HBM4EU science and policy for a healthy future

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HBM4EU

POLICY BRIEF

JUNE 2022

European Human Biomonitoring Initiative

Phthalates

This policy brief summarizes the adverse human health effects of Phthalates and the phthalate-substitute DINCH, their main exposure pathways for humans, and how Human Biomonitoring of phthalates could be of value in the development of EU policy.

Phthalates (also named phthalate esters or esters of phthalic acid), and their substitute Hexamoll® DINCH®, are a group of plasticizers with a production volume of millions of tons per year. They are widely used in the manufacturing of plastics, to make them soft and flexible, and in personal care products.

KEY MESSAGES

- **HBM4EU has generated EU-wide HBM data for ten different phthalates and the substitute DINCH from 12 countries in a harmonised way through the HBM4EU Aligned Studies.**
- **The HBM4EU Aligned Studies[1] (2014-2021) could establish baseline levels of recent internal exposure to phthalates and DINCH for European children (6-11 years) and teenagers (12-18 years) with highest average exposures observed for DEHP and DiBP in children and DEP and DEHP in teenagers.**
- **For some phthalates (BBzP, DiBP, DEHP, DiDP) and DINCH, higher levels were found in the more susceptible group of children as compared to teenagers. On the other hand, higher levels of DEP, DnBP and DiNP were measured in teenagers. Geographical differences in internal exposure were observed between European countries and regions as well.**
- **Results show that despite extensive regulatory measures for many phthalates, children and teenagers in Europe are still exposed to multiple phthalates and/or DINCH simultaneously.**
- **The ubiquitous exposure to health-impacting phthalates and their substitutes is a concern for the general population, especially for children and adolescents. At least 4 % of the European children exceeded the health-based guidance value HBM-GV for DnBP, and at least 4 % of the children and 1 % of the teenagers the HBM-GV for DiBP. The HBM-GV for DEHP was exceeded as well, although only to a minor extent (at least 0.32 % of all children and adolescents investigated).**
- **A mixture risk assessment revealed a toxicologically undesirable high exposure of ~17 % of the European children and adolescents from cumulative health effects of five reprotoxic phthalates (DEHP, DiBP, DnBP, BBzP, DiNP). The main drivers of the mixture risk are DiBP and DnBP.**
- **The HBM4EU analyses show decreasing time trends for most regulated phthalates since the 2000s, illustrating the effectiveness of policy action. At the same time, an increasing trend for the substitutes DINCH and DEHTP was observed. Further monitoring of phthalates is needed to assess the possible additional success of recent regulatory measures (ban of DEHP, DiBP, DnBP, BBzP in consumer articles since 2020) to ensure levels below HBM-GVs and to prevent regrettable substitution.**
- **Societal concern regarding phthalates underlines the importance of investigating their impacts on citizens and the environment.**

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.

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.

HBM4EU RESULTS

To support current and future HBM studies, the HBM4EU project has developed a framework to monitor human exposure to priority chemicals such as phthalates and the non-phthalate substitute DINCH and to determine the health impacts in the European population. This includes the development of publicly available groundwork materials for a harmonised approach to study planning, conduct and assessment methods, available in the HBM4EU online library. A Quality Assurance/Quality Control Programme was implemented to establish a European database of candidate laboratories that are equally qualified for exposure biomarker analysis.

The HBM4EU Aligned Studies (2014-2021) have generated baseline levels of internal phthalate and DINCH concentrations for 2,880 children (6-11 years) and 2,799 teenagers (12-18 years). A total of ten phthalates and DINCH were measured in urine samples of European adolescents and children from 11 and 12 different countries, respectively. Children have higher levels for DINCH and some of the phthalates (namely BBzP, DiBP, DiDP and DEHP) compared to teenagers, whereas teenagers have higher levels of DnBP, DiNP and DEP. In addition, geographical differences in internal exposure up to a factor of nine are observed between the countries.

Toxicologically-based human biomonitoring guidance values (HBM-GVs) for children and adults were derived for five phthalates (DEHP, DnBP, DiBP, BBzP and DPHP) and DINCH.

Comparison with exposure levels shows that at least 4% of the European children exceeded the health-based guidance value HBM-GV for DnBP, and at least 4% of the children and 1% of the teenagers the HBM-GV for DiBP. Thus, the risk of health impairment from exposure to DnBP, DiBP, and to a minor extent DEHP, alone is not adequately controlled for European children and teenagers. As concurrent exposure to many phthalates is evident and many phthalates have been shown to act in a cumulative manner, a mixture risk assessment of five selected phthalates (DEHP, DnBP, DiBP, BBzP, DiNP) was carried out. The analysis revealed that approximately 17% of European children and adolescents are at risk from exposure to these five phthalates. For the phthalates studied (DEHP, DiNP, BBzP, DnBP and the replacement DINCH), daily intake was on average in the range of 0.1 to 1 µg/kg bw/d in most studies, far below the existing regulatory thresholds.

