



HBM4EU

POLICY BRIEF

JUNE 2022



European Human Biomonitoring Initiative

Bisphenols

This policy brief summarizes the adverse human health effects of bisphenols, their main exposure pathways for humans, and how human biomonitoring

of bisphenols could be of value in the development of EU policy.

KEY MESSAGES

- HBM4EU has generated EU-wide human biomonitoring (HBM) data on bisphenols, both by collecting data from different studies and by generating new data in 11 countries representing the 4 European Regions (North, East, South and West). This is by far the largest collection of HBM data on bisphenol A (BPA) and its substituents bisphenol S (BPS) and bisphenol F (BPF) in Europe.
- BPA is ubiquitous in the environment, with all adult humans across Europe exposed to at least low levels. BPS and BPF, used as replacements, are detected in 50% of adults analysed under HBM4EU.
- BPA levels of exposure are higher than exposure levels for the substituents BPF and BPS in all Europe. Northern area is globally less exposed to these bisphenols than other areas.
- Risk from occupational exposure should not be disregarded (a potential risk for workers was identified, especially in industrial scenarios with BPA exposure levels 10-20-fold higher than background exposures).
- Based on previous studies and on exposure pathway modelling, the main route of human exposure appears to be through diet, where bisphenols may have migrated into food or drinks from food containers, packaging, or feeding bottles.
- HBM4EU modelling studies on toxicokinetics and tissue distribution (including the fetus), Adverse Outcome Pathways and effect biomarkers strengthen the concern that the internal exposure to BPA, BPS and BPF and other bisphenols could be linked to a variety of health outcomes in humans and in the environment. In eight sampling locations out of ten, at least 5% of the European adults (20-39 years) from the HBM4EU Aligned Studies¹ exceeded the HBM-GV of 1 µg/L for BPS, particularly in Southern Europe.
- Societal concern towards endocrine disrupting chemicals is highly connected to bisphenols and to the campaigns to regulate BPA in particular.

BACKGROUND: HBM4EU

The European Human Biomonitoring Initiative, HBM4EU, running from 2017 to June 2022, is a joint effort of 28 countries, the European Environment Agency and the European Commission, and co-funded under Horizon 2020. The main aim of the initiative is to coordinate and advance human biomonitoring in Europe. HBM4EU has provided a wealth of improved evidence of the actual exposure of citizens to chemicals and their possible health effects. Human biomonitoring allows us to measure our exposure

to chemicals by measuring either the substances themselves, their metabolites or markers of subsequent health effects in body fluids or tissues. Information on human exposure can be linked to data on sources and epidemiological surveys to inform research, prevention, and policy with the objective of addressing knowledge gaps and promoting innovative approaches. If you would like to read more about the project itself, please visit the HBM4EU [website](#).

¹ The HBM4EU Aligned Studies are a survey aimed at collecting HBM samples and data as harmonised as possible from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread.

HBM4EU RESULTS

The HBM4EU project has produced an updated [scoping document](#) to answer the main policy questions, and to discuss the latest research. In order to further support current and future HBM studies, HBM4EU developed a variety of [publicly available](#) groundwork materials for a harmonised approach to study planning and conduct of HBM studies in Europe. It also produced significant results on both exposure to bisphenols and health effects related to these exposures.

HBM4EU laid the foundations for a [European HBM Platform](#) to monitor human exposure to priority chemicals (including bisphenols) and related health effects in a harmonised and quality-controlled way. A Quality Assurance/Quality Control Programme was implemented in order to establish a European [database of candidate laboratories](#) that are equally qualified for exposure biomarker analysis.

The [HBM4EU dashboard](#) displays 33 aggregated HBM datasets from 8 European countries with sampling between 2002 and 2015. This includes a list of suitable biomarkers, matrices and analytical methods. IPCHEM displays HBM metadata for 44 datasets on bisphenols.

