HBM4EU science and policy for a healthy future

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 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].

Within WP 5.3 (D5.5.) the use of HBM data in risk assessment (RA) and health impact assessment (HIA) strategies was demonstrated. Our preliminary mixture risk assessment of PFAS and discussion of critical points in the framework of HBM4EU[2] was based on four PFAS that constitute the majority of PFAS in human blood according to currently available information.

EFSA has now assessed the risk of PFAS mixtures (EFSA,2020) and focused also on these four PFAS: PFOA, PFNA, PFHxS and PFOS. HBM4EU welcomes the mixture assessment approach EFSA has used to assess the risk associated with exposure to these four PFAS and acknowledges 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. HBM4EU will update the work in WP5.3 based on the new EFSA opinion. Relative potency factors will be derived for internal PFAS concentrations, and employing PBPK modelling, a mixtures RA will be performed. Further within WP 4.4. (AD5.5.) an indicator for PFAS exposure will be derived by the end of 2020/beginning 2021. In work package 5.5. a case study on PFAS will be conducted, for the use of HBM data for policies, including a workshop for discussing this with stakeholders.

New HBM data on PFAS from the aligned studies (WP 8,9) 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 10, 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, including PFAS. Based on these data, we collected information on the human exposure levels in Europe. From the 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.

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. Several evaluations are planned within WP 10 such as multimedia environmental contamination (soil, water, air, food web) and bottom-up exposure estimation in European regions

[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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contaminated with PFASs. In WP12 it is planned to reconstruct exposure of PFASs for various population groups.

Within WP13.1 work on adverse outcome pathways is ongoing. Selected effects for contribution to the OECD AOP framework were based on the endpoints for which benchmark dose levels were derived by EFSA (2028) : effects on the liver accompanied by increase in cholesterol levels, effects on birth weight and effects on the immune system, all of those based on human data (D13.4). Certain AOPs in the AOP wiki database were identified which could be relevant for PFAS exposure in humans, however considerable data gaps related to causality and mode of action are lacking. Though, the mechanistic pathway from PFAS exposure to adverse health outcomes will be further explored within WP13.1. Specifically, characterisation of the key events in the AOPs for disruption of cholesterol/lipid metabolism and inflammatory responses with links to cardiovascular disease; collection of information on potential mechanisms beyond PFAS-induced effects on birth weight and immune toxicity.

Suitable PFAS studies for the examination of exposure-health relationships were identified within WP13.2 (D13.3.) including studies in pregnant women, children and adolescents, adults and the elderly. Additionally, it is planned to merge individual data from several birth cohorts for the examination of associations of PFAS exposure and low birth weight, and birth weight as continuous outcome. A similar investigation will be conducted for the assessment of associations between PFAS and thyroid function in mothers and their new-borns. Results are expected to be reported this year.

Within WP13.2 several mixture exposure-effect associations are investigated i- cardiometabolic disorders, and offspring immune function and cognitive development, effects on the hormone system as well as birth outcomes.

Within WP 14 biomarkers of exposure for PFAS were successfully established. Placental extracts (alpha fractions), containing mixtures of persistent and lipophilic chemicals, showed significant anti-androgenic activity. The hormonal profile from placental tissue was quantified, as well as some epigenetic markers such as Histone H2AX phosphorylation (Gamma-H2AX), trimethylation of histone 3 at lysine (H3K4me) and DNA methylation of BDNF, in addition to untargeted metabolomic analysis. Finally, 8OHdG levels were assessed in urine samples coupled to the placentas from the same women. This work has shown that chemical mixtures isolated from human samples can be assessed, and its biological activity quantified using different biomarkers cell based tools. Placenta tissue could be used as a relevant biological matrix to assess both exposure and effect biomarkers. The placenta can also be used to explore the implementation of novel effect biomarkers in Human Biomonitoring programs, due to the volume and availability of this biological sample. Future work will focus on the relationship between exposure and effect biomarkers tested in placenta samples (included in D14.4 and AD14.4); ii) further to assess the implementation of the most appropriate biomarkers of effect and combined effects in other biological matrices more frequently recruited in HBM programs, such as blood and urine; to explore the concentration to specific chemical families, such as PFAS and metabolites, in placenta and serum samples, in order to assess its combined effects using different effect biomarkers such as some in vitro cell bioassays."

WP14 and WP15 interaction will be also extended to the implementation of biomarkers of effect (such as oxidative stress and in vitro research work for the liver-cholesterol related pathways of PFAS).

Several publications are planned, e.g. PFAS-Thyroid review titled "Exposure to Perflouroalkyl Acids and foetal and maternal thyroid status - a review (Boesen SAH et al.) PFAS-cholesterol

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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.

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