU unless specific conditions for workers training and risk management measures apply. The aim of the restriction is not, however, to ban the use of diisocyanates but rather to improve the control of diisocyanate use by obligatory training for good working practices and risk management. Diisocyanate sensitization can occur at very low exposure levels, and sensitive methods to assess exposure e.g. by measurement of diamine levels in urine are still needed in the future. There may be a need to study the possibility to improve the sensitivity of the current diisocyanate monitoring methods, and the effectiveness of the possible restriction on the occupational exposure to diisocyanates. Especially exposure to diisocyanates at small and medium sized enterprises is a concern.

There is also a need to better understand the exposure routes of isocyanates, e.g. via air, direct skin contact, or via ingestion of aerosols in order to target risk management measures correctly. In addition, sensitive biomonitoring methods, together with air and skin monitoring methods, are needed for the assessment of the effectiveness of the personal protective equipment.

9.1.2. Aniline and paracetamol

Aniline has been assessed under the existing chemicals regulation in EU (ESR, the pre-REACH EU-wide chemicals legislation). It is currently classified as a suspected carcinogen (carc cat 2) under the Classification, Labelling and Packaging Regulation (CLP) in the EU. In addition to the concerns related to the genotoxicity and carcinogenicity of aniline, it can cause methemoglobinemia and in long term exposure haemolytic anaemia. Major use of aniline is as an intermediate in the production of different chemicals, including rubber chemicals, dyes, some pesticides, drugs and polyurethane based polymers. It is also used in pH regulators and water treatment products and may also be formed in the degradation of MDI-based polyurethane and reactions in rubber industry. Smoking is also a source of exposure to aniline. The EU risk assessment report from 2008 (based on the ESR) concludes that there is a need to limit to risk especially for workers but also to general population near the point sources and consumers due to residues in different products. The main cause of concern is its carcinogenicity and genotoxicity (http://echa.europa.eu/documents/10162/d537626b-e5b6-43e9-a7d2-582468edcc24). Toxicity of aniline has been recently assessed also by SCOEL. There are validated biomonitoring methods available for aniline, and e.g. SCOEL has recommended a biological limit value based on the measurement of p-aminophenol in urine (SCOEL, 2016). It is also possible to measure aniline itself from the urine or haemoglobin adducts from blood samples. There are some biomonitoring data available both on the general population and workers exposure to aniline. Aniline has not been currently listed as SVHC substance, nor is it subject of any restrictions under REACH. However, it has been listed in the PACT-RMOA list under REACH, which includes substances for which a risk management option analysis (RMOA) or an informal hazard assessment for PBT/vPvB (persistent, bioaccumulative and toxic/very persistent and very bioaccumulative) properties or endocrine disruptor properties is either under development or has been completed since the implementation of the SVHC Roadmap commenced in February 2013. Further regulatory actions on the aniline could benefit on the additional data on the both occupational and general population exposure to aniline. A metabolite of aniline, N-acetyl-4-aminophenol, is a commonly used drug, paracetamol, which can cause severe liver toxicity if used at high amounts. Ubiquitous exposure to paracetamol among populations have been demonstrated by Holger Koch’s group (Modick et al 2014) who also measured paracetamol the Danish Democophes samples from 2011 (Nielsen et al 2015).

The studies from Denmark related self-reported paracetamol intake of the mothers and her reporting of child intake to the biomonitoring of paracetamol among general population, including children and found no clear associations indicating an unknown source (Jensen et al.2014, Nielsen et al 2015, Graungård et al 2016).