Two occupational studies have been conducted, as well as a risk assessment (RA) for several phthalates using HBM data to illustrate strengths and limitations in RA. A methodology for exposure reconstruction was developed and improved to deliver external exposure estimates from available HBM data, and a HBM4EU workshop was held in 2019 to create a space for dialogue with policy makers and stakeholders on available evidence and uptake to policy.

HBM4EU also laid the foundations for a European HBM Network to monitor human exposure to priority chemicals, including phthalates.

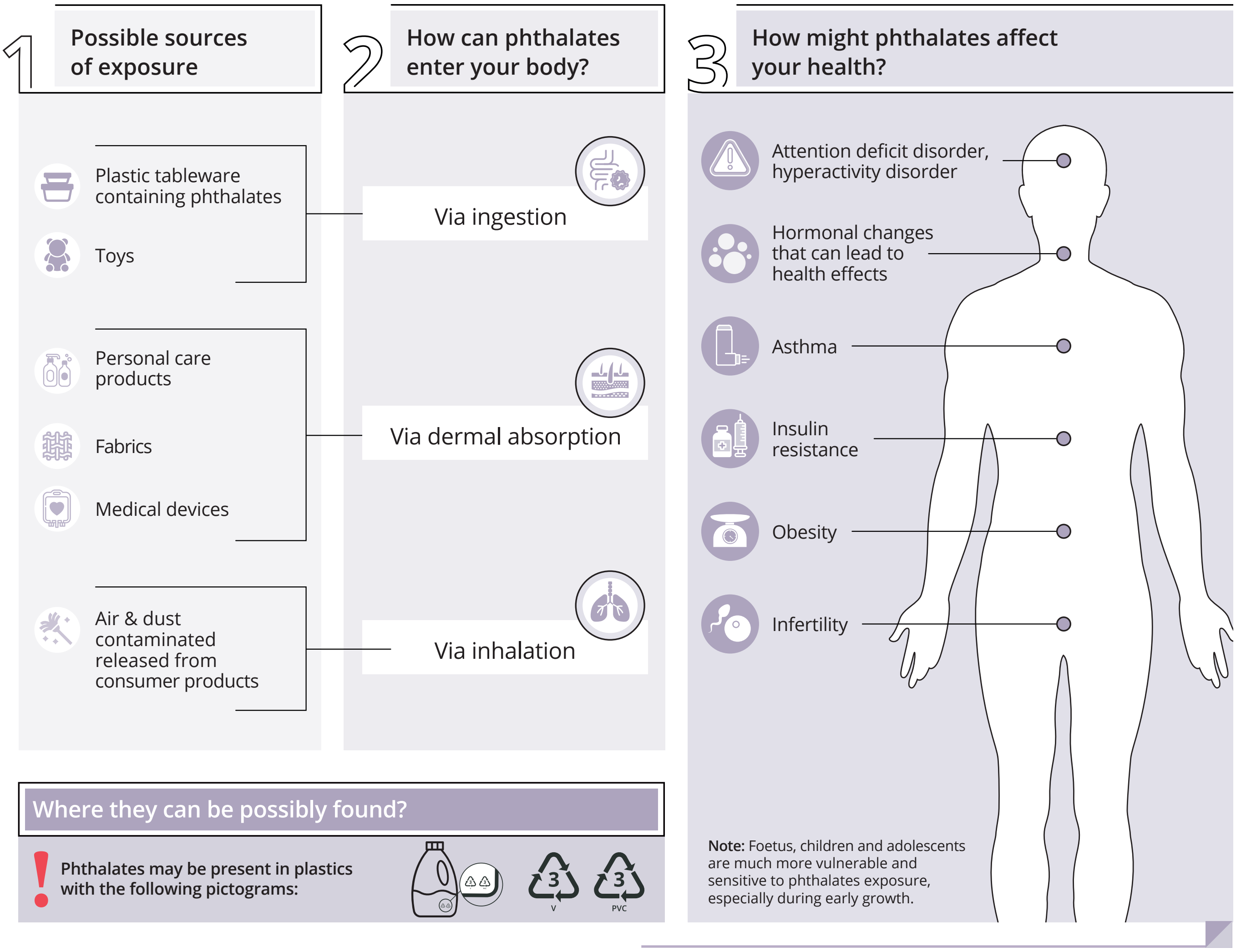
EXPOSURE & HEALTH EFFECTS

Figure 1 gives an overview of the main sources of exposure, exposure pathways and health effects associated with phthalate exposure.

