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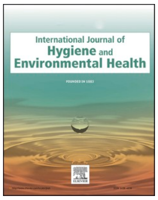

Phthalates and substitute plasticizers: Main achievements from the European human biomonitoring initiative HBM4EU

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ABSTRACT

Phthalates and the substitute plasticizer DINCH belong to the first group of priority substances investigated by the European Human Biomonitoring Initiative (HBM4EU) to answer policy-relevant questions and safeguard an efficient science-to-policy transfer of results. Human internal exposure levels were assessed using two data sets from all European regions and Israel. The first collated existing human biomonitoring (HBM) data (2005–2019). The second consisted of new data generated in the harmonized "HBM4EU Aligned Studies" (2014–2021) on children and teenagers for the ten most relevant phthalates and DINCH, accompanied by a quality assurance/quality control (QA/QC) program for 17 urinary exposure biomarkers. Exposures differed between countries, European regions, age groups and educational levels. Toxicologically derived Human biomonitoring guidance values (HBM-GVs) were exceeded in up to 5% of the participants of the HBM4EU Aligned Studies. A mixture risk assessment (MRA) including five reprotoxic phthalates (DEHP, DnBP, DiBP, BBzP, DiNP) revealed that for about 17% of the children and teenagers, health risks cannot be excluded. Concern about male reproductive health emphasized the need to include other anti-androgenic substances for MRA. Contaminated food and the use of personal care products were identified as relevant exposure determinants paving the way for new regulatory measures. Time trend analyses verified the efficacy of regulations: especially for the highly regulated phthalates exposure dropped significantly, while levels of the substitutes DINCH and DEHTP increased. The HBM4EU e-waste study, however, suggests that workers involved in e-waste management may be exposed to higher levels of restricted phthalates. Exposure-effect association studies indicated the relevance of a range of endpoints. A set of HBM indicators was derived to facilitate and accelerate science-to-policy transfer. Result indicators allow

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different groups and regions to be easily compared. Impact indicators allow health risks to be directly interpreted. The presented results enable successful science-to-policy transfer and support timely and targeted policy measures.

Abbreviations[*1]

AOP	Adverse Outcome Pathway
BE-value	Biomonitoring Equivalent value
bw	Body weight
CAS	Chemical Abstracts Service
CLP	Classification, Labelling and Packaging
crt	Creatinine
DE	Germany
DEMOCOPHES	DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale
DK	Denmark
DYMS	Danish Young Men Study
E-waste	Electronic waste
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFSA	European Food Safety Authority
ESB	German Environmental Specimen Bank
EU	European Union
GC-MS-MS	Gas Chromatography with tandem mass spectrometry
GM	Geometric mean
HBM4EU	The European Human Biomonitoring Initiative
HBM	Human Biomonitoring
HBM-GV	Human Biomonitoring guidance value
HBM-GV$_{GenPop}$	Human Biomonitoring guidance value for the general population
HBM-GV$_{Worker}$	Human Biomonitoring guidance value for occupationally exposed workers
HI	Hazard Index
HMW	High molecular weight
LMW	Low molecular weight
LOD	Limit of detection
LOQ	Limit of quantification
MAF	Mixture assessment factor
MRA	Mixture risk assessment
OEL	Occupational Exposure Limits
P50	50th percentile; median
P95	95th percentile
PARC	Partnership for the Assessment of Risks from Chemicals
PCP	Personal Care Products
QA/QC	Quality assurance/quality control
RA	Risk assessment
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
SVHC	Substances of very high concern
TDI	Tolerable Daily Intake

1. Introduction

The European Human Biomonitoring Initiative (HBM4EU) was an innovative European Joint Program co-funded by the European Union (EU) under Horizon 2020 and the partner countries which started in 2017 and was completed in June 2022. HBM4EU was conducted with 117 partners from 30 countries, the European Environment Agency (EEA) and the European Commission and was coordinated by the German Environment Agency (UBA) (Kolossa-Gehring et al., 2023). As an EU project at the interface between science and policy, it was designed already to create new scientific knowledge to improve chemical, health and environmental policies. The main goals of HBM4EU were to generate harmonized EU-wide data, give national and EU policy makers a fast and easy access to these data, evaluate existing policy measures, identify critical exposures and potential health impacts, and propose new policy recommendations. Accordingly, information on the exposure of the European population and on potential health impacts of prioritized substance groups was gathered. Human biomonitoring (HBM) - a tool for integral and internal exposure assessment - was the core activity of the research activities within HBM4EU.

Phthalates are widely used mainly as plasticizers and they can migrate into food or to the environment (e.g., house dust) and subsequently be taken up by humans (Heudorf et al., 2007; German HBM-Commission, 2011; German HBM-Commission, 2014; Lessmann et al., 2019). Phthalates and the substitute plasticizer di-isononyl cyclohexane-1,2- dicarboxylate (DINCH) belong to the first group of substances prioritized within HBM4EU (Ougier et al., 2021). The substitute di (2-ethylhexyl) terephthalate (DEHTP) initially was not included in the list but was nevertheless analyzed in time trend studies from Denmark and Germany (Vogel et al., 2023a).

Some phthalates have been shown to cause a range of adverse health effects in laboratory animals which are also observed in humans (e.g., German HBM Commission, 2011; EFSA, 2019; EC, 2021). Due to their toxic effects on reproduction and/or endocrine effects several phthalates have been identified in the EU as substances of very high concern (SVHC) (ECHA, 2022). In rodents, prenatal exposure during a critical time window can result in severe malformations of the reproductive organs, known as “phthalate syndrome” (e.g., Swan et al., 2005, 2015; for a review see EFSA, 2019). In terms of risk assessment, it should be noted that phthalates can act in a dose additive manner (e.g., Rider et al., 2010; Howdeshell et al., 2007, 2008, 2017; see Lange et al., 2022) and also together with other anti-androgenic substances (e.g., Rider et al., 2010; Howdeshell et al., 2017; Kortenkamp et al., 2022).

For more than 20 years the use of diethylhexyl phthalate (DEHP), butyl benzyl phthalate (BBzP), di-n-butyl phthalate (DnBP), and diisobutyl phthalate (DiBP) has been gradually restricted in more and more fields (for details see e.g., Vogel et al., 2023a; Rodriguez Martin et al., 2023a). Currently, (as of November 2023), there are 14 phthalates included in Annex XIV of REACH (REACH regulation (EC) No 1907/2006). The substitutes DINCH and DEHTP are however, not void of potentially toxic effects (e.g., EFSA, 2006; German HBM Commission, 2014; Moche et al., 2021; Campioli et al., 2017, 2019).

For phthalates and their substitutes (DINCH), policy-relevant questions had been identified before the start of the research project in 2017 by EU institutions and the partner countries (see Table 1). The research program was designed to answer these questions by targeted research. Information on hazard, exposure, regulations, and the activities planned in HBM4EU were compiled in scoping documents which were regularly updated throughout the project (HBM4EU, 2022a).

In this paper, we present answers to the policy-relevant questions as derived from the HBM4EU results, and we outline the science-to-policy transfer of these findings. Additionally, we report in the corresponding sections on project results that go beyond these questions but are important for the overall picture and will be tackled in the follow-up project "European Partnership for the Assessment of Risks from Chemicals" (PARC).

2. Material and methods

2.1. Compounds investigated

Sixteen phthalates (see Supplementary Material Table S1) and the substitute plasticizer DINCH were included in the prioritized group. They were grouped into different categories (i.e., A to C) according to the availability of HBM data, availability of analytical methods and toxicological information (HBM4EU, 2022a; Vogel et al., 2023b). The substitute DEHTP was included as an additional phthalate of interest in the time trend studies.

