HBM4EU science and policy for a healthy future

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SCOPING DOCUMENTS

(1st round of prioritization)

Prioritized substance group: PFAS

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1. Introduction

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

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

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

For further information see www.hbm4eu.eu

Template for Scoping document

Substance group: PFAS

2. Background Information

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 PFASs 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.

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 perfluorohexane sulfonic acid (PFHxS). A recent publication reports an estimated elimination range of 10.1 to 56.4 years – median 15.3 years for chlorinated polyfluoroalkyl ether sulfonic acids [Cl-PFESAs] (Shi et al., 2016). The CLP human health hazard classifications of the different substances are depicted in table 1. Substances which are best-known – perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) – are classified as carcinogenic (Carc. 2, suspected human carcinogens, such as kidney and testicular), 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 PFOA; perfluoroalkyl sulfonates with carbon chain lengths of 6 and higher, including PFHxS and PFOS; and precursors of these substances that may be produced or may be present in products. A recent report showed that in product samples the detected individual PFAS constituted only a very minor part of the total organic fluorine (TOF), illustrating large data gaps in the current knowledge which PFASs that are being used in these products (Borg, 2017).

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 (Barry et al., 2013).

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; Jensen et al., 2015; Joensen et al., 2013; Timmermann et al., 2014). Postnatal exposures have also been associated with thyroid hormone imbalances and reduced immune response to vaccination (Grandjean and Budtz-Jørgensen, 2013). The US National Toxicology programme has listed both, PFOA and PFOS, as presumed to be an immune hazard to humans (NTP, 2016).

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).

A recent systematic review on health effects of PFAS exposure and childhood health outcome observed generally consistent evidence for PFAS' association with dyslipidemia, immunity including vaccine response and asthma, renal function, and age at menarche (Rapazzo et al., 2017).

A comparison of birth outcomes in a PFAS contaminated region in italy with a less exposed population group showed a significantly increased risk for gestational diabetes, preeclampsia and small size for gestational age. Further biomonitoring data would be needed to confirm direct cause and effect (WHO, 2015).

Long chain PFASs (certainly PFOA, PFOS & PFHxS, and possibly others) are actively reabsorbed in the kidney and intestine. This active reabsorption varies and the determinants of the variation (e.g. renal function) may a) be a confounder in using serum levels as the exposure marker in analysing health effects, b) may make individuals more or less vulnerable to the adverse health effects and thus affect how health based limits are set, or c) may be a basis for identifying subgroups at extra risk.

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.

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 and PFOA-related substances which are currently under review as global POPs under the UNEP-Stockholm Convention. PFOA and related substances are subject of a restriction of the manufacturing, marketing and use (EU 2017/1000). 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 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). The OECD is currently updating its Lists of (PFOS), Perfluoroalkyl Sulfonic Acids (PFSAS), PFOA, Perfluorocarboxylic Acids (PFCAs), related compounds and chemicals that may degrade to PFCAs. The publication of the updated lists and results is planned

for December 2017. With the current regulations on PFOS and PFOA also these precursor substances are subject to the EU restrictions.

Another restriction proposal for long-chain PFCAs 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 was submitted to ECHA mid 2017 (Germany, 2017). Several long-chain PFASs are also on the Candidate List of substances of very high concern (SVHC) under REACH: 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): (in food contact materials and 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. First results are expected in the end of 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 (FCM) 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 Programme[1].

PFASs have been recognized as an issue for concern under SAICM (Strategic International Approach to International Chemicals Management)[2]. The OECD has established a web portal in order to facilitate information exchange among stakeholders[3].

[1] http://epa.gov/oppt/pfoa/pubs/stewardship/index.html

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 textiles and in 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. 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. Contamination of the drinking water resources as environmental health thread has been reported for PFASs e.g from the Veneto Region in Italy (WHO, 2017) but also from Sweden (Banzhaf et al, 2017) and other European countries. 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. Recent data demonstrate considerable exposure of alternatives such as GenX in the drinking water (e.g. Gebbink et al., 2017).

There are also concerns about short-chain PFASs, which are assumed to be less bioaccumulative but very persistent and mobile contaminants found in drinking water and food, including vegetables (Hedlund, 2016, Danish EPA, 2015).