Phthalates and DINCH are a group of plasticizers with a production volume of millions of tons per year. They are widely used in the manufacture of plastics, to make them soft and flexible, and in personal care products. Several human biomonitoring studies in the EU, US and Asia conducted in the past show that the ubiquitous use of phthalates lead to continuous internal exposure of the public. HBM4EU results show, that even today, children and teenagers in Europe are exposed to phthalates and DINCH. In > 99% of all samples investigated metabolites of DEHP, DnBP, DiBP and DEP were detected, for the other compounds in > 89%. Only DnOP, DnPeP and DCHP were detected in a small percentage of the samples (1 – 6%).

Many phthalates are endocrine disrupting compounds, that are shown to induce the so-called phthalate syndrome already at low doses, which covers different malformations of the reproductive organs and infertility. Recent scoping reviews conducted under HBM4EU reported a possible link between phthalate exposure and asthma, osteoporosis, metabolic syndrome and attention deficit hyperactivity disorder. However, more research is needed to confirm these observations. In terms of risk assessment, it is important to note that mixtures of some of the above-mentioned phthalates can act in a dose-additive manner and thus have direct cumulative health effects. Furthermore, cumulative health effects with other endocrine disrupting chemicals have been demonstrated, even though they function via a different mode of action.

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



INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as ECHA and the SCHEER (Scientific Committee on Health, Environmental and Emerging Risks). These are available in the HBM4EU Science to Policy section.

Under REACH, many phthalates that are classified as toxic to reproduction (Repr. 1B) are restricted on their own and in mixtures that are intended for consumer use. Due to their classification as reprotoxic substances and as endocrine disruptors, phthalates are identified as substances of very high concern.

The European Union has taken action to reduce citizens' exposure to phthalates known to cause risks to health:

- The use of DEHP, DnBP, DiBP and BBzP are restricted under REACH Annex XVII in consumer products on the EU market since July 2020. Several phthalates (DEHP, BBzP, DiBP, DnBP, DiPeP, DHNUP, DMEP, DnPeP and DnHP) cannot be used in the EU without authorisation for specific uses.
- DiNP, DEHP, DnBP, DiDP, DnOP, BBzP and DiBP are banned in toys and childcare articles under the same REACH Annex XVII.
- The use of phthalates classified as toxic to reproduction is prohibited in cosmetics.
- EFSA has set a tolerable daily intake (TDI) for the concentration of certain phthalates (for DnBP, BBzP, DEHP, DiNP and DiDP) in food contact materials.

POLICY QUESTIONS

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

1 Which are the most sensitive, reliable and cost-effective methods and biomarkers to measure phthalates and DINCH?

HBM4EU has elaborated a prioritised list with most suitable biomarkers, matrices and analytical methods. In total, 26 suitable biomarkers representing exposure to 14 parental compounds were selected. Two methods have been evaluated as being suitable to measure the metabolites: GC-MS-MS for measuring only DPHP metabolites and LC-MS-MS for all other biomarkers. Urine has been selected as matrix of choice for all compounds. In addition, a feasibility study was conducted that identified new, valuable urinary exposure biomarkers for EU-labelled, reprotoxic phthalates currently not covered in HBM analytical methods. This work will provide a harmonized method covering biomarkers for all EU-regulated phthalates.

The HBM4EU Quality Assurance/ Quality Control Programme was implemented for MEP, MBzP, MiBP, MnBP, MCHP, MnPeP, MEHP, 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP, MnOP, OH-MiNP, cx-MiNP, OH-MiDP, cx-MiDP, OH-MINCH, cx-MINCH. Throughout the ICI/EQUAS exercise, in combination with training and knowledge exchange, a substantial increase in capable laboratories being able to analyse DINCH/phthalates within HBM4EU was achieved.

2 What is the extent of the current exposure of the EU population to the 16 phthalates (Cat A, B and C) and their substitute Hexamoll® DINCH?

In children, highest median (P50) levels were observed for ∑DEHP metabolites (33.5 µg/L), followed by DiBP (26.7 µg/L), DEP (22.7µg/L) and DnBP (21.4 µg/L) metabolites. DINCH was one of the substances for which the lowest median concentration was observed with 3.4 µg/L (∑DINCH metabolites).