o-Toluidine is classified as carcinogenic, cat 1B (May cause cancer; H350). It is manufactured and/or imported in the European Economic Area in 10 000 - 100 000 tpa. SCOEL has recently published a recommendation on o-toluidine, which includes also a recommendation for a biological guidance value (SCOEL, 2016). Although there are published methods for the biomonitoring of o-toluidine, limited biomonitoring data is available on it. The main uses of o-toluidine include as a curing agent in epoxy resins and an intermediate in producing azo dyes and pigments, acid-fast dyestuffs, triarylmethane dyes, sulphur dyes, indigo compounds, photographic dyes and synthetic rubber and rubber vulcanising chemicals. The largest use is, however, as an intermediate in the manufacture of herbicides. Earlier it was used in dyes and pigments. o-Toluidine is banned from cosmetics by the EU Cosmetics Regulation, also the use of azo dyes that release o-toluidine during degradation is not permitted for textiles and other consumer articles in the EU. Still, there are recent reports describing hairdressers exposure to it via the hair waiving products (Johansson et al., 2015). Cherry et al (2011) has estimated that the number of o-toluidine exposed workers in EU is about 5500, mainly in the manufacture of other chemicals.

Taking into account that exposure may still occur via hair waiving products, the actual number may be higher. Also general population is exposed to background levels of o-toluidine.

p-Toluidine (4-aminotoluene) is manufactured and/or imported in the European Economic Area (1 000 - 10 000 tpa). It is classified as suspected carcinogen (H351). Its main use is in the manufacturing of other chemicals, including dyes, pigments, lubricants and polymer additives. Smoking causes exposure to p-toluidine and it is found in urine in the general population. In hairdressers, no increased exposure to p-toluidine compared to the exposure of general population was seen in a single study (Johansson et al., 2015).

p-PDA

p-Phenylenediamine (CAS 106-50-3) is a common contact allergen present in cosmetics and e.g. in hair dyes and e.g. tattoo inks. It has caused many occupational allergies e.g. among hairdressers exposed due to the contact with hair dyes. It has also been found in black nylon kitchen utensils, like 4,4'-MDA. It has not been regularly biomonitored, although analytical methods for the analysis of it or its metabolites in urine or blood have been published. In these studies exposure of hairdressers to p-PPD has been described. The main hazardous property of p-PDA is its skin sensitizing ability. It has not been listed as SVHC substance, nor is it subject of any restrictions under REACH. However, it has been listed in the PACT-RMOA list under REACH, which includes substances for which a risk management option analysis (RMOA) or an informal hazard assessment for PBT/vPvB (persistent, bioaccumulative and toxic/very persistent and very bioaccumulative) properties or endocrine disruptor properties is either under development or has been completed since the implementation of the SVHC Roadmap commenced in February 2013.

In addition, some of the available studies describe potential exposure to other sensitizing aromatic diamines, like 2,5-TDA, m- and p-aminophenols due to the hair dyes. For example, EU Scientific Committee on Cosmetic Products (SCCP, 2007) has concluded that 2,5-TDA is very potent sensitizer and its use in hair dyes cannot be considered safe based on the available data.

Other high production volume (HPV) aniline compounds

Other substances manufactured/imported in EU >1000 tpa include 1,3-diphenylguanidine (CAS 102-06-7). No biomonitoring studies were found. It is manufactured and/or imported in the European Economic Area in 1 000 - 10 000 tpa. 1,3-diphenylguanidine is used in polymers and manufacturing of rubber and can be released in the environment from many construction, textile, furniture and rubber materials. Few occupational contact allergies have been reported due to 1,3-diphenylguanidine. It is classified as suspected of damaging fertility (H361). It has been subject for substance evaluation under REACH and there are some concerns on its potential genotoxic activity. Another comment raised during the evaluation process relates to the degradation products which may be formed e.g. during rubber manufacturing. These may include e.g. aniline.