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

[2] http://www.saicm.org/EmergingPolicyIssues/Perfluorinatednbsp;Chemicals/tabid/5478/language/en-US/Default.aspx
[3] http://www.oecd.org/ehs/pfc/#Purpose_of_Web_Portal

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. Contrary, 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 detected in higher concentrations in human blood, there are good correlations between the measurement results in these two matrices (UNEP, 2016).

In several studies time trends of PFAS exposure in European countries were investigated. According to Axmon et al. (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 overall study period. Also Glynn et al. (2012) reported increasing concentrations of PFBS, PFHxS, PFNA and PFDA in Swedish breast milk samples between 1996 and 2010. This is also in line with the study from Gebbink et al. (2015) reporting increasing trends in pooled serum samples from Sweden for PFHxS, PFNA, PFDA, PFUnDA, PFODA and PFTrDA. 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, and for PfHxS and PfHpS no trend could be observed (Nøst et al., 2014). In Denmark, concentrations of seven PFASs (PfHXS, PfHpS, PFOS, PFOA, PfNA, PfDA, PfUnDA) decreased in the period 2008-2013 (Bjerregaard-Olsen et al., 2016). Schröter-Kermani et al. (2013) 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. Also Yeung et al. (2013a, 2013b) 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. Isomer profiling of perfluorinated substances can be used as a tool for source tracking. Depending on the two production processes i.e. electrochemical fluorination (ECF) or telomerisation different PFAS isomers are produced. Branched isomers of PFAS are mainly manufactured by the ECF method, which has historically been applied to produce PFOS and PFOA. The differing properties of linear and branched PFAS isomers can affect their fate, behavior and toxicokinetics. So the structural isomer patterns of PFOA and PFOS in humans may be useful for understanding routes and recent or historic sources of exposure (Benskin et al. 2010). Beeson et al. (2011) showed that branched isomers crossed the placenta more efficiently than did linear PFOS and PFOA isomers. Interesting results stem from autopsy analyses: Bioaccumulation occurs in different tissues to a different extent, e.g the short chain perfluorobutanoic acid (PFBA) accumulates predominantly in kidney and lung: 304 ng/g (to a ~10-fold higher concentration than PFOA) in the lungs and 464 ng/g (~230-fold higher concentration compared with PFOA) in the kidneys (Danish EPA, 2015).

There are major knowledge gaps on fluorinated 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 such as ADONA and GenX and PFESAs such as F-53 and F-53B) (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 DNELS[4] 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 (e.g. on the mammary gland) that may be more sensitive than the animal data currently used in the risk characterisation, as these data are not robust enough (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 early 2018.

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 PFASs (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 (Place and Field, 2012; Trier, pers. comm., 2017). 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 (2016) 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,

[4] DNEL: Derived No Effect Level:

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., 2007; 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).

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 is has been shown that several of them are very mobile, bioaccumulative and toxic, whereas for several others there is only some indication as scientific proof is lacking at present. Nevertheless, many PFASs, including fluorinated alternatives to long-chain PFASs, can be ubiquitously detected in the biotic and abiotic environment, in wildlife and in humans, even in remote regions such as the Arctic since several years. In several countries PFASs have been found in ground and drinking water (Domingo et al., 2012; KEMI, 2017). Currently, there are several contamination cases known in different countries (e.g. in Germany, Sweden, Italy, Spain and The 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). Recently, the PFOA replacement chemical GenX was detected at all downstream river sampling sites with the highest concentration (812 ng/L) at the first sampling location downstream from a fluorochemical production plant, which was 13 times higher than concentrations of sum perfluoroalkylcarboxylic acids and perfluoroalkanesulfonates (∑PFCA+∑PFSA) (Gebbink et al., 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 (KEMI, 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 PFASs.

A recent briefing provided by Chemtrust points out that children are currently not sufficiently being protected from chemicals that can disrupt brain development; they list per- and polyfluorinated compounds as one of the chemicals substance groups of concern (Chemtrust, 2017a). Chemtrust also raises the issue of use of PFASs as food contact materials and refers to a report on the implementation of the Food Contact Materials Regulation of the European Parliament which states that action at EU level is needed to address the lack of EU specific measures and the gaps in risk assessment, traceability, compliance and control (EU parliament, 2016) and an assessment of the Joint Research Center on the regulatory and market situation of the non-harmonised food contact materials in the EU (Simoneau et al., 2016). Also, European consumer organisations call for action on fluorinated compounds in fast food packaging (BEUC, 2017).

