HBM4EU science and policy for a healthy future

RESEARCH BRIEF

HBM4EU work on Per- and Polyfluoroalkyl Substances (PFAS)

KEY MESSAGES

- Aligning human biomonitoring studies across 9 countries have been harmonised in terms of the sampling, survey and analytical approach. This will deliver comparable data **on human exposure to PFAS across Europe**, an important input to the assessment and management of risks to human health
- Derivation of **first European reference levels** for PFOS, PFOA, PFNA and PFHxS from data obtained between 2014-2020
- Identification of HBM-studies for the examination of **exposure-health relationships**
- Investigation of the **effects of current PFAS mixtures**
- Identification of appropriate and relevant **effect biomarkers** to be implemented in HBM studies
- **Physiologically based pharmacokinetic (PBPK) models** for PFOS and PFOA, validated with human biomonitoring data. The model is available for oral and inhalation exposure and will be extended for dermal exposure. Ongoing work includes an age dependent PBTK model involving physiological and biological changes encompassing full course of a human lifetime (children, adult, and elderly). These models are being adopted for different case scenarios and can be applied as a tool for policymaking.
- Work defining **adverse outcome pathways (AOP)** for PFAS is ongoing and will elucidate mechanisms behind the adverse effects caused by these compounds.
- A **mapping of the policy context** and opportunities for PFAS was performed in 2019[1]. This helped to identify important policy processes that might benefit from the evidence that is being produced by HBM4EU and to further match the policy and project timelines. A science-policy dialogue on HBM4EU's results on PFAS has been launched, with a follow-up workshop to take place in March 2021

1. HOW WILL HBM4EU SUPPORT THE CHEMICAL'S STRATEGY FOR SUSTAINABILITY?

HBM4EU - the European Human Biomonitoring Initiative - is co-funded by the EU under the European Commission's Horizon 2020 programme and is investigating the exposure of the European population to 18 priority chemical substances and substance groups including per- and polyfluoroalkyl substances (PFAS) and resulting impacts on human health. PFAS were identified as a priority substance group by participating member states and the European Commission prior to the project start.

This briefing provides an overview of HBM4EU, the European Human Biomonitoring (HBM) initiative`s work on per- and polyfluoroalkyl substances (PFAS).

It is intended to support the work of the European Commission regarding the implementation of the **Chemicals – strategy for sustainability (toxic-free EU environment)** which has been published in October, 2020. The Chemicals – strategy for sustainability (toxic-free EU environment) aims to ensure a high level of protection for both the environment and human health, based on the precautionary principle and on the principles that preventive actions should be taken, that environmental damage as a priority should be rectified at the source and that the polluter should pay. In parallel, the Commission's regulatory framework will need to reflect scientific evidence on the risk posed by chemicals such as endocrine disruptors.

[1] See Additional Deliverable 5.9 Timelines of opportunity: How HBM4EU can support chemicals management policy needs

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The new chemical's strategy for sustainability on PFAS:

"PFAS require special attention, considering the large number of cases of contamination of soil and water - including drinking water - in the EU and globally, the number of people affected with a full spectrum of illnesses and the related societal and economic costs. That is why the Commission proposes a comprehensive set of actions to address the use of and contamination with PFAS. Aiming to ensure, in particular, that the use of PFAS is phased out in the EU, unless it is proven essential for society."

In order to secure the trust of the regulated communities, stakeholders and the public, it is essential to demonstrate the **effectiveness** of existing policies through monitoring activities. Human biomonitoring can be used to establish a baseline of exposure for the European population against which to measure the effectiveness of future risk management measures aiming at **minimizing human exposure** under the Chemicals – strategy for sustainability.

Conducted through harmonized approaches at a European scale, **human biomonitoring (HBM)** provides a tool for monitoring the exposure of the European population to chemicals. In addition, comparable human biomonitoring data from across Europe allow for an understanding of regional differences and will help to identify **vulnerable groups**, to allow decision making regarding **targeted measures to reduce exposure**. Internal exposure data provides a complete picture of human exposure, including exposure via the diet and drinking water as well as via other exposure pathways such as an array of consumer products. As such, human biomonitoring data can be used to improve chemical risk assessment by providing information on actual human exposure via multiple exposure pathways.