2.2. Study planning and implementation

To receive an overall, comparable picture of the body burden to chemicals in Europe the HBM studies need to be comparable. A variety of materials, such as common standard operating procedures (SOPs) for sample collection, or harmonized, translated questionnaires were developed within HBM4EU to support a harmonized approach to study planning and implementation (Pack et al., 2023).

2.3. HBM studies and data sets used

2.3.1. Existing HBM data sets and studies (2005–2019)

To make use of data that already existed within the HBM4EU Consortium HBM data from 2005 to 2019 from 29 studies from participating countries all over Europe as well as Israel were collated, prepared and aggregated by a harmonized procedure and named “**existing studies**” (Vogel et al., 2023b). These “existing studies” also included the studies from the DEMOCOPHES project (Den Hond et al., 2015) comprising studies from 17 European countries performed between 2011 and 2012.

2.3.2. HBM4EU Aligned Studies (2014–2021)

The HBM4EU Aligned Studies were set up to collate recent, harmonized, commonly quality controlled exposure data from European residents for prioritized substances (Gilles et al., 2021, 2022; Govarts et al., 2023). Individual exposure data for ten phthalates and DINCH were collected for two age groups in the period 2014–2021: children (6–11 years) and teenagers (12–18 years) (Supplementary Material Table S2).

2.3.3. Data used for reconstruction of external exposure via modelling

A methodology was developed and improved for exposure reconstruction to deliver external exposure estimates based on the summary statistics of HBM data available within the European HBM4EU Dashboard (see 2.3.7) (HBM4EU, 2022b; D12.8) and is described in the Supplementary Material. The data included both the existing data, as well as the Aligned Study data. Daily intake estimates could be established for DEHP, DiNP, BBzP, DnBP and DINCH (HBM4EU, 2022b; D12.8) and were used to answer policy questions on current exposure and on health impact.

2.3.4. Data sets used for comparison of time trends and time patterns

2.3.4.1. Time trends. To investigate time trends of exposure, studies from Denmark (Danish Young Men Study, DYMS) and Germany (German Environmental Specimen Bank, ESB) were analyzed (see section 3.2.1.3) (Vogel et al., 2023a). They were the only available studies with real time trend data (defined as at least three time points after 2000) and both their analyzed biomarker spectrum as well as the time frame investigated were comparable. Besides phthalates and DINCH also DEHTP was investigated. To estimate time trends and the role of covariates on the trend (e.g., BMI), Locally Estimated Scatterplot Smoothing (LOESS) and Generalized Linear Models (GLMs) were applied.

2.3.4.2. Time patterns. Time patterns were evaluated for phthalates and DINCH in children (5–12 years old) by comparing HBM data from different European studies from three time periods (Rodriguez Martin et al., 2023a). Firstly, existing studies (2000–2010), including aggregated data collected from literature and harmonized aggregated data collected during the HBM4EU project. Secondly, harmonized aggregated data from DEMOCOPHES studies (2011–2012). Thirdly, harmonized aggregated data from the HBM4EU Aligned Studies (2014–2021). The Theil-Sen regression was applied to assess whether there were any statistically significant changes/patterns in the internal exposure to different biomarkers over time. This regression was selected due to the

Table 1
Policy-relevant questions for phthalates and DINCH.

Policy-relevant questions
Harmonization
1. What are the most sensitive, reliable and cost-effective methods and biomarkers?
Exposure
2. What is the current exposure of the EU population to phthalates and DINCH (general population and occupational exposure)?
3. Are there differences in exposure between European countries and/or European regions?
4. Which are the high exposure groups, depending on the following factors:
a) Age: children, teenagers, adults
b) Sex: males and females
c) Household education level: high versus low
d) Others: occupationally exposed workers versus the general population?
5. Are there different time trends for non-regulated, regulated and strongly regulated phthalates and the non-regulated substitute plasticizers DINCH and DEHTP?
6. How effective have different mitigation steps been?
7. What are the main sources of exposure and the reasons for different exposure to phthalates and DINCH?
Impact on Health
8. Can EU-wide HBM guidance values be derived for single substances?
9. Is the exposure to phthalates and their substitutes (i.e., DINCH) of health-relevance for the general population and vulnerable groups?
10. Does the health relevance depend on age and gender?
11. How can cumulative risks of phthalates and other anti-androgenic substances be assessed for their health relevance?
12. Are their cumulative effects relevant for regulation?
Science-to-policy-transfer
13. How can HBM4EU results feed into the regulatory decisions of ECHA and EFSA?

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[*] Please note the abbreviations for phthalates and substitutes and the corresponding metabolites are given in the Supplementary Material Table S1

low number of observations and its robust estimates of slope and trend, as it is not biased by outliers.

2.3.5. *Occupational exposure*

2.3.5.1. Literature survey. A literature survey on occupational phthalate exposure was carried out to provide a comprehensive review of the available literature on occupational exposure to phthalates assessed using HBM and to determine future data needs on the topic as part of the HBM4EU project (Fréry et al., 2020). A systematic search was carried out in the databases of Pubmed, Scopus, and Web of Science for articles. Broad search terms included phthalate, workplace, worker, and occupation.

2.3.5.2. Risk assessment for occupational exposure based on literature data. A risk assessment on occupational exposure to DiNP, DiDP and DPHP was performed to evaluate the strengths and limitations of using HBM data in risk assessment (HBM4EU, 2022c). These phthalates are widely used in the manufacture of plastic products and their uses are not yet subject to comprehensive restriction. HBM data for the RA were searched in the literature.

2.3.5.3. The HBM4EU electronic waste (e-waste) study. An e-waste study was conducted to assess workers' exposure to a number of hazardous chemicals, among them phthalates (HBM4EU, 2022d; Cleys et al., 2023) and to contribute to the improvement of occupational health and safety by raising awareness of potential hazards and promote good working practices. The study protocol used was created as part of the project (Scheepers et al., 2021). Furthermore, several biomarkers of effect (see also chapter 3.3.2.2) were included as well as monitoring of the workplace environment (i.e., air, dust and hand wipe monitoring).

2.3.6. *Data sets used for investigating sources of exposure and exposure determinants*

To investigate sources of exposure and exposure determinants data from several existing HBM studies and the HBM4EU Aligned Studies were analyzed for the population groups children, teenagers and adults (HBM4EU, 2022e; Martinsone et al., in preparation). Individual data on concentrations of the phthalate metabolites in urine samples and information from questionnaires on potential determinants of phthalate exposure were requested from data owners and/or controllers. (HBM4EU, 2022e). Determinants of phthalates' exposure include socio-economical parameters (e.g., educational level, income), geographical location (e.g., European region, degree of urbanization), individual characteristics (e.g., age, body mass index) and habits (e.g., smoking, use of plastic objects, cosmetics, daily food consumption). Linear mixed-effects models (LMER) were used to evaluate exposure determinants in each population (Martinsone et al., in preparation).

2.3.7. *Making data accessible*

Aggregated data from existing HBM studies in which phthalates and DINCH were measured is publicly accessible on the European HBM Dashboard (https://hbm.vito.be/eu-hbm-dashboard). This was created and regularly updated within HBM4EU and is now further maintained within the follow-up EU project PARC. The EU HBM Dashboard allows one to visualize summary statistics from HBM data collections obtained through the HBM4EU project and beyond. Additionally, for the HBM4EU Aligned Studies, biomarker levels can be compared with the corresponding available health-based guidance values. The data included in the dashboard were compiled in a standardized and comparable way. The HBM metadata was also uploaded to IPCHEM (Information Platform for Chemical Monitoring) including summary statistics. Here aggregated data are available for risk assessors, national and European bodies and the public.

