Contribution to the Public Consultation on the draft scientific opinion of the EFSA CONTAM Panel on the Risk to human health related to the presence of PFASs in food

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HBM4EU, **the human biomonitoring initiative in Europe** from 2017 to 2021, is investigating the exposure and the health effects resulting from exposure to 18 priority chemical substance groups including PFAS.

PFAS are a compound group of high priority. The Council Conclusions of 26 June 2019 "Towards a Sustainable Chemicals Policy Strategy of the Union" addressed the growing evidence for adverse effects caused by exposure to highly fluorinated compounds (PFAS): The council noted in particular "the growing evidence for adverse effects caused by exposure to highly fluorinated compounds (PFAS), the evidence for wide spread occurrence of PFAS in water, soil, articles and waste and the threat this may cause to our drinking water supplies" and "Calls on the Commission to develop an action plan to eliminate all non-essential uses of PFAS."
European Ministers for the Environment and Heads of European Agencies expressed the urgency in a letter accompanied by elements for an EU-strategy for PFAS.
One of the main goals of HBM4EU is to strengthen the science-policy interface in the European Union and to support informed decision making. Therefore, HBM4EU would like to make a statement in the Public Consultation of the Scientific Opinion of the EFSA CONTAM Panel on the Risk to human health related to the presence of PFASs in food.

HBM4EU strongly welcomes the scientific opinion, acknowledges its scientific excellence, and highly values the grouping approach for PFAS in the current proposal.

PFAS are addressed in all pillars and several work packages of HBM4EU: from the science to policy interface in Pillar 1 and use of human biomonitoring to improve risk assessment, as well as in Pillar 2, covering aligned studies, harmonized methods and data management and in Pillar 3, where research on health effects, including modelling, adverse outcome pathways, effect biomarkers, evaluation of cohort studies and mixture effects are performed.

HBM4EU results are published in peer reviewed journals as well as on the HBM4EU website in the section deliverables[1].

The EFSA CONTAM Panel performed the assessment for the sum of four PFAS: **PFOA, PFNA, PFHxS and PFOS**, which represent half of the PFAS exposure, at least of those PFAS for which data are available. A preliminary mixture risk assessment of PFAS and discussion of critical points in the framework of HBM4EU[2] was also based on these four PFAS that constitute the majority of PFAS in human blood according to currently available information. **We therefore welcome the mixture assessment approach** EFSA has used to assess the risk associated with exposure to these four PFAS. We acknowledge that the immunotoxic effects of PFAS, observed in experimental animal as well as in human epidemiological studies, (e.g. inhibiting the vaccination response in children) are selected as most sensitive end-point of concern.

[1] HBM4EU deliverables

[2] Deliverable 5.5 Human biomonitoring in risk assessment: 2nd set of examples on the use of HBM in risk assessments of HBM4EU priority chemicals:

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Human biomonitoring (HBM) data were documented and used in the opinion. This work demonstrated that HBM data are an **essential part of the exposure and risk assessment**, and can be used to demonstrate the appropriateness of lower bound exposure values for a realistic dietary risk assessment in this specific case. Further, human internal values were used for risk characterisation, using internal exposure values of mothers to calculate the exposure of toddlers via breast milk. HBM4EU supports that the risk characterisation in the current opinion relies on the prevention of observed immune effects in one-year-old breastfed infants (Abraham et al. 2020)[3].

The present opinion also shows the **lack of data, leading to uncertainties in several aspects**. These include a lack of data on dietary and non-dietary exposure. Uncertainties in dietary exposures relate e.g. to precursors of PFAS, transfer of PFAS in the food chain, food and drinking water exposure, information on food contact materials and food processing. Further uncertainties include non-dietary exposure to precursors such as n:2 FTOHs and PAPs, via indoor air and house dust, which could lead to a relevant contribution to the PFAS body burden.

There is also **a lack of human biomonitoring data for PFAS** other than those addressed in the risk assessment (specifically those which are used in high volumes as **alternatives and substitutes to legacy PFAS**). Further, it was stated that for many PFAS also toxicity data were scarce. We support this observation.