As part of the HBM4EU Aligned Studies, BPA, BPS and BPF concentrations have been measured in urine samples obtained

from adults 20-39 years of age in 11 European countries between 2014-2021 (DK, IS, FI, PL, CZ, HR, PT, FR, CH, DE, LU) representing 2756 individuals.

A dedicated physiology-based toxicokinetic (PBTK) model to link HBM data, environmental monitoring and external exposure modelling was developed and implemented to obtain BPA, BPS and BPF intake estimates derived from the HBM4EU HBM data.

Adverse Outcome Pathways studies on BPA substituents, BPS and BPF suggested that these compounds are linked to health effects such as metabolic diseases and cancer.

New effect markers were developed linking BPA to health effects (e.g. behaviour) and were shown to have added value in human studies, increasing the weight of evidence for a causal relationship between exposure and adverse health outcomes.

Mixture studies were also conducted in HBM4EU that are relevant to the bisphenol family of compounds.

Human Biomonitoring Guidance Values (HBM-GVs) have been derived for BPA and BPS, and a substance dossier on BPF has been prepared. The health-based guidance value for BPA has been revised following the recent draft opinion of EFSA on TDI (see answer to Policy Question 7).

EXPOSURE & HEALTH EFFECTS

Based on data available from human biomonitoring studies, the adult population (20-39 years old) analysed under HBM4EU is continuously exposed to BPA and is at risk from internal exposure.

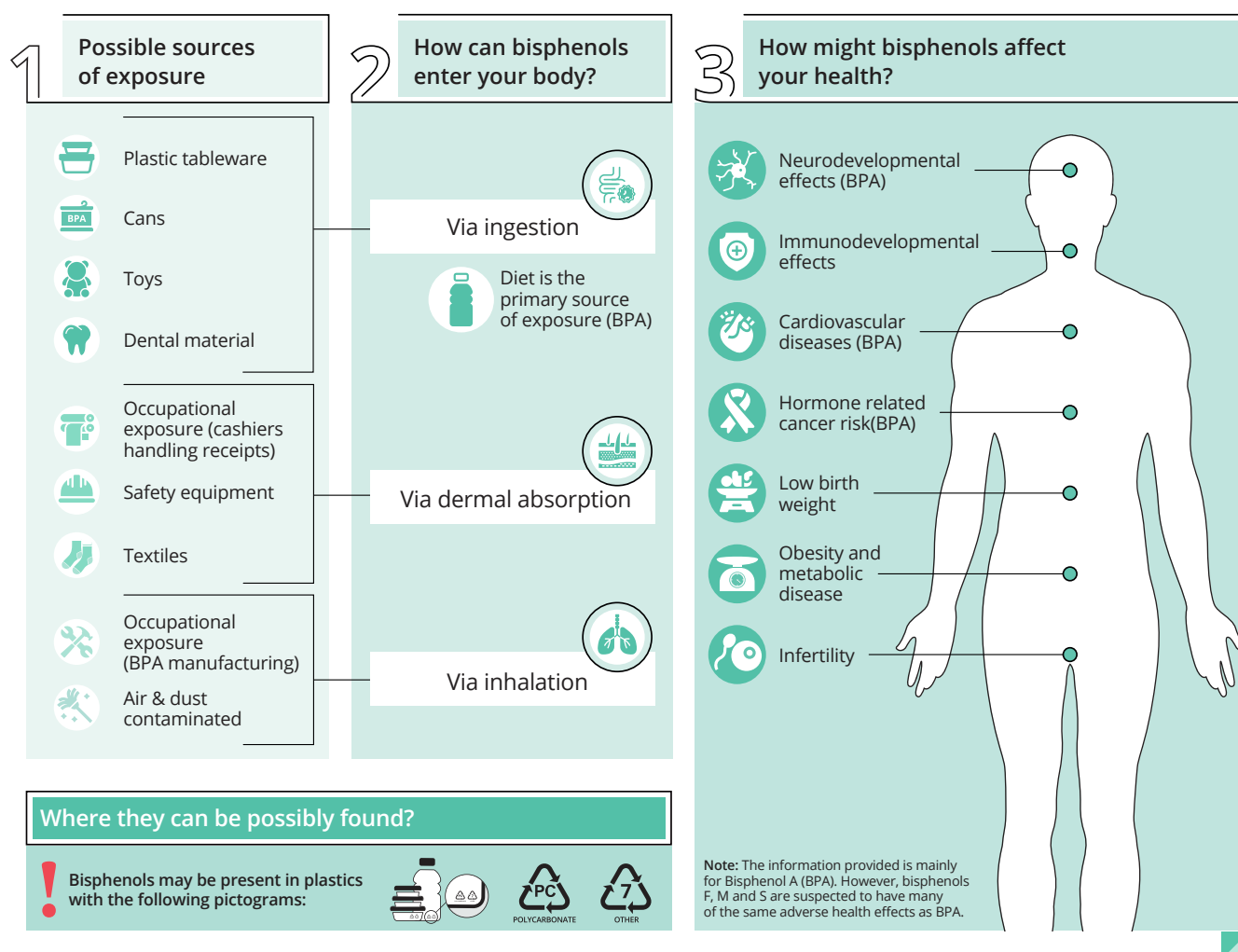
A number of other bisphenols are now being used in increasing amounts, resulting in rising levels of exposure to these substances. For example, elevated concentrations of BPF and BPS have been reported in adult samples of the HBM4EU Aligned Studies.