2.4. *Health assessment*

2.4.1. *Derivation of human biomonitoring guidance values*

Within the framework of HBM4EU, a concept for deriving health-based human biomonitoring assessment values (named: human biomonitoring guidance values, HBM-GVs) was developed and agreed in the consortium (Apel et al., 2020a), now enabling a harmonized assessment of HBM data. The HBM-GVs can be directly compared with the biomarker concentrations and allow an immediate toxicological interpretation. The derivation of HBM-GVs is described in detail in Apel et al. (2020a) and summarized in the Supplementary Material, together with additional information on HBM-GVs. HBM-GVs were derived for the general population and for workers for selected substances (Apel et al., 2023) including five phthalates and DINCH (Lange et al., 2021; see 3.3.1).

2.4.2. *Cumulative risk assessment*

2.4.2.1. Risk assessment of a mixture of five reprotoxic phthalates. Since simultaneous exposure to many phthalates is probable and many phthalates have been shown to have a cumulative effect (Conley et al., 2021; Howdeshell et al., 2008; Hannas et al., 2011), a risk assessment was carried out for a mixture of five selected reprotoxic phthalates (DEHP, DnBP, DiBP, BBzP, DiNP) using the hazard index (HI) approach (Lange et al., 2022). Mixture risk assessment was also previously addressed by Kortenkamp and Faust (2018), Kortenkamp and Koch (2020) and Apel et al. (2020b). As toxicity reference values consolidated HBM-$\text{GV}_{\text{GenPop}}$ for BBzP, DEHP, DiBP and DnBP have been chosen and for DiNP a provisional HBM-$\text{GV}_{\text{GenPop}}$ for the purpose of the MRA alone (pHBM-$\text{GV}_{\text{GenPop-MRA}}$) was established based on a common anti-androgenic endpoint (for details see Lange et al., 2022). The exposure assessment for this mixture risk assessment was performed using HBM4EU Aligned Studies data.

2.4.2.2. Case study: mixture risk assessment of male reproductive health. Case studies were carried out as a proof-of-concept for the identification of mixture health effects. Kortenkamp et al. (2022) performed a MRA of male reproductive health comprising 29 chemicals, including phthalates, focusing on semen quality. The objective was to find the main drivers of semen quality deterioration. The authors used the HI approach and calculated risk quotients (RQs).

2.4.2.3. Identification of real-life mixtures. Rodriguez Martin et al. (2023b) applied network analyses combined with clustering algorithms (community detection) to HBM datasets from Belgium, Czech Republic, Germany, and Spain, based on data availability, with the aim to explore its added value for exposure and risk assessment. The identification of groups of more closely correlated biomarkers, so-called "communities", within networks highlights which combination of substances should be considered in terms of real-life mixtures to which a population is exposed.

2.5. *Science-to-policy transfer*

Please note that all activities directly related to science-to-policy transfer are included in chapter 3.4 (including methodological aspects) to avoid duplication in the document.

3. Results and discussion

Within HBM4EU the policy-relevant questions formulated for phthalates and the substitute DINCH at the onset of the project (see Table 1) could be successfully answered. New, robust and comparable exposure data were generated and gaps in understanding and interpreting the data in a way not only intended for scientists but also understandable for the public and policy makers could be closed. This science-to-policy transfer of HBM4EU results was an overarching aim of the project. Therefore, active and timely communication of knowledge gains to policy makers was an integral part of the project. This did not finish with the end of the project in 2022, but has been continued through the follow-up EU project PARC (https://www.eu-parc.eu/). The interplay of these aspects (robust data generation and science-to-policy transfer) is illustrated in Fig. 1.

3.1. Harmonization

3.1.1. Study planning and implementation

The developed materials to support a harmonized approach to study planning and implementation (such as common standard operating procedures (SOPs) are essential for comparability, allowing the harmonized collection of data on a participant's individual characteristics and their potential exposure pathways from different sources, and to identify questions for future studies (Pack et al., 2023). For phthalates and DINCH, questionnaires are available for adults, teenagers and children (González-Alzaga et al., 2022).

3.1.2. Analytics

What are the most sensitive, reliable and cost-effective methods and biomarkers?

In total 25 biomarkers representing exposures to 14 phthalate parent compounds and 3 biomarkers for DINCH exposure were selected for principal consideration in HBM4EU based on transparent discussions as to their suitability, relevant matrices and state-of-the-art analytical methods (Vorkamp et al., 2021). For 2 of the originally selected 16 phthalates no suitable biomarkers could be identified (i.e., di (methoxyethyl)phthalate (DMEP) and di-C7-11-(linear and branched)-alkyl phthalate (DHNUP)). Concerning cost-effectivity the commercial availability of standards at reasonable costs was assessed.

In general, the simple monoesters (without modification) are the biomarkers of choice for low molecular weight (LMW) phthalates, whereas oxidized secondary metabolites are the biomarkers of choice for phthalates with long alkyl chains (e.g., Koch and Calafat, 2009). For DINCH, the oxidized monoesters were found to be more suitable than the simple monoesters (Koch et al., 2013).

For all compounds, urine was selected as the most suitable matrix. While no immediate demands for specific analytical methodologies were made (the only demand was passing the quality assurance/quality control (QA/QC) program), high performance liquid chromatography with tandem mass spectrometry (LC-MS-MS) was found to be the most suitable for all phthalate and DINCH metabolites. Specific determination of di (2-propylheptyl) phthalate (DPHP) exposure (a specific di-isodecyl phthalate (DiDP) isomer) was accessible only with the higher separation power of gas chromatography (GC-MS-MS).

An important milestone was the implementation of the HBM4EU QA/QC program ensuring the quality and comparability of the analytical results in HBM4EU (Esteban López et al., 2021). This program covered 15 phthalate metabolites and two DINCH metabolites (Mol et al., 2022), namely MEP, MBzP, MiBP, MnBP, MCHP, MnPeP, MEHP, 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP, MnOP, OH-MiNP, cx-MiNP, OH-MiDP, cx-MiDP, OH-MINCH and, cx-MINCH.

The number of laboratories that qualified for the analyses of phthalates and DINCH biomarkers increased considerably from the first round to the end of the program. The program thus succeeded in its aim of building capacity and establishing a network of suitable laboratories with a consistent satisfactory performance for generating reliable and comparable phthalate/DINCH among others) HBM data. A current list of laboratories eligible for measurements can be found on the HBM4EU website (https://www.hbm4eu.eu/what-we-do/european-hbm-platform/hbm-european-network/).

3.2. Exposure

3.2.1. Current exposure

What is the current exposure of the EU population to phthalates and DINCH?