2. WHAT POLICY QUESTIONS WILL HBM4EU ANSWER?

HBM4EU reviews available evidence and generates new data on human exposure and associated health impacts in order to address key policy questions. In the **HBM4EU Scoping Document for PFAS** 13 policy questions were defined. They are related to the following topics:

1. **Exposure:** What are current exposure levels and patterns of the EU population to regulated, non-regulated and emerging PFAS as well as to PFAS mixtures?
2. **Effects:** What are the health effects related to the current exposure to PFAS in the general population and in vulnerable groups such as pregnant women and children, and in inhabitants of hotspot areas?
3. **Policy:** What is the impact of existing regulations on PFAS exposure and is there a need for further regulations on PFAS?

3. HOW IS HBM4EU ANSWERING THESE POLICY QUESTIONS

HBM4EU is implementing a **broad range of activities** in order to address policy questions on human exposure to chemicals. These activities are set in all three pillars of HBM4EU: 1) Science to Policy, 2) European HBM platform, and 3) Exposure and Health. The table below outlines the most important activities:

EXPOSURE TO PFAS
• Collecting and assessing existing human biomonitoring data on PFAS from across European partner countries
• Integration of the data collections into the European **IPCHEM** platform
• Derivation of first European reference levels for PFOS, PFOA, PFNA and PFHxS from data obtained between 2014-2020
• Evaluation of aggregated and individual data
• Implementing a quality assurance/quality control programme to ensure quality and comparability of the chemical analyses of PFAS
• Establishment of a EU laboratories network with capacities for the chemical analysis of PFAS
• Analysis of up to 12 different PFAS in teenager's plasma/serum samples from studies aligned to produce comparable data across 9 European countries and in total 2,232 samples – available in 2021: **Overview**
• Analyses of pooled data from countries across the European Union in order to assess time-trends, differences between countries and population groups, including identification of subpopulations with high exposure levels (occupational exposure will not be assessed due to the lack of HBM data in Europe)
• Assessment of occupational PFAS exposure in chromium plating facilities
• Establishment of external and internal exposure models and correlations thereof

HEALTH EFFECTS OF PFAS

- Identification of HBM- studies for the examination of exposure-health relationships
- Investigation of the effects of current PFAS mixture exposure and effects
- Establishment of an inventory of existing HBM- studies, including prospective cohort studies
- Investigation of associations between PFAS and health outcomes (e.g. birth outcomes, thyroid function, metabolic and immune function)
- Investigation of the use of HBM data in PFAS risk assessment and health impact assessment
- Assessment of potential Adverse Outcome Pathways (AOPs) related to PFAS exposure
- In vitro studies to assess whether associations between PFASs and health outcomes can be substantiated with/supported by mechanistic data
- Feasibility studies combining HBM with health studies
- Identification of appropriate and relevant effect biomarkers to be implemented in HBM studies

4. COLLATING EXISTING HUMAN BIOMONITORING DATA ON EXPOSURE TO PFAS

Human biomonitoring data are available in many countries but are heterogeneous with respect to age groups and substances measured. The reported median-values and 95th percentiles of the individual studies on PFAS 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 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. Data on PFAS exposure were summarized in the Deliverable D10.4 and D10.6.

Metadata and aggregated data from HBM studies having measured PFAS were integrated in IPCHEM.

A dashboard will be established to visualise the aggregated HBM data; accessible via the HBM4EU website.

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5. PRODUCING DATA ON THE EXPOSURE OF THE EUROPEAN POPULATION TO PFAS