It is worth noting that most of the information available on human exposure to bisphenols is derived from studies investigating BPA, with relatively few studies to date investigating other bisphenols. BPA is becoming increasingly restricted and substituted with other bisphenols.

BPA is an [endocrine disruptor](#), thus affecting human health. It has been indicated that BPA elicits a variety of endocrine disrupting effects targeting steroid hormones as well as thyroid hormones. Other bisphenols, including BPF, BPS, BPAF, BPZ, BPE and BPB are also suspected to be endocrine disrupting chemicals. Studies in HBM4EU have provided additional support for the toxicity of BPA substituents, particularly concerning fetal exposure and outcomes such as obesity, cancer.

HBM4EU produced an infographic with an overview of the main sources of exposure (environmental, occupational, consumer), exposure pathways (oral, inhalation, dermal) and health effects of BPA Figure 1.

Figure 1. Overview of exposure sources, pathways and health effects associated with bisphenols



INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

Different measures to regulate bisphenols have been taken during the last decade and additional regulations are expected in the next few years. HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as EFSA consultations. These are available in the [HBM4EU Science to Policy section](#).

At EU level, several policy measures have been introduced to address human exposure to bisphenols. These cover i) implementation of wider chemicals legislation; ii) consumer products (e.g., toys, medical devices); iii) occupational exposure, and iv) the environment (e.g., emissions to air and water).

ECHA identified BPA as a substance of very high concern (SVHC) under Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) due to potential endocrine disrupting (ED) effects for human health and the environment.

BPA has been restricted under REACH for use in thermal paper since 2016 (taking effect from 2020) – migration limit of ≤ 0.02%. BPA is also prohibited in varnishes or coatings applied to materials and articles for use in packaging for children's food items (e.g., infant formula, baby food) as per [Regulation \(EU\) 2018/213](#).

Additional measures have been taken in several countries. For example, France banned BPA in all food contact materials (French Law No 2012-1442), other countries (Denmark, Belgium and Sweden), banned it in those materials intended for children under the age of 3.

In its 2015 re-evaluation of BPA exposure and toxicity, EFSA used a more refined methodology and new data, revising the t-TDI for BPA from 50 to 4 µg/kg bw/day. More recently, in December 2021, EFSA published a draft opinion which proposes lowering the tolerable daily intake (TDI) of BPA from 4 mg/kg bw/day to 0.04 ng/kg bw/day. This is a decrease of five orders of magnitude from the previous value established in 2015.

German authorities are investigating the potential risks of BPA and other similar bisphenols to the environment. They are expected to submit their restriction proposal to ECHA in April 2022.