In the HBM4EU Aligned Studies (2014–2021) (see 2.3.2), metabolites of ten phthalates (i.e., BBzP, dicyclohexyl phthalate (DCHP), DEHP, diethyl phthalate (DEP), DiBP, DiDP, diisononyl phthalate (DiNP), DnBP, di-n-pentyl phthalate (DnPeP), di-n-octyl phthalate (DnOP)) and the substitute DINCH were analyzed and this enables an assessment of the exposure of both children and teenagers in the EU (Vogel et al.,

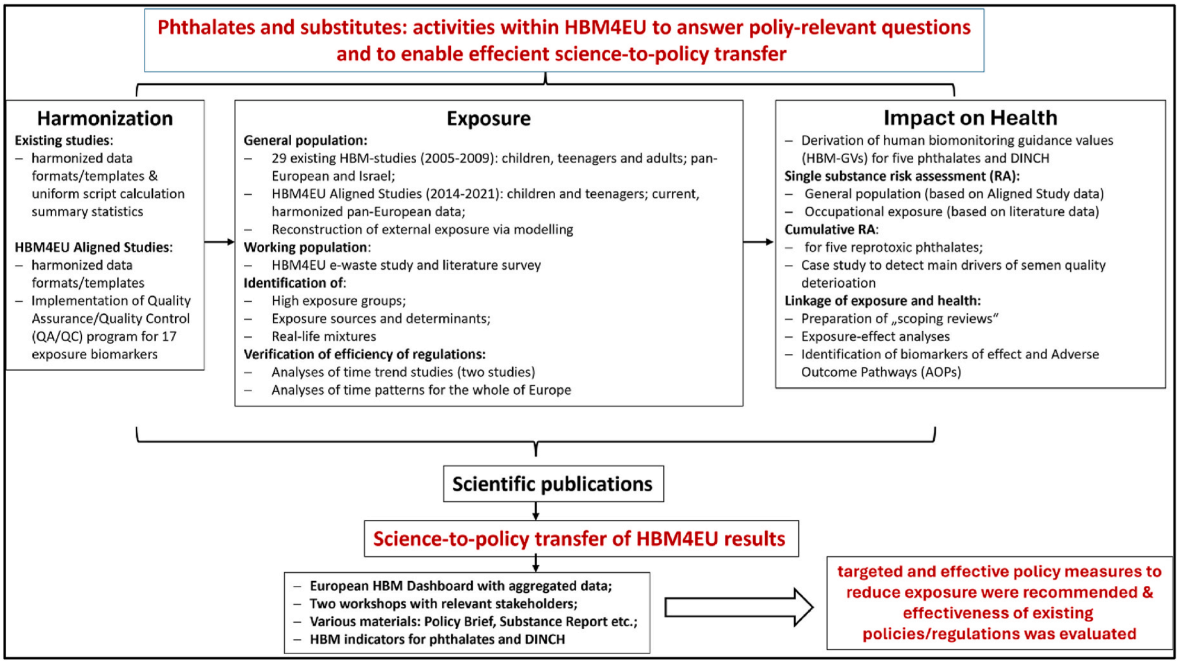

Fig. 1. Overview of activities within HBM4EU concerning phthalates and substitute plasticizers assigned to the three areas: harmonization, exposure and impact on health and their application within science-to-policy transfer.

2023c).

Metabolites of seven phthalates (i.e., BBzP, DEHP, DEP, DiBP, DiDP, DiNP, DnBP) and DINCH were detected in the vast majority of samples in all European regions, with detection rates ranging from 65 to 100%. This clearly indicates that children and teenagers in Europe are ubiquitously exposed to phthalates and DINCH. The metabolites of DCHP, DnOP and DnPeP were only found in 1–5% of all urine samples (Vogel et al., 2023c) suggesting scarce applications/use patterns. The resulting exposure levels were also low.

Table 2 shows, for both children and teenagers, geometric mean (GM), median (P50) and 95th percentile values (P95) for the seven phthalates with high detection rates as well as DINCH in the European population (Vogel et al., 2023c) together with the corresponding confidence intervals (CIs). The resulting concentration levels, stratified for European region, sex, household education level, and degree of urbanization can be used as comparison to other national, European or international study samples.

The qualitative comparison of Aligned study data with other international HBM data (see Table S5 in Supplementary Material to Govarts et al., 2023) showed that in general, phthalate and DINCH biomarker levels in children and teenagers are comparable to those reported by HBM programs in the US (NHANES: CDC, 2019) and Canada (Health Canada, 2019, 2021; Govarts et al., 2023).

The results of the exposure reconstruction via modelling (see 2.3.3) revealed that for most of the analyzed studies the mean daily intakes were close to or above 1 μg/kg bw/d, while the estimates for DINCH and BBzP were lower (HBM4EU, 2022b. D12.8).

3.2.1.1. Geographical differences. Are there differences in exposure between European countries and/or European regions?

Country/regional differences in internal exposure were found for both children and teenagers (Vogel et al., 2023c). The observed differences ranged from a factor of 2 up to a maximum factor of 9 between the lowest and the highest exposure value for a substance. This means that for a given phthalate, the exposure in the study with the highest determined value was nine times as high as in the study with the lowest determined geometric mean value (Vogel et al., 2023c). This underlines the importance of Europe-wide HBM studies to obtain an adequate picture of exposure and to generate a reliable database for EU-wide regulation and its control. It should be noted at this point that one should be careful with comparing the levels between the countries, as different sampling periods and ages could have been covered.

Furthermore, significant differences ($p < 0.05$) were observed, among the different European regions (Vogel et al., 2023c). Regional differences were also observed within the previous European HBM study DEMOCOPHES (Den Hond et al., 2015). Also, Vogel et al. (2023b) found regional differences when analyzing 29 studies from 2005 to 2019. However, the differences observed in the “existing studies” (with different protocols, no common quality assurance) were more substantial than previously assumed by DEMOCOPHES data alone (harmonized sampling protocol, common quality assurance). The authors conclude that additionally, regional and country to country differences could be substantial. Possible reasons for different exposure patterns between the countries include: country-specific behavioral patterns as well as differences in the regional presence of a naturally occurring substance and/or difference in product placement of regional markets (Den Hond et al., 2015; Wang et al., 2019).

As a caveat, some of the country/regional effects might be enhanced by “time trend effects” (see 3.2.1.3) strengthening the argument for a timed collection of samples. The possible bias due to the eight-year time span of the sampling years should therefore be considered when interpreting the results.

3.2.1.2. High exposure groups. Which are the high exposure groups? Can differences be observed for the following groups.

a) Children, teenagers and adults?

When analyzing both the “existing studies” (2.3.1) as well as the HBM4EU Aligned Studies (2.3.2), age differences were observed (Vogel et al., 2023b, 2023c). In the Aligned Studies children had higher concentrations in MBzP, ΣDEHP metabolites, ΣDiDP metabolites, MiBP, and ΣDINCH metabolites, and teenagers had higher concentrations in MEP, MnBP, and ΣDiNP metabolites (Vogel et al., 2023c).

An age dependence of phthalate exposure has also been reported in numerous studies when comparing exposure of children versus adults as well as for the comparison of children and teenagers (e.g., Bastiaensen et al., 2021; Choi et al., 2017; Den Hond et al., 2015; Schwedler et al., 2020a; Fillol et al., 2021; Hartmann et al., 2015; CDC, 2019). A general finding for many phthalates is that decreasing body burdens of the phthalates investigated are reported with increasing ages with the exception of DEP (MEP) which was regularly found to be higher in older study participants compared to children (e.g., Choi et al., 2017; Bastiaensen et al., 2021). Reasons for the age dependency of phthalate exposure are age-dependent behaviors and related exposures (Wormuth et al., 2006).

The age dependency of DINCH exposure observed in the HBM4EU Aligned Studies with higher metabolite levels in children compared to teenagers (Vogel et al., 2023c) is supported by data from the literature (e.g., Schwedler et al., 2020b). This might indicate an increased use of DINCH as a phthalate replacement in soft toys for younger children (Papp et al., 2023).

b) Male and female participants?

Sex differences were investigated based on “existing studies” and Aligned Studies (Martinsone et al. in preparation). Preliminary results are available for DiBP (MiBP) and DEP (MEP). For both compounds higher metabolite levels were found in females ($p < 0.05$) in all age groups.