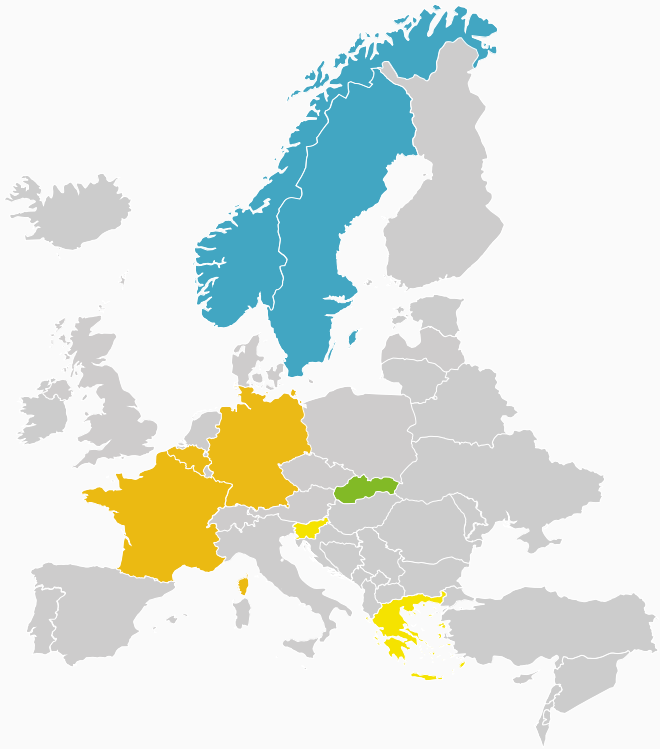
A principal activity under HBM4EU is the establishment of a **European human biomonitoring platform** to collect data on the internal chemical exposure of citizens across Europe. Aligning national studies across Europe to deliver comparable coherent datasets has proven a challenging task.

Under HBM4EU, human biomonitoring studies across 21 countries[2] have been harmonised in terms of the sampling, survey and analytical approach, known as the **aligned studies**. This will deliver comparable data on **human exposure to PFAS across Europe**, an important input to the assessment and management of risks to human health.

Each participating country provides 300 samples, except for a few smaller countries that are providing a lower number of samples. HBM4EU will deliver **PFAS data for all four European regions** (North (with approx. 21% of the population), South (28% of the population), East (11% of the population) and West (41% of the population) according to the United Nations geoscheme of Europe).

For the PFAS, **samples from teenagers aged 11-19 years** are used to assess exposure in Belgium, Germany, Greece, France, Norway, Slovakia, Slovenia, Spain, Sweden (see graph below).

Figure 1: Geomap of the aligned studies with colour coded European regions (Blue: north, yellow: south, orange: west, green: east) Analyses of these data are still ongoing and will provide European exposure distributions, European exposure values, geographical comparisons, exposure determinants.



[2] Of the 30 partner countries, 21 countries were able to align ongoing studies to the HBM4EU approach and the prioritised chemicals, in order to generate comparable exposure data, with 9 of these supplying data on PFAS.

6. UNDERSTANDING EXPOSURE PATHWAYS

To enable translation of HBM data into external exposure levels for comparison with e.g. TWI values, **information on toxicokinetic properties** is needed. Physiology-based toxicokinetic (PBTK) modelling will be used to link external exposure to internal dose in humans (e.g. concentration in urine) by describing the process of absorption, distribution, metabolism and excretion (ADME) that a substance undergoes in living organisms.

Within HBM4EU a review of published models for PFAS was performed. Based on the PBPK models available, an improvement of the model was conducted for PFOS and PFOA and validated with human experimental data. Currently, the model is available for oral and inhalation exposure and will be extended for dermal exposure for the named two PFAS.

Ongoing work includes an **age-dependent PBTK model** involving physiological and biological changes encompassing the full course of a human lifetime (children, adult and elderly). This PBTK model considers age-dependent changes of system parameters like tissue volume, tissue blood flow, renal elimination and plasma protein binding for estimating age-related risk from chemical exposure. These models are being adopted for running **different case scenarios** including sensitive age groups, which can be applied as a tool for policymaking.

Comprehensive work on external and internal exposure modelling has been performed, which is published in deliverables related to "from HBM to Exposure" within work package 12 (see respective Deliverables: D12.1-12.5, AD 12.12 and AD12.13).
Ongoing work of exposure assessment of the European population to PFAS will allow to develop an extended pan-European exposure modelling.