Moreover the Europen Environmental Bureau (EEB) addressed concerns on exposure of humans to the big group of PFASs: “We would like HBM4EU to address in particular the lack of human exposure information on the substances of the group that are being used as alternatives to other substances of the group that are under regulatory activity, such a PFOS and PFOA” (EEB, 2017).

According to the EEA, PFASs contamination has the potential of a planetary boundary threat (Trier, 2017).

3. Categorization of Substances

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 categories A-E is an attempt to categorize possibly relevant substances that contribute to the overall PFAS burden in humans. Several substances are listed in category A due to their restriction as PFOS- and PFOA-related substances, although limited or no HBM data are available. Efforts should be made to improve the methods to detect the broader spectrum of Category A substances. However, the priority for future HBM research should cover PFOS and PFOA alternatives with high production volume, wide dispersive use and identified or suspected hazardous properties which qualifies for SVHC identification. 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 the list of substances in categories C-E is open ended and should regularly be updated.

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

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
A	PFOA	Perfluorooctanoic acid (linear and branched isomers)	335-67-1	REACH Annex XVII restriction (Regulation (EU) 2017/1000)[5], SVHC Candidate List (PBT, Repr.), CLH (Carc. 2, Repr. 1B, STOT RE 1, Acute Tox. 4, Eye Dam. 1), proposed for inlcusion in the Stockholm Convention, Norman 2011, sufficient EU HBM data available
	PFOS	Perfluorooctane sulphonate, Heptadecafluorooctane-1-sulphonic acid (linear and branched isomers)	1763-23-1	REACH Annex XVII restriction, CLH (Carc. 2, Repr. 1B, Lact., STOT RE 1, Acute Tox. 4, Aquatic Chron. 2), PIC regulation, POP Regulation (EG) No. 757/2010, Stockholm Convention, environmental legislation (Seveso, Directive 2012/18/EU; Regulation 649/2012 concerning export and import of hazardous chemicals), sufficient EU

[5] http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32017R1000

				HBM data available
	PFNA	perfluoro-n-nonanoic acid	375-95-1	Restriction proposal[6], CLH (Carc. 2, Lact., STOT RE 1, Repr. 1B, Acute Tox. 4, Eye Dam. 1), SVHC Candidate List (Repr., PBT), PACT list (CMR, PBT), Annex III Directive 2008/98/EC on waste, Norman 2011, EU HBM data available
	PFDA	perfluoro-n-decanoic acid	335-76-2	Restriction proposal, SVHC Candidate list (PBT, Repr.), PACT list (PBT), Norman 2011, EU HBM data available
	PFU(n)DA	perfluoro-n-undecanoic acid	2058-94-8	Restriction proposal, SVHC Candidate List (vPvB), self classification (Acute tox. 4, Skin irrit. 2, Eye irrit. 2, STOT SE 3), Norman 2011, EU HBM data available
	PFDoDA	Perfluorodeconaoic Acid	307-55-1	Restriction proposal, SVHC Candidate List (vPvB), self classification (Skin irrit. 2, Eye irrit. 2, STOT SE 3, Metal corr. 1, Skin corr. 1B, Eye dam. 1), Norman 2011, EU HBM data available
	PFTrDA	perfluoro-n-tridecanoic acid	72629-94-8	Restriction proposal, SVHC Candidate List (vPvB), self classification (Skin corr. 1B), EU HBM data available
	PFTeDA	perfluoro-n-tetradecanoic acid	376-06-7	SVHC Candidate List (vPvB), Restriction proposal, Norman 2011, EU HBM data available
	PFHxS	perfluoro-1-hexanesulfonate (linear and branched isomers)	355-46-4	PACT list, proposed for inlcusion in the Stockholm Convention, Norman 2015, EU HBM data available, longest half-live in humans (8.5-30 years)

[6] https://echa.europa.eu/documents/10162/13641/rest_pfcas_axvreport_sps-013246-17_en.pdf/ab1c11b0-4ec9-4287-b9c5-32cb98607152