Sex differences in exposure were investigated in several studies (e.g., Garí et al., 2019; Schwedler et al., 2020a; Liao et al., 2018; Hartmann et al., 2015; Porras et al., 2020; Bastiaensen et al., 2021), however, results are not consistent. The only exception is DEP (MEP), for which

Table 2

Exposure biomarker concentrations for seven phthalates and DINCH in urine from the HBM4EU Aligned Studies. Geometric mean (GM), P50 and P95 values are given in μg/L (data from Vogel et al., 2023c) together with the corresponding confidence intervals (CIs).

Parent Compound	Biomarker	Children (6–11 years)			Teenagers (12–18 years)		
		GM (95% CI)	P50	P95 (95% CI)	GM (95% CI)	P50	P95 (95% CI)
BBzP	MBzP	3.64 (2.22, 5.95)	3.60	28.6 (17.3, 47.6)	2.76 (1.71, 4.47)	2.71	27.9 (14.9, 45.6)
DEHP	∑5oxo + 5OH-MEHP	33.6 (25.7, 43.9)	33.5	127 (110, 152)	28.8 (23.3, 35.6)	28.4	116 (82.4, 181)
DEP	MEP	24.4 (13.9, 43.0)	22.7	214 (138, 396)	43.3 (31.4, 59.8)	37.9	387 (260, 615)
DiBP	MiBP	26.6 (20.1, 35.2)	26.7	122 (96.2, 172)	25.6 (20.5, 32.1)	24.4	112 (87.7, 141)
DiDP	∑OH-MiDP + cx-MiDP	1.91 (1.26, 2.90)	1.87	8.61 (5.93, 18.8)	2.02 (1.54, 2.63)	1.94	8.80 (6.41, 12.5)
DiNP	∑OH-MiNP + cx-MiNP	8.31 (5.18, 13.3)	8.50	43.1 (26.5, 105)	10.2 (7.19, 14.3)	9.45	57.9 (34.3, 116)
DnBP	MnBP	21.1 (17.1, 26.1)	21.4	80.5 (65.4, 103)	24.8 (16.7, 36.9)	24.8	163 (59.0, 443)
DINCH	∑OH-MINCH + cx-MINCH	3.57 (2.70, 4.70)	3.38	23.7 (16.1, 37.9)	2.51 (2.00, 3.16)	2.35	17.0 (12.1, 26.1)

regularly higher metabolite levels were reported for female teenagers and adults compared to males of the same age groups (e.g., Bastiaensen et al., 2021; Porras et al., 2020).

Reasons for some of the observed mainly minor differences in urinary biomarker levels between the sexes might be physiological differences related to urinary excretion, but also sex-related lifestyle behaviors such as differences in the use of personal care products and cosmetics (e.g., Heudorf et al., 2007; Hartmann et al., 2015). Frederiksen et al. (2022) investigated the exposure to phthalates and substitutes in trios of infants and their parents. They reported significantly higher osmolality adjusted urinary concentrations of selected phthalate metabolites in men compared to women. However, no significant differences were observed in estimated daily intakes. The authors point out the importance of normalization to individual bodyweight and total urine excretion per day to obtain the relative exposure for comparison between groups.

c) High household education level versus low-household education level?

Based on HBM4EU Aligned Study data (see 2.3.2), Govarts et al. (2023) found that for some biomarkers the educational attainment (used as a proxy for socio-economic status) of the household where the children and teenagers were raised, influenced the concentrations of some biomarkers. In general, a low household educational level was associated with increased levels of phthalate metabolites in teenagers and a high household educational level was associated with decreased levels of phthalate metabolites in teenagers except for DiDP. For DINCH metabolites a more equal distribution across the social gradient was observed (Govarts et al., 2023).

d) Occupationally exposed vs. general population

Existing studies have shown that workers involved in plastic manufacturing may be exposed to phthalates (Fréry et al., 2020). Less data are available from other sectors. In the HBM4EU e-waste study (HBM4EU, 2022d; Cleys et al., 2023) occupationally exposed individuals had higher levels for some phthalate metabolites than the control group. The investigation of occupational exposure within HBM4EU is described in detail in section 3.2.1.4.

3.2.1.3. Time trends and time patterns. Concerning the EU regulation under REACH with respect to authorization and restrictions: Are there different time trends for non-regulated, regulated and strongly regulated phthalates and the non-regulated substitute plasticizers DINCH and DEHTP? How effective have different mitigation steps been?

3.2.1.3.1. Time trends. Vogel et al. (2023a) analyzed time trend studies from Denmark (Danish Young Men Study, DYMS) and Germany (German Environmental Specimen Bank, ESB) (see 2.3.4.1) and described the impact of regulations and changes in production and use of phthalates and their substitutes on internal exposure patterns since the beginning of the 2000's.

For the strongly regulated phthalates DEHP, BBzP, DnBP and DiBP decreasing concentrations were observed (with an annual decrease of up to 17 %) (this is shown for DnBP in Fig. 2), illustrating the effectiveness

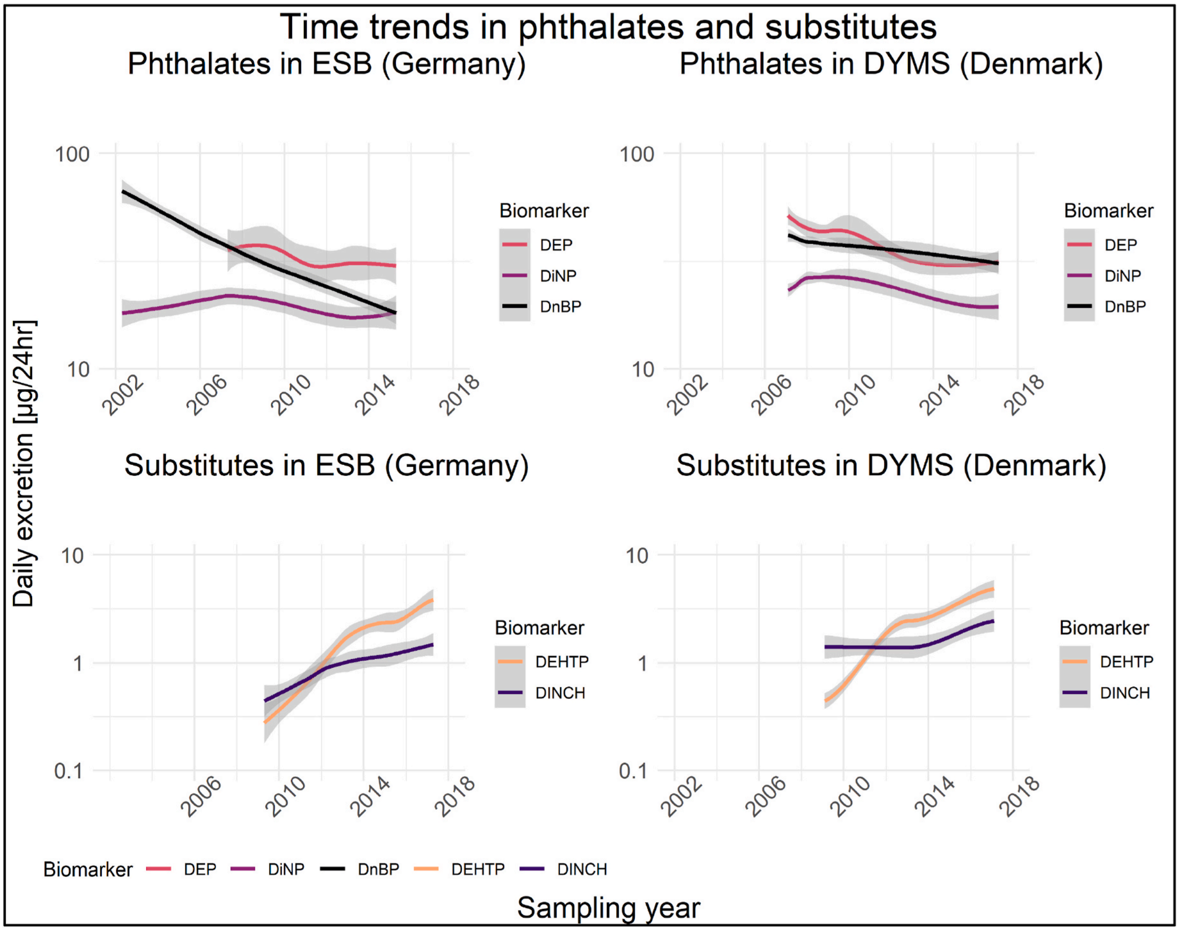

Fig. 2. Impact of REACH regulatory status of phthalates and substitutes on concentrations over time, shown exemplarily for the metabolites of DnBP, DiNP, DEP, DINCH and DEHTP. Data from Denmark (Danish Young Man Study, DYMS) and Germany (German Environmental Specimen Bank, ESB) (modified after Vogel et al., 2023a).