Whereas in teenagers, the highest median levels (P50) were observed for the DEP metabolite (37.9 µg/L), followed by DEHP metabolites (28.4 µg/L). For DiBP (24.4 µg/L) and DnBP (24.8 µg/L) metabolites, similar median levels were observed. The lowest median levels in teenagers were found for DiDP metabolites (1.9 µg/L) and ∑ DINCH metabolites (2.35 µg/L).

In addition, data from 33 existing HBM-studies that measured phthalates and DINCH can be consulted in the online European HBM dashboard, created and populated under HBM4EU.

Further analysis and comparison between P95 exposure levels and geometric means may be found in the Phthalates Substance Reports.

3 Do the exposure levels differ significantly between the countries?

The HBM4EU Aligned Studies revealed geographical differences in average internal exposure up to a factor of 9 between the countries. It appears that higher exposure differences exist among the countries rather than among the age groups in each country; this in turn reflects the differences in the use of consumer products and food contact materials in the different countries, that are mostly related to sociodemographic determinants.

Based on the HBM4EU Aligned Studies for children, Greece, Italy and France, have the highest levels (geometric means) in phthalates and DINCH compared to the European average, and Denmark, Hungary, and Netherlands have the lowest concentrations. For teenagers, France, Slovakia, and Norway are exposed the most (geometric mean) and Belgium, Poland, and Germany are the least exposed to phthalates and DINCH.

HBM4EU found differences between European regions in most phthalates and DINCH. For example, in children's levels, there were no differences in DnBP and DiBP. But Eastern Europe had lower levels in DINP, BBzP, and DiDP compared to at least one other European region. For DINCH, Eastern and Western Europe had lower levels than Southern and Northern Europe. Regional differences for children indicate, however, a complex result pattern where pairwise comparisons between European regions depend on the phthalate studied.

4 What are the main sources of exposure and the reasons for differences in exposure (different regulations in different countries) to phthalates and Hexamoll® DINCH?

The main source of exposure for phthalates and DINCH is likely diet and food contact materials. However, depending on the properties of the phthalate, other exposure pathways might be of importance, such as indoor dust through ingestion or inhalation in gaseous and particles phase. Currently, analyses to determine exposure factors by using HBM4EU Aligned Studies data is being carried out. Results will be available before end of June 2022.

5 What are the high-exposure groups? (Is there a statistically significant and toxicological relevant difference in mean concentration between adults and children? […] between occupational exposed and non-exposed adults? […] between male and female?

In the HBM4EU Aligned Studies, higher levels for some phthalates are found in children compared to teenagers. No obvious and consistent differences between the sexes or the household's education are apparent with regards to phthalate and DINCH exposure. In the analyses of existing HBM studies since 2005, including all European regions and Israel, HBM4EU finds indication for age differences (age groups between 3 to 60 +). For example, DnBP and DiDP children's levels are higher than in adolescents and these, in turn, are higher than adults' levels.

6 Are there different time trends for the less regulated (DEP, DMP, DCHP, DPHP) and regulated phthalates (DEHP, BBzP, DnBP, DiBP, DiNP, DnOP, DiDP) and DINCH?

HBM4EU is evaluating time patterns for phthalates and DINCH in children and four European geographical areas by comparing three different time points. Data analyses from Danish and German time trend studies show decreasing concentrations since the 2000s in the more regulated phthalates DEHP, BBzP, DnBP, and DiBP (up to 17% yearly decrease), and stability in DINP and DIDP/DPHP. Time trends since 2006, for less regulated phthalates (DEP, DMP) show decrease by about 17% per year and substitutes DINCH and DEHTP show strong increases.

7 How effective have the different mitigation steps and regulations been for phthalates? (i.e. the restriction under REACH for 6 phthalates since 2007; the introduction of the Authorisation obligation under REACH since 2015; the identification as SVHC)?

The data from the time trend analyses of Danish and German samples illustrate the effectiveness of policy action for the highly regulated phthalates. For the less-regulated substitute compounds, such as DEHTP and DINCH, these analyses show an increasing trend. Data from existing HBM studies since 2005, from various European regions analysed in HBM4EU, support these findings, indicating decreases in the more regulated phthalates DEHP, DnBP, DiBP, DiDP, BBzP, but also the less regulated phthalates DEP and DMP. However, the mitigation steps have not been sufficient since the levels of highly regulated phthalates exceed the HBM-GVs. In addition, regulatory steps might be necessary for the substitutes to prevent regrettable substitution.

8 Is the exposure to phthalates and their substitutes of health-relevance for the general population and vulnerable groups (inter alia children and pregnant women)? What part of the population has exposure levels exceeding the HBM guidance values - if existing- or TDI)?