In 2020, ECHA Committee for Risk Assessment adopted BPS harmonized classification as [H360FD](#). There is a proposal for a harmonized classification of BPAF as [H360F](#).

In 2022, ECHA and the Member States have assessed a group of 148 bisphenols and recommended that more than [30 bisphenols need to be restricted](#) due to their potential hormonal or reprotoxic effects.

POLICY QUESTIONS

1 What is the current exposure of the EU population to BPA, BPS and BPF?

The answers below are summarised. For more details, please consult the substance report available on the [dedicated substance page](#) of the HBM4EU website.

The HBM4EU Aligned Studies show that median levels of urinary BPA are still pronounced in all European regions, between 0.55 and 2.35 µg/g creatinine and P95 values between 2.41 and 12.19 µg/g creatinine in adults from 11 countries all over Europe.

P50 and P95 of urinary BPS concentrations are in the range of 0.06 – 0.34 µg/g creatinine (4 studies have a P50 value < detection limit: 0.01, 0.09 and 0.05 µg/L) and 0.39 – 8.77 µg/g creatinine respectively. P50 and P95 of urinary BPF concentrations are in the range of 0.10 – 0.72 µg/g creatinine (3 studies have a P50 value < detection limit: 0.03, and 0.15 µg/L) and 0.56 – 17.03 µg/g creatinine respectively. The median levels of urinary BPA substitutes (BPS and BPF) are increasing in some European countries (as compared to DEMOCOPHES), which triggers a growing concern for exposure to BPS and BPF in Europe.

2 Do different regulatory controls across the EU concerning BPA lead to different exposures?

Since 2011, different measures have been taken to limit population exposure to BPA on a European level. It has been banned from infant feeding bottles across Europe (Commission Directive 2011/8/EU) and since 2018 was further restricted to use in certain food-contact materials. Comparing the results of different HBM4EU Aligned Studies in the 4 European geographical areas (North, East, South and West) revealed that BPA levels of exposure are higher than exposure levels for substituents (BPF and BPS) in all Europe. Northern area is globally less exposed to bisphenols than other areas. When HBM4EU data are compared to DEMOCOPHES data, some changes can be observed (e.g. a decrease of BPA in Denmark and an increase in Poland and Luxemburg, and concerning BPS an increase in the Czech Republic), but whether this is related to differences in regulation is unclear at this stage.

3 Are bisphenols exposure levels of concern for health?

BPA exposure levels measured in the adult population from the HBM4EU Aligned Studies are below the established human biomonitoring guidance values based on the temporary tolerable daily intake (t-TDI) of 4 µg/kg bw/day. If the new EFSA proposal for TDI is considered, all measured values largely exceed the HBM guidance value that can be derived from the new TDI.

In eight sampling locations out of ten, at least 5% of the European adults (20-39 years) from the HBM4EU Aligned Studies exceed the HBM-GV of 1 µg/L for BPS. The most affected studies were conducted in Southern Europe.

A cohort HBM4EU case study linked BPA childhood exposure to a potential biomarker of effect, the brain-derived neurotrophic factor (BDNF), and an adverse outcome pathway leading to behavioural and cognitive alterations.

Since the aligned studies indicated co-exposure to BPA and to its substituents BPS and BPF, mixture studies should be considered, particularly since BPA substituents appear to display similar effects to BPA and to be linked to similar AOPs.

4 Is occupational exposure of cashiers a health concern?

The presence of BPA in thermal paper represents a threat most especially to cashiers, who are in constant contact with the material. BPA was restricted from use in thermal paper in 2016, with entering into force in 2020. Because of the background environmental exposure, it has not been possible to derive an HBM-GV for workers. A HBM4EU systematic review on biomonitoring exposure to BPA, BPS and BPF (Bousoumah et al. 2021) retrieved 30 studies on occupational Human Biomonitoring of BPA and only 4 and 2 publications on BPS and BPF, respectively. Considering the current policies leading to the substitution of BPA by analogue substances, there is a need for research on the occupational exposure to these compounds, including BPS and BPF. This would include studying cashier work in which BPS may have replaced BPA.