Anilines manufactured or imported (in commerce) in EU at amounts of 100-1000 tpa include following substances:

- *N,N-diethylaniline* (CAS 91-66-7), in commerce in the European Economic Area (EEA) in 100 - 1 000 tpa and finds its main uses in the manufacture of other chemicals and in textile treatment products and dyes, rubber and polymers. It is classified as toxic via all routes of exposure and causing organ damage in long term exposure.
- *N-1-naphthylaniline* (CAS 90-30-2); which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its main uses in lubricants and greases, polymers, metal working fluids and hydraulic fluids as well as in the manufacture of rubber products. It is harmful when swallowed and classified as causing damage to organs through prolonged or repeated exposure. It may also cause skin sensitization.
- *N-ethyl-N-[2-[1-(2-methylpropoxy)ethoxy]ethyl]-4-(phenylazo)aniline (CAS 34432-92-3) which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its uses in polishes and waxes, lubricants and greases, adhesives and sealants, washing & cleaning products, fillers, putties, plasters, modelling clay, inks and toners, leather treatment products, paper chemicals and dyes, polymers and textile treatment products and dyes. It is classified as harmful if swallowed, may cause damage to organs through prolonged or repeated exposure, and may cause skin sensitization.*
- *p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline, (CAS 5026-74-4) and m-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline, (CAS 71604-74-5) which are manufactured and/or imported in the EEA in 100 - 1 000 tpa per substance. The para-isomer is used in the manufacturing of other substances. There is limited information on the uses of the m-isomer. Both isomers are classified as suspected of causing genetic defects, it may also cause organ damage in long term exposure and skin sensitization.*
- *1,1'-(p-tolylimino)dipropan-2-ol (CAS 38668-48-3) which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its main uses adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, non-metal-surface treatment products and polymers. It is classified as fatal if swallowed.*
- *dapsone or diaminodiphenyl sulfone (CAS: 80-08-0) which is manufactured and/or imported in the EEA in 100 - 1 000 tpa and finds its main uses in polymers, adhesives and sealants as well as manufacturing of other chemicals, plastics, and rubber. It is also a widely used antibiotic for leprosis and some other diseases. It is classified as harmful.*
- *4,4-oxodianiline (CAS 101-80-4) is an aromatic amine, which is on the candidate list of SVHCs due to its carcinogenic and mutagenic properties. It is manufactured or imported in the EEA in 10-100 tpa and used in the production of polymers*.

For these, no systematic data search have been performed but according to the available information only limited/no biomonitoring data exists for these compounds.

9.2. Categorisation of Substances

*C**ategory A** compounds: many studies were recently conducted. Data may be sufficient to provide an overall picture across Europe, interpretation of health risks is possible and we expect to answer important policy-related research questions within the first two years of the project. For **category B** substances: spatial gaps within Europe, have been identified. For **category C** substances: very little or no data or toxicological/health effect information is available.*

Table 15: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C substances (see above)

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Regulation
A	MOCA	2,2'-dichloro-4,4'-methylenedianiline	101-14-4	REACH: authorization
	MDA	4,4'- Diaminodiphenylmethane	101-77-9	REACH: authorization
B	o-toluidine	o-toluidine	95-53-4	REACH: candidate for SVHC substance
	aniline	aniline	62-53-3	REACH: PACT-RMOA process ongoing
	diisocyanates (MDI/TDI)	methylene diphenyldiisocyanate; toluene diisocyanate	101-68-8 584-84-9 91-08-7	REACH, restriction proposal under consideration
	paracetamol	N-acetyl-4-aminophenol	103-90-2	medicines regulations
	p-PDA	p-phenylenediamine	106-50-3	REACH: PACT-RMOA process ongoing
	p-toluidine	p-toluidine	106-49-0	Registered under REACH, no other current regulatory actions
C		1,3-diphenylguanidine	102-06-7	Registered under REACH, subject for substance evaluation (CoRAP), decision available
		4,4-oxodianiline	101-80-4	REACH, candidate for SVHC
		N,N-diethylaniline	91-66-7	registered under REACH
		N-1-naphthylaniline	90-30-2	registered under REACH
		N-ethyl-N-[2-[1-(2-methylpropoxy)ethoxy]ethyl]-4-(phenylazo)aniline	34432-92-3	registered under REACH
		p-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline m-(2,3-epoxypropoxy)-N,N-bis(2,3-epoxypropyl)aniline	5026-74-4 71604-74-5	registered under REACH
		1,1'-(p-tolylimino)dipropan-2-ol	38668-48-3	registered under REACH
		dapsone	80-08-0	registered under REACH