Knowledge on the mode(s) of action underlying these critical effects, provided in the form of *in vitro*, *in vivo* and physical-chemical mechanistic studies, could help identify which compounds 1) should be prioritized for future studies 2) could be grouped in chemical assessment groups, as input to risk assessment 3) could inform risk management at an early stage to prevent regrettable substitution. Also PBPK models should be further optimised and refined.

HBM4EU also supports the call **for longitudinal epidemiological studies** to address the human endpoints including prospective vaccination studies covering more types of vaccines and other immune outcomes including the risk of infections. The current COVID-19 pandemic clearly shows the **importance of an intact immune system for individuals and populations**.

HBM4EU is working on these and other related questions. **New HBM data from the aligned studies within HBM4EU are expected in 2020/2021** and will be important when it comes to updating the current exposure situation in European teenagers and exposure pathways, and will present knowledge about potential health risks.

Within the work package data management in HBM4EU aggregated data were obtained in a standardized and comparable way from existing European data collections for 1st and 2nd set prioritized substances. One of these substance groups was PFAS. Based on these data, we collected information on the human exposure levels in Europe.

From these **aggregated data,** we extracted the obtained data for PFOS, PFOA, PFNA and PFHxS from European studies with samples collected between 2008 and 2015. Aggregated data for the selected PFASs were reported for 4 birth cohorts, with measurements in cord blood plasma or cord serum, one study reported blood plasma levels of children, one study blood serum levels of teenagers, and 6 studies measured blood serum/plasma levels of adults. All studies included at least 100 participants.

[3] Abraham et al: https://doi.org/10.1007/s00204-020-02715-4

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As was stated also in the EFSA opinion, despite variations in design, populations, analytical methods, and geographic location, the median concentrations in the different European studies are rather similar, with ratios between the highest and lowest median concentration always being less than 10. In the table (annex of this document) the reported median-values and 95th percentiles of the individual studies were averaged (by taking the median) over the different studies of newborns, children & teenagers combined, and adults. These levels support the concentration levels reported in the EFSA opinion. The EFSA opinion was based on more European studies, 32-37 studies for adults and 7-9 studies for children for the selected PFAS compounds from 2007-2008 onwards.

The **individual data collections** prepared and made available within HBM4EU also contained aggregated data stratified by age, sex and educational level. From these stratifications it can be seen that the PFAS concentrations are in general higher in men compared to women for the teenager and adult studies. This could probably be explained by the elimination of PFASs through menstruation, and for mothers also through delivery and lactation (Berg et al. 2014; Bjerregaard-Olesen et al. 2016; Brantsaeter et al. 2013; Cariou et al. 2015; Colles et al. 2020; Lien et al. 2013; Wong et al. 2014)[4]. Also, there seems a trend that participants with higher educational level have higher exposure levels compared with low to medium educational level. This trend was however less obvious and could not be observed in all studies and for all compounds. In some studies, higher levels of PFASs were observed with increasing age, indicating possible cumulative exposure over time. This was however not observed for all studies and for all compounds[5].

HBM4EU collaborates with researchers addressing human exposure and its relation to human body burdens in hotspot regions in terms of PFAS contamination**. Environmental contamination and contamination of drinking water resources by these persistent, mobile and bioaccumulative chemicals is of high concern** since it is known to lead to significantly higher body burdens in biota and residents. Also the PFASs which are persistent and mobile are of concern, as they have the **potential to contaminate ground- and drinking water and to enter the food chain**, which will lead to high bioavailability and irreversible exposures to humans and the environment.

The recent EFSA opinion defines a tolerable weekly intake of 8 ng/kg body weight for the sum of the 4 PFASs (PFOA, PFNA, PFHxS, PFOS) corresponding to a safe body burden. The EFSA CONTAM panel concludes that parts of the European population exceed this TWI, and the corresponding serum levels. HBM4EU results confirm this.
This **calls for and supports further regulatory actions** and demonstrates the importance of a strong partnership for risk assessment in the European Union.

HBM4EU would very much welcome the opportunity working together in future within the **Partnership for the Assessment of Risk from Chemicals (PARC)** to further and more specifically supporting the regulatory process and environmental and human safety.