of EU regulations. This decrease over time was also confirmed in time-trend studies from the German Environmental Specimen Bank (ESB) (Koch et al., 2017; Apel et al., 2020b) and studies from other European countries (e.g., Frederiksen et al., 2020; Bastiaensen et al., 2021; Gyllenhammar et al., 2017).

For the differently regulated DiNP and DiDP/DPHP stable concentrations were reported (for DiNP this is shown in Fig. 2). Vogel et al. (2023a) point out that the regulatory measures (such as the restriction in childcare articles and toys) apparently had only a very limited effect on the exposure of the young adult general population.

For the non-regulated phthalates DEP and DMP the time trends since 2006 show an annual decrease of about 6–18%. This is noteworthy, since both DMP and DEP are not labelled as phthalates toxic to reproduction. The authors suggest that this may be due to increasing societal concern about phthalate exposure in general and reduced uses of phthalates in personal care products and cosmetics.

For the non-regulated substitutes DINCH and DEHTP, very steep annual increases (~10–68% and ~100%, respectively) between 2009 and 2017 are observed (Fig. 2). These findings are supported by data from the literature both for DINCH (e.g., Kasper-Sonnenberg et al., 2019; Lemke et al., 2021; Schwedler et al., 2020b; Frederiksen et al., 2020), and DEHTP (e.g., Lessmann et al., 2019; Bastiaensen et al., 2021; Lemke et al., 2021; Frederiksen et al., 2020). The sharp increase in exposure mirrors the increasing importance of DINCH and DEHTP in industrial and product use.

The time trend pattern in Europe (represented by Germany and Denmark) seems to follow the same pattern as in, e.g., the US (CDCs NHANES HBM data) (CDC, 2019).

These rapid changes in exposures caused by EU and worldwide regulations and subsequent market changes highlight the need to closely monitor exposure trends especially for the substitutes, to enable a timely intervention if exposure levels are likely to surpass acceptable levels, or if new toxicity data leads to lower acceptable levels.

3.2.1.3.2. Time patterns. Findings from the time pattern investigations for the whole of Europe (Rodriguez Martin et al., 2023a) confirm the observations from the time trend studies. Results showed visually decreasing levels through time for regulated phthalate metabolites for both the 50th (P50) and 90th (P90) percentiles, confirmed via Theil-Sen regression (Figure S1).

Regarding unregulated phthalate metabolites, MEP showed the highest P50 values. Visually, exposure level patterns are decreasing less clearly. Results from the Theil–Sen regression, showed significant decreasing trends (p-values <0.001) for all the phthalates (regulated and unregulated) included in this study.

For the substitute plasticizer DINCH, results from the Theil-Sen Regression show significantly increasing trends for the two metabolites investigated (Rodriguez Martin et al., 2023a).

A time-trend analysis on the human exposure to phthalates and phthalate replacements in various non-European countries was performed by Domínguez-Romero et al. (2023). This analysis shows that levels of high molecular weight (HMW) phthalates such as DEHP in humans are generally decreasing at rates of around 10% per year, but that concentrations of phthalate replacements such as DINCH and DEHTP are increasing at even faster rates of 50–60% per year (data for the US) (Domínguez-Romero et al., 2023).

3.2.1.4. Occupational exposure.

Fréry et al. (2020) carried out a systematic review on study needs concerning phthalate exposure in occupational settings. The main findings are that the majority of studies focused on DEHP and only two studies were on “newer” phthalates such as DiNP and DPHP and highlight the lack of recent studies on occupational exposure to both “old” and “new” phthalates as well as the need for a more harmonized approach and inclusion of other sectors including waste management in these studies.

In HBM4EU two occupational investigations were carried out. The first one being a risk assessment on occupational phthalate exposure based on literature data. In this study, the risks related to DiNP, DiDP and DPHP exposure were investigated (see 2.3.5.2). For all three phthalates, the comparison with toxicological assessment values for the working population showed that the determined exposure is not a health concern according to the current state of knowledge when considering the individual substances (HBM4EU, 2022c).

The second study examining occupational exposure to phthalates was the HBM4EU e-waste study (see 2.3.5.3). Data on the analysis for exposure biomarkers of phthalates indicates an occupational exposure to these compounds in various tasks related to the handling of e-waste. When comparing urine samples of e-waste workers to the control population, significantly higher urinary concentrations of seven out of thirteen metabolites were found in the e-waste worker group. Plasticizers concentrations in dust and in urine were positively correlated, especially for DnBP. The results raise a concern on occupational exposure to phthalates in the e-waste sector (HBM4EU, 2022d; Cleys et al., 2023).

3.2.1.5. Sources of exposure.

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

Data from several existing HBM studies regarding exposure determinants including the HBM4EU Aligned Studies have been analyzed (HBM4EU, 2022e; Martinsone et al. in preparation) (see 2.3.6). Preliminary results of the study are presented (HBM4EU, 2022e).

The main source of exposure to phthalates and DINCH was found to be consumption of food (via food contact materials). The daily use of personal care and cosmetic products is also an important determinant of exposure. Depending on the properties of the phthalate, other sources such as indoor dust by ingestion or inhalation in the gaseous and particulate phase may also contribute to the overall exposure. A biomonitoring study in Czech teenagers and young adults showed widespread exposure to phthalates and DINCH in this population and indicates that time spent indoors and use of personal care products contribute to phthalate exposure (Stuchlík Fišerová et al., 2022).

Analyses of the main significant determinants of phthalate exposure for children, teenagers and adults are still in progress (Martinsone et al. in preparation), preliminary results are available for DiBP (MiBP).

For DiBP exposure was significantly positively associated with: the consumption of jelly candies in children and teenagers, the usage of plastic toys in children and vacuuming in teenagers. Positive associations were found in girls with the time spent in cars, cleaning activities and PVC flooring in the household, in boys with passive smoking, and in teenagers with the use of hair products. Significantly lower exposure to DiBP was found in children living in renovated houses and in children consuming local food. In teenagers and in adults living in rural areas was associated with significantly lower DiBP exposure.

3.3. Impact on health

3.3.1. HBM guidance values and health-related evaluation of exposure data

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

HBM-GVs were derived for five phthalates and for the substitute DINCH, both for the general population and the working population (Lange et al., 2021) (see 2.4.1) (Supplementary Material Table S3). For the general population different values were set for children and adults, including teenagers; these values are presented in Table 3.

3.3.1.1. Single substance risk assessment of phthalate and DINCH exposure.

Is the exposure to phthalates and their substitutes (i.e. DINCH) of health-relevance for the general population and vulnerable groups?