9.3. Objectives / Policy-related questions

Policy-related questions defined for the priority group “Anilines” are as follows:

1. What is the current occupational exposure to aniline and MOCA in the EU?
2. What is the impact of REACH on levels of anilines? (Feed HBM data into risk assessments of anilines and MOCA)

9.4. Research activities to be undertaken

As explained in this scoping document, “Anilines” is a large group of compounds. Therefore, it is suggested to focus on some priority compounds. These priorities are presented below. These have been selected largely on the basis of regulatory interests. Current information related to MOCA is considered sufficient and further research activities related to MOCA are not considered relevant.

Table 16: Listing of research activities to be carried out to answer the policy questions

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
MOCA	We have sufficient information on the toxicity and occupational exposure to MOCA. Validated biomonitoring methods are available in EU and information for the use of available biomarkers in occupational risk assessment.	No need for further research actions.
4,4’-MDA	We have sufficient information on the toxicity and occupational exposure to 4,4’-MDA in the industrial use of this substance. Validated biomonitoring methods are available in EU and information for the use of available biomarkers in the risk assessment of occupational MDA exposure. However, exposure to MDA formed from methylene diphenyl diisocyanate needs further studies (see below, item “diisocyanates”	No need for further research actions related to the occupational exposure to 4,4’-MDA in its industrial use. Exposure to MDA in the use of methylene diphenyl diisocyanate (MDI), see below, item “diisocyanates”
aniline	Methods for the biomonitoring of aniline exist. Toxicity has been evaluated. Some biomonitoring data available among general population and workers, however, gaps exists. EU risk assessment concludes concern for workers, general population and consumers.	Risk assessment based on the available biomonitoring data for both workers and general population. Identification of the best biomarker for occupational and general population studies, paracetamol intake as confounder in the biomonitoring of aniline. Setting of reference and health based values. Bridging gaps related to exposure.

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
o-toluidine	Methods for the biomonitoring exist. Toxicity have been evaluated. Limited biomonitoring data among general population and workers.	Bridging gaps related to the exposure of workers and general population. Risk assessment based on biomonitoring data. Setting of reference and health based values.
p-toluidine	Methods for the biomonitoring exists. Toxicity have been evaluated. Only very limited biomonitoring data among general population and workers.	Bridging gaps related to the exposure of workers and general population. Risk assessment based on biomonitoring data. Setting of reference and health based values
diisocyanates	Important causes of occupational asthma. Biomonitoring methods available but since asthma may occur at very low exposures, sensitivity of the methods should be high. Some occupational biomonitoring studies are available demonstrating exposure.	If/when restriction is going to become in force, there is a need to follow its effectiveness. Appropriateness/sensitivity of methods to detect low level exposures, still relevant for sensitization. This may need further development. Characterization of the all relevant exposure routes. Risk assessment and setting of limit values based on biomonitoring data.
paracetamol	There are general population biomonitoring data on paracetamol exposure available mainly from Denmark.	What is the general population exposure to paracetamol? Sources of the paracetamol exposure of general population. Paracetamol intake as a confounder in the biomonitoring of aniline. Identification of high exposures and risk assessment of exposure.
p-PPD	There are publications on the development of a method to measure exposure to p-PPD and testing of this method in hairdressers.	What is the exposure of general population and specific occupational groups, e.g. hairdressers to p-PPD, which is a common constituent of cosmetics and e.g. hair dyes.
anilines in general	Different aniline compounds can exist in various products or be formed as degradation of other products. Exposure may occur e.g. due to the pigment used in various products like hair dyes.	Screening of aniline exposure of general public and workers (including professionals like hairdressers), identification of compounds and sources of exposure. Identification of new biomarkers for anilines.