[4] https://doi.org/10.1016/j.envint.2014.04.010; DOI: 10.3390/ijerph15050989; doi: 10.1016/j.envint.2012.12.014; doi: 10.1016/j.envint.2015.07.014.; https://doi.org/10.1016/j.chemosphere.2019.125250; doi: 10.1016/j.chemosphere.2013.04.038; doi.org/10.1021/es500796y,

[5] Source data: merged harmonized aggregated data obtained from Deliverable D10.6 (2nd annual list of exposure distributions and/or European reference values[5]) Excluded data collections before 2008, and after 2015

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HBM4EU science and policy for a healthy future

Experts involved in the work on PFAS in the framework of HBM4EU have noted some specific recommendations for the future without making any claim to be exhaustive; these recommendations do not necessarily reflect the consensus of the group:

Exposure and Human biomonitoring

- There is a need for human biomonitoring data for PFAS other than those addressed in the risk assessment (specifically those which are used/formed in high volumes as a result of substituting legacy PFAS).
- There is a need to measure the total organic fluorine content in humans in order to assess the magnitude of the so far unknown or not yet assessable contribution of PFAS in humans.
- The very limited knowledge of PFAS in other human tissues (fatty tissues, organs such as brain, lung, testes, spleen, lymph nodes…) and corresponding serum levels should be expanded.
- A better understanding of the relationship between external and internal exposure levels is needed.

Toxicity, modes of action and grouping

- More longitudinal epidemiological PFAS studies are needed. Research on immunotoxicity, endocrine disruption and birth outcomes is required. Research on other toxicological endpoints is also needed including effects on the lungs/respiratory system from prenatal exposure, and cancers such as breast cancer in adults.
- Research on adverse outcome pathways is needed.
- To support the science-based grouping of PFAS, a better understanding of the modes of action of different PFASs is needed.
- Further studying relative potencies of PFAS for mixture risk assessment would be of added value.
- To complement exposure biomarkers with mechanistically based effect biomarkers to further elucidate causal pathways between PFAS and adverse health outcomes. The difference between short versus long chain compounds in terms of bioavailability has to be clarified.

In vitro and in silico methods in combination with HBM

- Robust research combining NAM (non-animal methods or new approach methodologies) with human epidemiology supported by HBM could provide more evidence on the knowledge gaps and potency of different PFAS.

PBPK modelling

- Given the large molecular weight and large extent of ionization of many PFAS, we also propose to apply permeability limited PBPK models in which substance uptake rates to tissue compartments are limited by cell membrane permeability, not by blood flow rate.
- Consider passive diffusion and active transport facilitated by various transporters, association with serum albumin in circulatory and extracellular spaces, and association with other cellular proteins (i.e., liver-type fatty acid binding protein and α2μ-globulin in kidney).

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- Optimisation of kinetic parameters with HBM data in multiple human tissues.
- Improved mixture kinetics.
- Establish a lifelong PBPK model with advance dynamic organs growth model, pregnancy-PBPK and lactation model.

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Annex:

Table: Summary statistics describing (cord) blood serum/plasma concentrations of PFASs (µg/L) in the European population stratified for newborns (0y), children & teenagers (6-19y), and adults (≥20y) based on studies included in the HBM4EU harmonized aggregated data (sampling years between 2008-2015)

	PFOS			PFOA			PFNA			PFHxS		
	Newborns 0y	Children & teenagers 6-19y	Adults ≥20y	Newborns 0y	Children & teenagers 6-19y	Adults ≥20y	Newborns 0y	Children & teenagers 6-19y	Adults ≥20y	Newborns 0y	Children & teenagers 6-19y	Adults ≥20y
Median	1.3	5.8	7.4	1.2	2.8	1.8	0.23	/	0.66	0.34	/	0.32
P95	3.4	12.4	16.8	2.6	4.6	4.5	0.59	/	1.51	0.75	/	0.79
Number of studies*	4	2	6	4	2	6	2	1	5	3	1	5

*N in each individual study is at least 116

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