	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	PFOS-related substance; POP Regulation (EG) No. 757/2010, OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), environmental legislation (Seveso, Directive 2012/18/EU), self classification (Acute tox. 3, Skin irrit. 2, Eye irrit. 2, STOT SE 3), Norman 2011, some (but not sufficient) EU HBM data available (e.g. Haug et al., 2009), other non-EU HBM data (e.g. Jin et al., 2016)
	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	PFOS-related substance; POP Regulation (EG) No. 757/2010, PIC Regulation, Norman 2011, some (but not sufficient) EU HBM data available (e.g. Bartolomé et al., 2017), other non-EU HBM data (e.g. Jin et al., 2016; Yeung and Mabury, 2016)
	N-Et-FOSAA, Et-PFOSA-AcOH, Et-FOSAA	N-Ethyl-perfluorooctanesulfonamido acetic acid; 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-heptadecafluoro octyl)sulfonyl]-glycine (IUPAC)	2991-50-6	PFOS-related substance, transformation product, POP Regulation (EG) No. 757/2010, its salts may be marketed under different trade names, may be marker of food or consumer exposures, Norman 2015, limited EU HBM data available (ELFE study – serum samples), other non-EU HBM data (e.g. Kato et al., 2014)
	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	PFOS-related substance, POP Regulation (EG) No. 757/2010, PIC Regulation, environmental legislation (Seveso, Directive 2012/18/EU), self classification (Acute tox. 4), Norman 2011, investigated in human samples but not

				detected (Jin et al., 2016, Miyake et al., 2007, Yeung and Mabury, 2016), detected in indoor dust and air samples (Gebbink et al., 2015)
	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	PFOS-related substance; POP Regulation (EU) No. 850/2004 idgF, PIC Regulation, Norman 2011, detected in indoor dust and air samples (Gebbink et al., 2015), quickly and extensively metabolised to PFOSA with an elimination half-life of 16-20 h, metabolites of N-EtFOSE werde found in human samples (Thayer and Houlihan, 2002), HBM data scarcely available
	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	PFOS-related substance, POP Regulation (EU) No. 850/2004 idgF, PIC Regulation, detected in indoor dust and air samples (Gebbink et al., 2015), no HBM data available at current knowledge
	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	PFOA-related substance, REACH Annex XVII restriction (Regulation (EU) 2017/1000), Norman 2015, Priority HBM List California, limited EU HBM data available (Yeung et al., 2013a, 2013b); other non-EU HBM data (e.g. Lee and Mabury, 2011; Yeung and Mabury, 2016)
	6:2/8:2 diPAP	6:2/8:2 polyfluoroalkyl phosphoric acid diesters	943913-15-3	PFOA-related substance, REACH Annex XVII restriction (Regulation (EU) 2017/1000), Priority HBM List California, no HBM data available at current knowledge

	8:2 monoPAP	8:2 polyfluoroalkyl phosphoric acid monoester	57678-03-2	PFOA-related substance, REACH Annex XVII restriction (Regulation (EU) 2017/1000), no HBM data available at current knowledge
B	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	Alternative to APFO, possible PPARα antagonist, use in food contact material,according to EFSA no risk under specific conditions of use (EFSA, 2011 b) , CoRAP (suspected PBT/vPvB, exposure of environment, wide dispersive use), highlighted by ECHA, limited EU HBM data available (e.g. Fromme et al., 2017)
	PFBA	perfluoro-n-butanoic acid	375-22-4	REACH RMOA[7], Annex III (suspected P), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), self classification (Skin corr. 1A, Eye dam. 1, STOT SE 3, Metal corr. 1), Norman 2015, highlighted by ECHA, levels rising in environment and human tissues (Scheringer et al., 2014), some (but not sufficient) EU HBM data available in plasma, serum, breast milk[8]
	PFPeA	perfluoro-n-pentanoic acid	2706-90-3	REACH Annex III (suspected P, skin irritant), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), self classification (Skin corr. 1B, Metal corr. 1, Eye dam. 1), Norman 2015, highlighted by ECHA, some (but not sufficient) EU HBM