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10. Prioritised substance group: Mixtures

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10.1. Background Information

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 HBM4EU 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 HBM4EU 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 HBM4EU 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 HBM4EU were further developed through e-mail exchanges, with periodic presentations to the HBM4EU Steering Group Meetings.

10.1.1. Hazardous properties

Since a wide range of chemical substances comprise the mixture of chemical substances in the body, and metabolites thereof, all classes of hazardous properties are potentially involved. This poses the challenge to identify where antagonism, addition or synergies in effects come into play, based on modes of action.

Dealing with mixtures in research poses specific challenges e.g. (Kortenkamp 2007, Slama 2015). 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 e.g. (Woodruff 2011, Lenters 2015, Agier 2016). To optimally benefit from these developments new forms of cooperation between traditionally separated research communities and projects need to be build. HBM4EU provides an excellent opportunity and platform to build such alliances.

10.1.2. Exposure characteristics

A central problem in the discussion on mixtures is the virtual absence of adequate exposure data. 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.

In 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. Therefore, also existing data merit re-evaluation from a mixture perspective.

10.1.3. Policy relevance

Dealing with mixtures poses substantial regulatory challenges, with numerous pertinent EU and national regulations.

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 stakeholders[15]. Also JRC has published several reports on assessment of mixtures, that advocate a new test strategy to define the relevant mixtures[16]. EFSA takes pesticides as a concrete point of departure to develop strategies for dealing with mixtures.

[15] http://www.efsa.europa.eu/en/events/event/140211
[16] http://publications.jrc.ec.europa.eu/repository/handle/JRC97522

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.

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[17]. 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.

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.

Based on, among other things, the above, the challenge from the Policy Board laid out for HBM4EU activities reads "We encourage the consortium to start addressing identification of chemical mixtures to which humans are exposed and develop concrete activities, across all three pillars, which would be carried out in the second half of the project. The pre-defined mixtures of substances having common mode of action could frame the initial perspective on this topic.".

10.2. Categorisation of Substances

Mixtures as a group fall into category C (Very little or no human biomonitoring data and/or information on toxicological/health effects or external exposure is available). 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. Data coming available under category D and E would ultimately also fall under the Mixture umbrella.

[17] 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.

10.3. Objectives / Policy-related questions

The overarching objective of the mixture activities in HBM4EU is to improve the efficacy of HBM to inform science, policy/regulatory actions and societal debate with respect to dealing with mixtures.

Some underlying questions include:

- What is the information need of regulatory bodies and stakeholders?
- What are common HBM mixture patterns in the European population?
- Can we identify hotspots or risk groups with high mixture exposures?
- Which sources & pathways contribute most to HBM mixture values?
- Which effect markers can we use to assess health risks of mixtures?
- What action perspectives are available to reduce mixture levels?

The more specific objectives are:

- Develop summary indicators to describe the exposure and body burdens of mixtures with an emphasis on defining priority mixtures and drivers of mixture toxicity
- Re-evaluate existing HBM mixture data to identify real-life exposure patterns to mixtures
- Collect new HBM mixture data in selected European countries
- Further develop and apply practical approaches to assess the potential health risks and impacts of mixtures
- Inform policy makers, stakeholders and the public at large about mixture exposures, possible health risks and action perspectives

10.4. Research activities to be undertaken

Table 17: Listing of research activities to be carried out to answer the policy questions summed up in 8.3

Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
All	What is the information need of regulatory bodies and stakeholders?	In 2017 preparations started for develop exchange of information and establish cooperation amongst Horizon2020 funded projects on mixtures. To this end, a workshop will be organised mid-2018. HBM4EU will taken part in this effort
All	What are common HBM mixture patterns in the European population?	In WP15, task 15.1 We will develop summary indicators to describe the exposure and body burdens of mixtures with an emphasis on defining priority mixtures and drivers of mixture toxicity. With these indicators we will re-evaluate existing HBM mixture data to identify real-life exposure patterns to mixtures. In addition to data-driven approaches, we will aggregate HBM mixture data based on MoA/AOP into cumulative assessment groups as an approach tested by EFSA on pesticides. In WP15, task 15.1 we will collect new HBM mixture data in selected European countries
All	Can we identify hotspots or risk groups with high mixture exposures?	In WP15, task 15.1 and 15.2 will analyse existing and newly generated HBM mixture data to identify possible hotspots and risk groups
All	Which sources & pathways contribute most to HBM mixture values?	In WP15, in concert with WP12 we will address source attribution to observed HBM mixture data
All	Which effect markers can we use to assess health risks of mixtures?	In WP15, task 15.3, we will in concert with WP14 address possible effect markers for mixtures
All	What action perspectives are available to reduce mixture levels?	In WP15, together with WP5, we will evaluate possible action perspectives

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11. Prioritised substance group: Emerging Chemicals

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11.1. Background Information

Emerging Chemicals (ECs) should be understood as chemicals of emerging concern, which can reach human tissues via direct usage of consumer products or uptake via the environment and food. Most of them are manufactured or manmade and their toxicity or persistence are likely to significantly alter the metabolism of a living being (Sauvé and Desrosiers, 2014). Those substances are not yet included in existing HBM programs, partially due to the absence of analytical method available to determine the considered chemical or its metabolites in human specimen. In any case there is a lack of knowledge about the burden of the general population with these so-called emerging substances.

Chemicals can be considered as emerging substances when: (i) they are really '**new substances'** (e.g. recently developed substitutes for substances currently under regulation or which have been banned) or (ii) substances possibly already present for a while in the environment-food-human continuum, but '**causing a new concern'**. Such new concerns can arise due to sensitivity improvements of analytical methods, allowing the detection at low concentrations of formerly not detected substances in the environment or human. In addition, new application fields developed by the chemical industry for a known chemical can open up a new route of exposure. Alongside, recent toxicological facts including increasing presence in the environment and effects on environmental species can be an alert and can also change the perspective for human risk assessment on a given chemical.

In interaction with the prioritization process established within WP4, a complementary list of emerging chemicals candidates is being generated in the first year by WP16. This inventory is based on existing lists of emerging chemicals, e.g. generated by ECHA, EFSA, NORMAN network, and/or from occupational data, but also on bottom-up suggestions originated from WP16 partners daily involved in the characterization of the Human chemical exposome in various contexts. This inventory will be shared and crossed with the WP4 related activity, and further prioritization will occur by considering available exposure, toxicological, and metabolism data as well as analytical considerations. Besides this *a priori* inventory based approach, the development and application of untargeted approaches will be operated within WP16 in the scope of revealing, then identifying, new (i.e. not yet known) markers of exposure related to chemicals of concern for HBM (parent compound or metabolite).

Globally, work on emerging chemicals within the HBM4EU project aims at providing anticipation and early warning, and generating exploratory human data for guiding next orientations of HBM in terms of relevant targets. So that this component has something to do with the sustainability of the program, even after its end. Concretely the outputs of this dedicated chemical group and associated WP16 are expected to contribute mainly to the third and last round of prioritization. This is also referring to a reactivity process and ambition to minimize the delay before warning and real measurement at HBM scale. It is globally based on a principle of reality-driven approach, and a bottom-up characterization of current human exposome as observed to help prioritization of further investments and methodological effort targeted toward certain biomarkers of exposure rather than others. Now all this proposed work in relation with emerging substances still remains a front-of-science associated to a significant level of necessary innovation and methodological research besides these clearly finalized objectives.

11.2. Categorization of Substances

Emerging chemicals may fall in two categories.