Comparison of the newly generated HBM4EU Aligned Studies data with HBM-GVs showed that currently, exposure to DnBP and DiBP is a health concern in some countries, since the percentage of children and teenagers exceeding these values is highest for these highly regulated phthalates (up to 4% of European children and 2 - 7% of European teenagers, depending on the substance). The exposure to BBzP, DEP and DINCH is well below the corresponding health-based guidance values for both children and teenagers. One child exceeds the HBM-GV for BBzP. Some participants exceed the HBM-GV for DEHP. An impact on health cannot be excluded for these children and teenagers.

In addition, a mixture risk assessment of 5 selected reprotoxic phthalates (DEHP, DiBP, DnBP, BBzP, DiNP) is being carried out, since animal mixture toxicity studies revealed that some phthalates can act in an additive manner. The mixture risk assessment shows that ~17 % of European children and adolescents are at risk from adverse effects of combined exposure to these 5 phthalates. Furthermore, the mixture risk assessment revealed that for most European children and adolescents combined risks are driven by multiple phthalates, and the main drivers are DnBP and DiBP.

9 Can EU-wide HBM guidance values be derived for single substances?

Within HBM4EU, human biomonitoring guidance values (HBM-GVs) were derived for five phthalates (DEHP, DnBP, DiBP, BBzP and DPHP) and for the non-phthalate substitute DINCH. These HBM-GVs were derived for the general population and for workers. Different values were set for children and adults including adolescents. Below is an overview of the $HBM\text{-}GV_{GenPop}$ for the different age groups. More details and the values for the working population can be found in Lange et al., 2021.

Table 1. Human biomonitoring guidance values for the general population ($HBM\text{-}GV_{GenPop}$) derived for selected phthalates and the substitute Hexamoll® DINCH

Parent compound	Biomarker(s)	$HBM\text{-}GV_{GenPop}$ in µg/L[1]	
		Children[2]	Adults incl. adolescents[3]
DEHP	∑ 5-oxo-MEHP + 5-OH-MEHP	340	500
	∑ 5-cx-MEPP + 5-OH-MEHP	380	570
DnBP	MnBP	120	190
DiBP	MiBP	160	230
BBzP	MBzP	2000	3000
DPHP	∑ oxo-MPHP + OH-MPHP	330	500
Hexamoll® DINCH	∑ OH-MINCH + cx-MINCH	3000	4500

[1] rounded value; [2] including children 6-13 years of age; [3] including women of child-bearing age

5-oxo-MEHP: mono(2-ethyl-5-oxohexyl)phthalate); 5-OH-MEHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; 5-cx-MEPP: mono (5-carboxy-2-ethylpentyl) phthalate; MnBP: monobutyl phthalate; MiBP: monoisobutyl phthalate ; MBzP: monobenzyl phthalate (CAS No.: 2528-16-7); oxo-MPHP: mono(propyl-6-oxo-heptyl) phthalate; OH-MPHP: hydroxy-mono-propylheptyl phthalate; OH-MINCH: cyclohexane-1,2-dicarboxylic acid-mono(hydroxyl-iso-nonyl) ester; cx-MINCH: cyclohexane-1,2-dicarboxylic acid-mono-(carboxy-iso-octyl) ester.

9 How can cumulative risks of phthalates and other anti-androgenic substances be assessed for their health relevance? Are their cumulative effects relevant for regulation?

A mixture risk assessment of five selected phthalates (DEHP, DnBP, DiBP, BBzP, DiNP) has been carried out within the HBM4EU Aligned Studies. Since some of these phthalates act in a cumulative manner, the hazard index approach, based on the concept of dose addition, was applied using the HBM-GVs. Furthermore, case studies were carried out to evaluate a proof-of-concept for the identification of mixture health effects, one case study being a mixture risk assessment for male reproductive health with a focus on semen quality, which included certain phthalates and other anti-androgenic substances. Results will be available in June 2022.

KNOWLEDGE GAPS

For the phthalate and DINCH substance group, most HBM studies reported were for children, conducted primarily in Western Europe. In most instances, sampling is not representative of the entire national population. The majority of available HBM data concerns data for well-known phthalates (such as DEHP), while newer phthalates and alternatives (such as DINCH) have been studied less.

Next HBM studies in Europe should include extended monitoring of phthalate and substitute plasticizer exposure.

Regarding the study of health impacts linked to phthalate and DINCH exposure, targeted human studies assessing exposures and health outcomes are limited and there is a need to confirm causality. In addition, there is a clear gap for toxicological knowledge on substitutes and chronic low dose effects that needs to be addressed in order to prevent regrettable substitution.

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