[7] RMOA: Analysis of the most appropriate risk management option: https://echa.europa.eu/de/rmoa
[8] e.g. Antignac et al., 2013; Schröter-Kermani et al., 2013; Sochorová et al., 2017

				data available in plasma, serum, urine[9]
	PFHxA	perfluoro-n-hexanoic acid	307-24-4	RMOA, REACH Annex III (suspected P, C), PACT list (PBT), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), self classification (Skin corr. 1B, Metal corr. 1, Eye dam. 1, Acute tox. 4), Norman 2011, highlighted by ECHA, in Spain higher levels were found in liver samples (68-141 ng/g) (Perez et al., 2012), some (but not sufficient) EU HBM data available in plasma, serum, whole blood, breast milk, urine, liver[10]
	PFHpA	Perfluoro-n-heptanoic acid	375-85-9	REACH Annex III (suspected B, P, C, acute tox via oral route, toxic), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), self classification (Acute tox. 4, Skin corr. 1B, Metal corr. 1, Eye dam. 1), Norman 2011, highlighted by ECHA, some (but not sufficient) EU HBM data available in serum, plasma, whole blood, urine, breast milk[11]
	PFBS	perfluoro-1-butanesulfonate	375-73-5	RMOA, PACT list, REACH Annex III (suspected P, R), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers, Council Directive 94/33/EC on the protection of young people at work), self classification (Acute Tox. 4, Skin corr. 1B,

[9] e.g. Hartmann et al., 2017; Schröter-Kermani et al., 2013; Sochorová et al., 2017
[10] e.g. Antignac et al., 2013; Ericson et al., 2007; Glynn et al., 2012; Hartmann et al., 2017; Perez et al., 2012; Schröter-Kermani et al., 2013; Sochorová et al., 2017
[11] e.g. Antignac et al., 2013; Ericson et al., 2007; Glynn et al., 2012; Hartmann et al., 2017; Schröter-Kermani et al., 2013; Umweltbundesamt, 2013) (unpublished report)

				Metal corr. 1, Eye dam. 1), highlighted by ECHA, ground water contaminant, some (but not sufficient) EU HBM data available in serum, whole blood, breast milk[12]
	PFHpS	perfluoro-heptanesulfonate	60270-55-5	REACH Annex III (suspected B, P, C, R, toxic, acute tox via oral route), self classification (Acute tox. 3, Eye irrit. 2, STOT SE 3), EU HBM data available
	PFDS	perfluoro-1-decanesulfonate	335-77-3	REACH Annex III (suspected B, P, C, R, acute tox via oral route), some (but not sufficient) EU HBM data available in plasma, serum, breast milk, urine[13]
	N-Me-PFOSA-AcOH, Me-FOSAA	N-Methyl-perfluorooctane sulfonamido acetic acid	2355-31-9	transformation product, may be marker of food or consumer exposures, limited EU HBM data available (ELFE study – serum samples), other non-EU HBM data (e.g. Kato et al., 2014)
	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	REACH Annex III (suspected P, B, C, skin irritant), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers, Council Directive 94/33/EC on the protection of young people at work), Annex III Directive 2008/98/EC on waste, self classification (Skin corr. 1B, Eye dam. 1, Acute tox. 4, STOT RE 2), other non-EU HBM data (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	39108-34-4	REACH Annex III (suspected P, C, skin irritant), Priority HBM List California, other (non-EU) HBM data (Yeung

[12] e.g. Ericson et al., 2007; Glynn et al., 2012; Umweltbundesamt, 2013 (unpublished report)
[13] e.g. Antignac et al., 2013; Hartmann et al., 2017; Haug et al., 2009; Schröter-Kermani et al., 2013; Umweltbundesamt, 2013 (unpublished report)

		sulfonic acid		and Mabury, 2016 – levels in all human blood samples below LOQ)
	PFODA	Perfluorostearic acid; Perfluorooctadecanoic acid	16517-11-6	REACH Annex III (suspected C, P), priority HBM List California, limited EU HBM data available (Gebbink et al., 2015)
	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	REACH Annex III (suspected P, B, C), Priority HBM List California, no HBM data available at current knowledge
C C	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	Priority HBM List California, no EU HBM data available at current knowledge, other non-EU HBM data (Yeung and Mabury, 2016 – levels in all human blood samples below LOQ)
	5:3 FTCA 7:3 FTCA	Fluorotelomer carboxylic acids 5:3 Fluorotelomer carboxylic acid 7:3 Fluorotelomer carboxylic acid	-	Fluorotelomer metabolites, Priority HBM List California, detected in blood samples of ski way technicans (Nilsson et al., 2013), HBM data scarcely available
	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	Fluorotelomer metabolites, Priority HBM List California, detected in blood samples of ski way technicans (Nilsson et al., 2013), HBM data scarcely available
	PFECA (GenX)	Perfluoroether carbocylic acids for example: Ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate (GenX)	62037-80-3	CoRAP (suspected PBT/vPvB, exposure of environment), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers, Council Directive 94/33/EC on the protection of young people at work), Annex III Directive 2008/98/EC on waste, self classification (Acute tox. 4, Skin corr. 1C,