The first one is related to a priori already identified substances. The second one is related to not yet known/identified substances. For the first category, the prioritization process and related criteria established within WP4 will be used as a basis for dispatching the different compound candidates between Cat. C and Cat. D. In particular, main criteria considered for this categorization will rely on (i) the investment needed in term of method development and (ii) the knowledge gap in term of exposure data. Indeed, the total number of substances finally classified into Cat. C after application of the systematic process developed within WP4 is expected to be very high. One part of these substances will be handled in WP9 with regard to the development and/or adaptation of appropriate quantitative methods. But realistically this will not be the case for the whole set of compound candidates. For some of these substances (constituting the Cat. D group), the development and application of a semi-quantitative suspect screening approach is then proposed in WP16, with the objective to generate a first level of data enabling to document the reality of human exposure and better justify further investment in a full quantitative and validated method development.

For the second category (constituting the Cat. E group), non-targeted screening approaches coupled to identification of unknowns capabilities and competences will be developed and applied in order to reveal, and further identify, new (i.e. not yet known) markers of exposure related to chemicals of concern for HBM (parent compound or metabolite). From a methodological point of view, this main component of the WP16 work plan will be based on the last generation of mass spectrometric technologies, that offer a unique and never achieved perspective for such global and untargeted sample characterization. High resolution mass spectrometry, already in place in several labs in EU, will be the main support of these investigations, coupled to hyphenated competences in terms of data processing and analysis for extracting the relevant information from the generated global chemical profiles.

Table 18: Substances included in the substance group, listed according to availability of toxicology and human biomarker data.

Cat.	Abbrev./ Acronym	Systematic name	Regulation
A	-	-	-
B	-	-	-
C	-	-	-
D	*a priori* already identified compounds but not yet measured in humans to be measured by suspect target screening	To be defined as a result of the first year prioritization process	-
E	substances measured by non-target screening and (1) described in chemical databases or (2) not yet described (unknowns)	-	-

11.3. Objectives / Policy-related questions

1. Providing early warning of presence of unknown and emerging concern chemicals in EU population
2. Inform REACH process to identify substances of very high concern
3. Inform development of strategy for a non-toxic environment (7th Environment Action Programme)

11.4. Research activities to be undertaken

Table 19: Listing of research activities to be carried out to answer the policy questions

Substance	Policy question	Knowledge gaps / Activities needed to answer policy question
D	Early warning of presence in EU population	Not all listed emerging concern chemicals, e.g. generated by ECHA, EFSA, NORMAN network , and/or occupational data, but also on bottom-up suggestions originated from WP16 partners daily involved in the characterization of the human chemical exposome, can be monitored in human samples for various reasons (budgetary/analytical). ▸ Develop prioritisation tool for these chemicals based on kinetics and toxicological properties, production volume and policy/societal concerns (WP4). ▸ Improve screening methods to allow detection of emerging chemicals, among which some listed by the NORMAN network, in human matrices (urine, blood, placenta, maternal milk, adipose tissue, meconium, hair…) including sample preparation, information extraction, data processing and provide guidelines for method validation. ▸ Select biobanked samples for screening. ▸ Screen human matrices for the presence of emerging chemicals, among which some listed by the NORMAN network. ▸ Collate existing data on mammalian metabolism/distribution/excretion of the selected Cat. D emerging chemicals. If not available: predict potential metabolites using computer models/software and existing data as input for the screening above.
	Inform REACH process to identify substances of very high concern	For NORMAN chemicals detected in human matrices provide information on biological half-life in human matrices and if possible also linkage to effect and health outcomes.
	Development of strategy for a non-toxic environment -> first step	▸ Develop an indicator to monitor in humans the bioaccumulation of the above identified NORMAN chemicals. ▸ Develop an indicator to monitor in humans the decrease of total chemical load of environmental chemicals.

Substance	Policy question	Knowledge gaps / Activities needed to answer policy question
E		▸ Improve non target screening methods to detect not yet identified emerging chemicals in human matrices including sample preparation, information extraction, data processing and provide guidelines for method validation. ▸ Select biobanked samples for first screening steps. ▸ Screen human matrices (urine, blood, placenta, hair, maternal milk, adipose tissue, meconium…) for the presence of unknowns. ▸ Generate databases for identification of the unknowns in human samples, based on mass spectral information

11.5. References

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