7. ASSESSING IMPACTS ON HEALTH

The group of PFAS include **several thousands of different chemical substances**. Within HBM4EU, these compounds were categorized in terms of data availability and knowledge on exposure, hazard and human biomonitoring (see table in the scoping document on PFAS). Data on health impacts of different PFAS are available for a comparatively small number of PFAS, of which especially PFOS and PFOA are well investigated. PFOS and PFOA are classified as carcinogenic (Carc. 2 – suspected human carcinogens), toxic to reproduction (Repr. 1B), toxic to specific target organs (STOT RE 1) and acute toxic (Acute Tox. 3-4). They are further classified as PBT (persistent bioaccumulative and toxic) substances and POPs (Persistent Organic Pollutants).

The recent scientific opinion of the EFSA CONTAM Panel on the risk to human health related to the presence of PFASs in food, defined the decreased response of the immune system to vaccination as the most critical human health effect, besides potential effects on birth weight and disruption of cholesterol metabolism. Within HBM4EU these health effects will be further specified concerning their **mode of action** in order to define **Adverse Outcome Pathways** related to PFAS exposure. A text-mining tool (AOP-helpFinder) has been developed. This tool screens automatically abstracts from the PubMed database. It has been applied to the HBM4EU prioritised PFAS to identify linkages with Adverse Outcome Pathway.

(AOP) events existing in the AOP wiki database. This tool will help identifying relevant AOP events.

Work on assessing the exposure to actual mixtures (extracted from human serum and tissues (placenta)) and analysing the effect on estrogen receptor function /androgen receptor effects is ongoing.

Considering **modes of action** underlying changes in lipid metabolism in the liver, an extensive literature review on the effects of PFASs on serum levels of cholesterol and triglycerides was conducted. Further studies were performed to study effects of PFASs on triglycerides and cholesterol in human liver (HepaRG) cells. Also, whole genome gene expression (microarray) studies were performed, to provide underlying mechanistic insights. Intracellular concentrations of PFASs were determined to relate measured effects to cellular concentrations.

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IN COHORT STUDIES COLLECTED IN HBM4EU THE ASSOCIATION OF PFAS EXPOSURE ARE BEING EVALUATED IN RELATION TO:

- Low birth weight, fetal growth, preterm delivery and other pregnancy complications
- Maternal and offspring thyroid function
- Cardiovascular health, i.e. cholesterol
- Later offspring immune function, including asthma and allergies
- Offspring cognitive development
- Triangular relationship between circulating PFAS, endogenous hormones (thyroid hormones, estrogens and androgens) and fetal growth

Effect biomarkers have been selected and were applied to a selected cohorts to inform about early effects of exposure to these compounds. Kisspeptin and clinical markers will be measured in relation to PFAS exposure and sexual maturation, body mass index and metabolism in teenagers. These mechanistically-based effect biomarkers may further elucidate causal pathways between chemical exposure and adverse health outcomes (e.g. BMI/metabolism, sexual maturation, asthma & allergy). Analysis on exposure-effect biomarker-health effect path (for sexual maturation and metabolism) will be also performed.

HBM4EU is conducting mixture risk assessment on the new exposure data from European teenagers, which also includes exploring the possibility for deriving relative potency factors specifically for human serum data.

8. SUPPORTING NUMEROUS POLICY INITIATIVES

In recent years, **policy attention for the PFAS** has increased strongly at various policy levels (from the local, to the national, European and international level). Various policy processes have been started for which HBM4EU can provide relevant input on time. This applies to regulatory initiatives, policy evaluation, agenda-setting and various other complementary policy instruments (such as information campaigns, targeted exposure prevention, monitoring and research). In the context of HBM4EU a **mapping of the policy context and opportunities for PFAS** has been performed in 2019 (see additional deliverable 5.9).

The mapping of policy opportunities helped to identify important policy processes that might benefit from the evidence that is being produced by HBM4EU and to further match the policy and project timelines. Following this mapping exercise, a **science-policy dialogue** on HBM4EU results on PFAS has been launched to further explore how the results can be of use for policy making. A workshop will be organised in March 2021 with HBM4EU project partners, regulatory scientists from member states, European agencies and the European Commission to facilitate the discussion on uptake of HBM data into policy and will support the intention of a restriction of PFAS as a group and other relevant policy processes.