				Eye dam. 1, STOT SE 3, Skin corr. 1B), Norman 2015, highlighted by ECHA, no HBM data available at current knowledge
	PFECA	perfluoro-1,1-ethylene glycol, terminated with chlorohexafluoropropyloxy groups Perfluoro[(2-ethyloxy-ethoxy)acetic acid], ammonium salt	908020-52-0	CoRAP (suspected PBT/vPvB, exposure of environment), resistent, not easily to metabolise, maybe bioaccumative, expected increase in production and use, partially used in food contact materials, restriction on use according EFSA, no safety concern under the respective conditions identified (EFSA, 2011) no HBM data available at current knowledge
	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	CoRAP (potential endocrine disrupter, suspected PBT/vPvB, other hazard based concern, exposure of environment, wide dispersive use), PACT list, OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), self classification (STOT RE 2, STOT SE 3, Skin irrit. 2, Eye irrit. 2), fully registered substance 100-1.000 tonnes, suspected endocrine disrupter, used for polymer production, in human blood propably only metabolites detectable (FTOH, FTCA, FTUCAs), no HBM data available at current knowledge
	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	CAS# 17527-29-6: CoRAP (potential endocrine disrupter, suspected PBT/vPvB, other hazard based concern, exposure of environment, wide dispersive use), PACT list; CAS# 27905-45-9 and CAS# 17741-60-5: REACH Annex

			27905-45-9 17741-60-5	III (suspected P, C, respiratory sensitiser, skin irritant, skin sensitiser); FTAC is a PFOA-related compound; used for polymer production, Priority HBM List California, in human blood probably only metabolites detectable, no HBM data available at current knowledge
	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	REACH Annex III (suspected P, B, C), Priority HBM List California, no HBM data available at current knowledge
	C4/C4 PFPiA	Bis(nonafluorobutyl)phosphinic acid	52299-25-9	CoRAP (suspected PBT/vPvB, other hazard based concern, exposure of environment), no HBM data available at current knowledge
	8:2 FTOH	8:2 fluorotelomer alcohol	678-39-7	CLH proposal (Repr 1B), OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers), self classification (Skin irrit. 2, Eye irrit. 2, STOT SE 3), Norman 2011, no HBM data available at current knowledge
	C6/C6 PFPiA	Bis(perfluorohexyl)phosphinic acid	40143-77-9	Limited HBM data available (Human sera , single and pooled donor sample 2009, US : <1 - 50.2 ng/Land <1 - 201.4 ng/L (median) Lee & Mabury (2011)
	C6/C8 PFPiA	Bis(perfluorohexyloctyl)phosphinic acid	610800-34-5	Priority HBM List California, Limited HBM data available (Human serasingle and pooled donor sample 2009, US : <1 - 60.9 ng/L and <1 - 283.4 ng/L(median) Lee &

				Mabury (2011)
	C8/C8 PFPiA	Bis(perfluorooctyl)phosphinic acid	40143-79-1	Limited HBM data available (Human sera , single and pooled donor sample 2009, US : <1 - 22.2 ng/Land <1 - 50.7 ng/L (median) Lee & Mabury (2011)
D	HFPO	hexafluoropropylene oxide	220182-27-4	Highlighted by ECHA, no HBM data available at current knowledge
	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	CAS# 3107-18-4, CAS# 68156-01-4, CAS# 335-24-0: REACH Annex III (suspected C, P) ; no HBM data available at current knowledge
	6:2/8:2 diPAP	6:2/8:2 polyfluoroalkyl phosphoric acid diesters	943913-15-3	PFOA-related substance, REACH Annex XVII restriction (Regulation (EU) 2017/1000), Priority HBM List California, no HBM data available at current knowledge
	8:2 monoPAP	8:2 polyfluoroalkyl phosphoric acid monoester	57678-03-2	PFOA-related substance, REACH Annex XVII restriction (Regulation (EU) 2017/1000), no HBM data available at current knowledge
	PFOPA	Perfluorooctylphosphonic acid, 2-(Perfluorohexyl)ethyl] phosphonic acid	252237-40-4	Sodium salt REACH registration (ECHA, 2017) High environmental exposure, Priority HBM List California, limited HBM data available, not detected in US human sera in Lee &Mabury (2011)
	Perfluorinated Siloxane	Trimethoxy(1H,1H,2H,2H-heptadecafluorodecyl)silane	83048-65-1	OSH legislation (Council Directive 98/24/EC on protection of health and safety of workers, Council Directive 94/33/EC on the protection of young people at work), Annex III Directive