Data gathered under the project framework indicate that the risk from occupational exposure should not be disregarded (a potential risk for workers was identified, especially in industrial scenarios with BPA exposure levels 10-20-fold higher than background exposures), and that protective measures need to be taken regarding BPS exposure.

5 What is the toxicity of BPA substitutes and are current exposure levels of concern?

Using computational tools developed under the project framework, it was possible to highlight obesity as one of the major potential health endpoints of BPS and to link BPF to an adverse outcome pathway (AOP) for thyroid cancer.

The recommended HBM-GVs for BPS are based on endocrine disrupting health effects occurring in animals at very low doses and was set in HBM4EU at 1 µg/L based on animal toxicity studies for mammary gland and neurodevelopmental toxicity.

6 Can we find evidence for low-dose effects within mixtures?

Two different HBM4EU case studies refer to low-dose effects within mixtures. A biomonitoring survey of co-exposure to bisphenols (BPA and analogues) by consumers of canned foodstuffs indicate that participants with a diet rich in canned food were more exposed to BPA when compared to the control group (Nadal et al. 2020). A mixture risk assessment with focus on male reproductive health shows that combined exposures to bisphenols and other chemicals is associated with declines in semen quality in Western countries.

7 How can HBM feed into assessment of the Tolerable Daily Intake (TDI) for BPA, as set by the European Food Safety Authority (EFSA)?

HBM4EU has derived a HBM-GV of 230 µg /L for BPA exposure in adults and 135 µg/L for BPA exposure in children (>3 years) (Ougier et al. 2021). This HBM-GV was set at a urinary concentration of total BPA consistent with the temporary TDI (t-TDI) of 4 µg/kg bw/day as derived by EFSA in 2015. Recently, the EFSA Panel on Food Contact and Materials, Enzymes and Processing Aids (CEP) released a re-evaluation of the t-TDI where this is to be lowered from 4 µg/kg bw/d to 0.04 ng/kg bw/d of total BPA. If this new TDI is confirmed, all the European samples measured will be above the TDI. HBM4EU would then recommend that the guidance values for the BPA substituents be revisited and adjusted.

8 Is it important to eliminate legacy BPA from material cycles (i.e. waste till receipt rolls) when implementing a circular economy in order to protect human health?

HBM4EU is preparing a report on specific chemicals in the circular economy, including bisphenols. The report will focus on how human biomonitoring can support understanding of exposure to chemicals via secondary material flows and recycling. This will be addressed through five case studies, three of which will focus on bisphenols - in consumer goods made from recycled plastics, in recycled paper, and in dietary exposure from reusing sewage sludge and wastewater on agricultural lands.

KNOWLEDGE GAPS

HBM4EU has developed quality research in support of the policy questions. However, certain knowledge gaps remain.

A mapping of BPA substitution which includes human biomonitoring data on less regulated bisphenols is needed as well as the investigation of human exposure and the assessment of need for further regulation.

Since bisphenols are short half-life contaminants, it is important to reassess the sampling protocols: are spot samplings sufficient to reflect exposure or should we combine several samples per individual to decrease errors from exposure variation?

There is a need to explore the health impacts of bisphenols further (particularly substituents), to support hazard and risk assessment as well as evaluate the impact of regulatory actions - those already in place and future wider restrictions on bisphenol exposure in European population.

It is also necessary to identify additional effect biomarkers associated to bisphenol exposure (including biochemical and epigenetic) and to determine whether those effect markers are common to all bisphenol compounds.

It is urgent to continue the investigation of exposure to bisphenol mixtures and their health effects.

HBM4EU coordinator:

German Environment Agency hbm4eu@uba.de

Knowledge Hub coordinator:

European Environment Agency hbm4eu@eea.europa.eu

www.hbm4eu.eu



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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.