The comparison of the newly derived HBM-GVs (Lange et al., 2021) with the exposure levels from the HBM4EU Aligned studies shows that despite regulation, bans and restrictions being in force, up to 4 % of

Table 3
Percentage of participants of the HBM4EU Aligned Studies exceeding the HBM-GVs/BE-values (after Govarts et al., 2023).

Substance (Metabolite (s))	Age group	Guidance value [μg/L]	Type of guidance value (reference)	N	% participants exceeding GV (main output)
Phthalates:					
DEP (MEP)	children	18,000	BE-value (Aylward et al., 2009)	2580	0%
	teenagers	18,000	BE-value (Aylward et al., 2009)	2499	0%
DiBP (MiBP)	children	160	HBM-GV (Lange et al., 2021)	2279	3.1%
	teenagers	230	HBM-GV (Lange et al., 2021)	1631	1.7%
DnBP (MnBP)	children	120	HBM-GV (Lange et al., 2021)	2579	2%
	teenagers	190	HBM-GV (Lange et al., 2021)	2499	4.0%
BBzP (MBzP)	children	2000	HBM-GV (Lange et al., 2021)	2279	0.04%
	teenagers	3000	HBM-GV (Lange et al., 2021)	2799	0%
DEHP ($\sum$5oxo + 5OH-MEHP)	children	340	HBM-GV (Lange et al., 2021)	2577	0.3%
	teenagers	500	HBM-GV (Lange et al., 2021)	2798	0.3%
DEHP ($\sum$5cx-MEPP + 5OH-MEHP)	children	380	HBM-GV (Lange et al., 2021)	2579	0.5%
	teenagers	570	HBM-GV (Lange et al., 2021)	2799	0.3%
DiNP (cx-MiNP)	children	490	BE-value (Hays et al., 2011)	1980	0%
	teenagers	490	BE-value (Hays et al., 2011)	2618	0.2%
Substitute:					
DINCH (OH-MINCH + cx-MINCH)	children	3000	HBM-GV (Lange et al., 2021)	2579	0%
	teenagers	4500	HBM-GV (Lange et al., 2021)	2317	0%

Main output: this is based on the data with the quality label “biomarker data quality assured by HBM4EU QA/QC program” (Govarts et al., 2023). n = number of participants.

children and teenagers exceed the individual HBM-GVs (see Table 3). The largest share of HBM-GV exceedances were related to exposure to DnBP and DiBP, and to a lesser extent to DEHP (Vogel et al., 2023c). One child exceeded the HBM-GV for BBzP. For DiNP (cx-MiNP) a biomonitoring equivalent (BE) value of 490 μg/L exists both for children and teenagers (Hays et al., 2011). The BE value was exceeded by one child and six teenagers. For DEP a BE value exists (Aylward et al., 2009). Both for children and teenagers this value is 18,000 μg/L. This value was neither exceeded by children nor teenagers. For children and teenagers exceeding the HBM-GV or the BE a health risk cannot be excluded, based on current knowledge for the single substance risk assessment.

For the substitute DINCH determined exposure was well below the corresponding HBM-GVs both for children and teenagers in the HBM4EU Aligned Studies.

In another approach, the daily intake of DEHP, DiNP, BBzP, DnBP and the substitute DINCH calculated from exposure reconstruction based on data from the HBM4EU Aligned Studies was compared to existing regulatory thresholds. On average, the calculated daily intake was in the range from 0.1 to 1 μg/kg bw/day in most studies, and generally far below the tolerable daily intakes derived by EFSA (EFSA, 2019) (HBM4EU, 2022b). However, this approach does not target potentially more highly exposed individuals.

Occupational exposure to DiNP, DiDP and DPHP (determined in a literature study within HBM4EU, see 3.2.1.4, (HBM4EU, 2022c; D5.5) did not exceed health-based guidance values for workers. The calculated risk characterization ratios (RCRs) were well below one for DiNP and DiDP, based on a rough Biomonitoring Equivalents (BE) approach. The urinary concentration of the DPHP metabolite OH-MPHP is far below the HBM-GV$_{Worker}$ of 0.3 mg/L. Although occupational exposure in the e-waste study can be considered low, it does not allow conclusions to be drawn for other fields.

3.3.1.2. Mixture risk assessment of phthalate exposure. How can cumulative risks of phthalates and other anti-androgenic substances be assessed for their health relevance? Are their cumulative effects relevant for regulation?

3.3.1.2.1. Mixture risk assessment of five reprotoxic phthalates. A risk assessment was carried out for a mixture of five selected reprotoxic phthalates (DEHP, DnBP, DiBP, BBzP, DiNP) using the hazard index (HI) approach (Lange et al., 2022) (see 2.4.2). The analysis showed that for about 17% (n = 708) of European children and teenagers a health risk (HI > 1) from combined exposures to these five phthalates cannot be excluded with certainty. The drivers of the mixture risk were DnBP and DiBP, both in children and teenagers. It is particularly noteworthy that for the majority (63%) of these participants with a potential cumulative mixture risk, this would have gone unnoticed in the traditional single substance risk assessment (Lange et al., 2022).

These results clearly show that the inclusion of mixture RAs in current regulatory practice is imperative. Conventions for the integration of mixture effects into regulatory RAs are essential, e.g., through a mixture assessment factor (MAF) (e.g., Kortenkamp and Faust, 2018; Backhaus, T., 2022; Escher et al., 2022; Nikolopoulou et al., 2023).

In follow-up analyses investigating the role of sex and age on the HI, Lange et al. (2022) found no difference between children and teenagers or between sexes. However, when investigating geographical regions, the Eastern European region was found to have the highest HIs. The investigation of sampling years showed that participants whose urine samples have been taken in the years 2014–2016 seem to have a higher average HI than participants from later sampling years (i.e., 2017–2021). This might be due to the aforementioned time-trend effect with higher concentrations of phthalate metabolites in the earlier years and thus higher numbers of exceedance of the HBM-GVs.

Irrespective of the fact that some of the samples had been collected before the ban on phthalates in consumer products in 2020, exceedances of tolerable levels can still be observed today, both with regards to individual substances but even more so for mixtures. While much of the exposure reduction is probably due to the stricter regulatory measures, a stricter enactment and control of these measures is needed to prevent mixture risk. Furthermore, the above mixture RA only took account of concurrent exposures to five phthalates. Future mixture risk assessments (for phthalates) also have to include other anti-androgenic chemicals, although they do not act via the same mechanism of action or even the same pathway (Christen et al., 2012; Howdeshell et al., 2017; Rider et al., 2010; Kortenkamp and Koch, 2020) (see also 3.3.1.2.2). This will likely significantly increase the share of the population that is at risk (Lange et al., 2022; Luijten et al., 2023).

3.3.1.2.2. Case study: mixture risk assessment of male reproductive health. Within HBM4EU, Kortenkamp et al. (2022) performed a MRA of male reproductive health (see 2.4.2.2). The authors found that tolerable exposures to substances associated with deteriorations of semen quality are exceeded by a large margin. Drivers of these risks were bisphenols, polychlorinated dioxins, phthalates and analgesics. These findings, again, underline the importance of including other anti-androgenic substances in mixture RAs for phthalates.

3.3.1.2.3. Identification of real-life mixtures. Within the project a proof of concept study was performed aiming at identifying real-life mixtures (see 2.4.2.3) in order to be able to describe the distribution (patterns) of biomarkers of exposure and to identify possible determinants that explain the observed variation in these patterns in biomarkers of exposure (Rodriguez Martin et al., 2023b).