				2008/98/EC on waste, self classification (Skin irrit. 2, Eye irrit. 2, Skin corr. 1B), no HBM data available at current knowledge
	FL16.119	N-(2-methylcyclohexyl)-2,3,4,5,6-pentafluorobenzamide	1003050-32-5	more information on use and use levels needed EFSA (CEF panel, 2017) Other health hazard, no HBM data available at current knowledge
E	6:2 FTCA 8:2 FTCA 10:2 FTCA	Fluorotelomer carboxylic acids: 6:2 Fluorotelomer carboxylic acid, 8:2 Fluorotelomer carboxylic acid 10:2 Fluorotelomer carboxylic acid	53826-12-3 27854-31-5 53826-13-4	Fluorotelomer metabolites, Priority HBM List California, no HBM data available at current knowledge
	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	resistent, not easily to metabolise, maybe bioaccumative, expected increase in production and use, partially used in food contact materials, restriction on use according EFSA, no safety concern under defined conditions (EFSA, 2010) no HBM data available at current knowledge
	FBSA	Perflurobutane sulfonamide	30334-69-1	Alternative to PFOS, tranformation product, recently detected in biota (fish) (Cu et al., 2016)
	MeFBSE	N-Methyl perfluorobutane-sulfonamidoethanol	34454-97-2	REACH, registered substance, Intermediate; Surfactants; Repellents for porous hard surfaces; Tile grout additive, Registered 12 – 100 t/y
	6:2 PAP	6:2 polyfluoroalkyl phosphoric acid monoesters	57678-01-0	Priority HBM List California, no HBM data available at current knowledge
	6:2 diPAP	6:2 polyfluoroalkyl phosphoric acid diesters	57677-95-9	Priority HBM List California, no HBM data available at current knowledge

	PFHxPA	Perfluorohexylphosphonic acid	40143-76-8	high environmental exposure, Priority HBM List California, not detected in US human sera in Lee &Mabury (2011) limited HBM data available
	PFDPA	Perfluorodecylphosphonic acid	52299-26-0	Priority HBM List California, not detected in US human sera in Lee &Mabury (2011) limited HBM data available
	C8/C10 PFPiA	Bis(perfluorooctyldecyl)phosphinic acid	500776-81-8	no HBM data available at current knowledge
	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	no HBM data available at current knowledge
	Krytox	Krytox-H	60164-51-4	no HBM data available at current knowledge
	Fomblin Z-DIAC,	Fomblin Z-DIAC, bis(pentafluorophenyl) ester	97462-40-1	no HBM data available at current knowledge
	-	C3; C15-C20 PFCA	-	no HBM data available at current knowledge
	-	C3, C15-C20 PFSA	-	no HBM data available at current knowledge
	TFEE-5	Polyfluoro-5,8,11,14-tetrakis(polyfluoralkyl)-polyoxaalkane	-	CoRap, suspected PBT
	polymers: PTFE PVDF PVF TFE HFP	 Teflon: Polytetrafluoroethylene 1,1 Difloroethene (PVDF) Polyvinyl fluorine (PVF) Tetrafluoroethylene (TFE) Hexafluoropropylene (HFP)	 9002-84-0 24937-79-9 24981-14-4 116-14-3 116-15-4	More research on polymers Building blocks: CAS# 9002-84-0: REACH Annex III (suspected CMR); CAS# 24937-79-9: REACH Annex III (suspected P, M, hazardous to aquatic environment); CAS# 24981-14-4: - CAS# 116-14-3: PACT list (CMR); CAS# 116-15-4: CLH (Press. Gas, Acute Tox. 4, STOT SE 3), CoRAP (suspected CMR, high (aggregated) tonnage);

				production of toxic products if overheated; production of ultrafine particles by degradation; lung inflammation (PTFE), toxic monomers (PTFE); no HBM data available at current knowledge

4. 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?
14. How much are HBM values dependent on host characteristics and does this have implications for identifying vulnerable groups?

5. Research Activities to be undertaken

Table 2: Listing of research activities proposed to answer the policy questions summed up in

1.3

Policy question	Substance	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
1	**CAT A and B 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 WP 10
1	**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 PFOS and PFOA exposure values with the newly derived HBM values from the German HBM Commission and the upcoming EFSA health guideline values, develop health based HBM4EU guidance values values for PFOS and PFOA WP 5
1	**CAT A and B 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. WP 5, 8,9,10,15
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	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

		PFBS, PFBA) are increasing.	studies WP 8,9, WP14 (effect biomarkers)
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. WP 8,9,10 and WP14 (effect biomarkers)
4	**Cat A and B 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 a detailed questionnaires based on current knowledge on exposure pathways. Therefore a PFASs related questionnaire should be developed. WP 8,9 Link with dietary surveys if possible (WP11) External modelling: WP12
5	**Cat A and B substances**	Currently there are several hot spots known in different countries (e.g. Germany, Sweden, Italy, Spain, 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. “Bioambient.es” project (IISCIII, Spain) could be taken into account. http://democophes.blogs.isciii.es/2012/04/04/bioambient-es/. http://democophes.blogs.isciii.es/category/biomonitorizacion-espana/ If so, I guess that further information regarding this activity have been (or will be) provided by IISCIII. Exposure modelling in relation with HBMdata

			(WP12)
6	**Cat A and B Substances**	The EFSA opinion will be published in 2018. 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
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. WP 4, 5 WP 10 time trend data analysis
8	**Cat A Substances**	According to experts in different fields it is anticipated to eliminate legacy PFASs from waste streams.	It is not clear whether this question can be tackled within HBM4EU; Research on the life cycle of products may identify potential exposure routes. [Studies near landfields could clarify if PFASs exposure occurs.] WP 7,8,9
9	**Cat A, B, C substances**		To identify differences in the exposure levels of unregulated and regulated Cat. A substances (and Cat B and C substances if data are available) between countries and time periods, and to identify the main reasons for differences in exposure.*Population groups: living in different areas and divided by sex and gender. WP 10, 12
10	**Cat A , B and C 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 , B and C substances as well as the total PFASs burden. *Vulnerable population: children (high half lives of PFAS) and those affected by health effects linked to the potential PFAS exposure. WP 8,9 WP13 exposure effect studies
10	**Cat A**		Study how PFASs affect AOPs that lead to critical

	substances		endpoints in humans such as effects on liver and thyroid, developmental toxicity, immunotoxicity and non carcinogenic toxicogenicity. Prenatal exposure is suspected to cause reduced birth weight and or small for gestational age, suggesting unborn as vulnerable exposure group. WP 13
11	**Mixture of substances** **Identification of Cat E 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 and also address multipollutant (PFASs) exposure in relation to adverse health effects in epidemiological studies WP 13, WP15
12	**Cat D and E 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 WP 4,5 Identify lead chemicals in mixtures of PFAs WP14 and WP15 Design new studies that measure these exposure biomarkers WP8
14	**PFOA/PFOS**	There is evidence of wide variability in half life, with gender, renal function and genetics shown to explain some of the variation and HBM levels.	Taking into consideration the differences in toxicokinetics of linear and branched isomers, fuller characterization of role of gender, existing disease use of medicines and other causes affecting measured HBM in serum WP8 and WP10

6. Results Report

In Year 2 (M18) a short overview of the results achieved within the HBM4EU programme shall be depicted here. Please, briefly state the main results answering the corresponding policy questions in a general understandably manner.

Table 3: Short overview of results of the activities carried out within HBM4EU to answer the policy questions with reference to corresponding deliverables

Policy Question No. (keyword)	Short Summary of Results
	If there is a Deliverable you extracted the results from, please mention it

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