The network analysis identified in all four studies (i.e., 3xG (Belgium), CELSPAC—FIREexpo (Czech Republic), GerES V (Germany), and BIOAMBIENT.ES (Spain)), as expected, several communities of chemical families, e.g., phthalates and PAHs. However, exposure patterns involving substances from different chemical families were also observed. Examples include the dependency between 1-PYR (biomarker for PAHs), TTMA (biomarker for benzene), and the phthalates DiBP (MiBP) and DnBP (MnBP) in the 3xG study. Such communities, comprising substances from different chemical families, possibly reflect a commonality in exposure patterns and thus reflect real-life mixture patterns. The communities observed may also be impacted by similarities in physicochemical properties of the substances involved. This knowledge is relevant for regulatory risk assessment as well as for mixture exposure.

3.3.2. Linking exposure and health effects

3.3.2.1. Scoping reviews. In the frame of HBM4EU so-called “scoping reviews” were prepared. The scoping documents which have been prepared for priority substances (see above) were taken as a basis and extended by a complementary literature review. This resulted in a number of publications which report possible links between phthalate exposure and reproductive health effects, but also between phthalate exposure and: asthma (Mattila et al., 2021), osteoporosis (Elonheimo et al., 2021), metabolic syndrome (Haverinen et al., 2021) and attention deficit hyperactivity disorder (Moore et al., 2022). However, more research is needed to confirm these findings.

3.3.2.2. Effect biomarkers and Adverse Outcome Pathways (AOPs). Information on effect biomarkers previously implemented in human observational studies was combined with mechanisms of action reported in experimental studies and with information from published Adverse Outcome Pathways (AOPs), focusing on adverse reproductive effects of phthalate exposure. The term effect biomarkers refers to observable and quantifiable changes in an organism resulting from exposure to pollutants. These biological changes may be associated with the development of a disease (HBM4EU, 2022f). The inventoried effect biomarkers include both long-established “traditional” effect biomarkers like disruption of testosterone production and signaling and AOPs which were inventorized and new ones like the activation of several receptors such as PPARα, PPARγ, and GR which emerged as early markers for a range of health effects of phthalate exposure. A strategy for the selection of effect biomarkers underpinned by mechanistic information (e.g., AOPs), health effects and exposure time periods (e.g., biomarkers for reproductive effects associated with phthalate exposure in children/teenagers) has already been published (Baken et al., 2019).

To strengthen the weight of evidence in observational studies that link chemical exposures to health outcomes, the identified effect biomarkers could be used to provide evidence of adverse effects on nervous system development, the immune system, sexual maturation, testicular function and metabolism, and body mass index (BMI) in future studies.

3.3.2.3. Exposure-effect associations. Statistical analyses on HBM4EU Aligned Studies data have been performed to look into the association of exposure to phthalates/DINCH with health effects: Neurodevelopment (Rosolen et al., 2022), asthma and allergy (Wauters et al., in preparation), sexual maturation (Cox et al., 2023), and BMI (Desalegn et al., in preparation). Moreover, results have been published on linking phthalate exposure with established and novel effect biomarkers, like thyroid hormones (Rodríguez-Carrillo et al., 2023) and kisspeptin and sex hormones (Rodríguez-Carrillo et al., in preparation). These data will be explored further in PARC, also by applying causal pathway analysis that is the analysis of health outcomes and biomarkers of effect in association with internal exposure concentrations, including mediation analysis.

3.3.2.4. PBPK modelling. A review of data needed to parameterize physiologically based pharmacokinetic (PBPK) models with a focus on data for rats and humans was performed (Domínguez-Romero and Scheringer, 2019). The review of PBPK models for phthalates and of the data needed for model parameterization illustrates that four factors govern the tissue distribution of phthalates. These are protein binding, ionization, passive partitioning, and metabolism, always in relationship to a phthalate’s hydrophobicity, which increases from lighter to heavier phthalates and impacts all pharmacokinetic steps. This review also shows that a better understanding of protein binding of phthalates is desirable.

3.4. Science-to-policy

How can HBM4EU results feed into the regulatory decisions of ECHA and EFSA?

One overarching aim of HBM4EU was to form a bridge between science and policy. Therefore, the active communication of scientific knowledge to policy makers was an important pillar. Scientific evidence contributes to targeted and effective policy measures to reduce human exposure to chemicals as well as evaluating the effectiveness of existing policies (HBM4EU, 2022g). The main achievements on science-to-policy transfer within HBM4EU are outlined in Lobo Vicente et al. (2023) and are summarized here briefly for phthalates and substitutes.

3.4.1. Science-to-policy workshops

With the aim of supporting policy implementation, science-to-policy workshops were organized. An interactive workshop was held in Brussels (2018) on science-to-policy transfer during the project with the aim of supporting policy implementation for the phthalates and DINCH substance group as a first case study. Prior to the workshop, a preparatory phase of desk research was followed by a series of interviews with key actors in the area of phthalates and bisphenols (including policymakers, stakeholders and experts). The main aim of the interviews was to map perspectives on the topic of phthalates and bisphenols. During the workshop, opportunities were provided for joint reflection and dialogue on how to communicate research results. The participants of this workshop were HBM4EU researchers, representatives from various Directorates-General (DGs) of the European Commission, EU agencies, representatives of national HBM studies and national authorities, and – depending on the research context – societal stakeholders (including NGO’s and industry representatives)

The main conclusion of the first workshop was that “Facts do not speak for themselves”. Instead, the joint interpretation of knowledge is achieved on a case-by-case commitment of all parties in well balanced configuration. In other words, not only by experts and authorities but also a balanced representation of market parties, NGO’s and citizens and intermediary professional groups (Coertjens et al., 2019).

During the second workshop which was held in virtual format on 30–31 May 2022, the derived HBM indicators (see 3.4.2.2) were presented. Suggestions were made to simplify the indicators, possibly through an interactive graphical design (e.g. US EPA (2022)). Furthermore, an integration of information on exposure sources into the indicator concept is desirable.

Coertjens et al. (2022) reported on lessons learned from these (and other) case studies which had been implemented to facilitate the joint interpretation of HBM-results and their translation into policy options, in co-creation between scientists, policy makers and societal stakeholders. "Lessons learned" and recommendations for similar activities in the future were formulated: The Science to Policy workshops connected policy actors and stakeholders to results of the project (Lobo Vicente et al., 2023). While HBM4EU has been able to renew the science-policy interface in the field of chemicals management and environmental health, there still lies much work ahead to anchor risk governance activities more structurally, e.g. in the follow-up project PARC (Marx-Stoelting et al., 2023). In this respect, Coertjens et al. (2022) recommended developing a broader network for environment and health including experts from the social sciences and humanities.

3.4.2. *Tools to support science-to-policy transfer in a more accessible way*

3.4.2.1. Policy brief, Substance Report, factsheet and video. A variety of materials were produced to support science-to-policy transfer in a more accessible way. These materials were produced by the European Environmental Agency involving the corresponding work packages and chemical group leads (see HBM4EU websites).

The Policy Brief (HBM4EU, 2022h) and Substance Report (HBM4EU, 2022i) both summarize the adverse health effects of phthalates and DINCH, their main exposure pathways for humans and outline how HBM of these substances can be of value in the development of EU policy. Additionally, a factsheet with an infographic on exposure and health effects as well as a video highlighting the main aspects were developed.

3.4.2.2. HBM indicators for phthalates and DINCH. HBM indicators were derived to help answer key policy questions and support chemical policies (Buekers et al., 2018). The main objective of the HBM indicators is to enable monitoring of human internal exposure to chemicals in Europe. These indicators aim to translate complex scientific information into clear and short messages and make it accessible to a broader audience. Two types of indicators were derived (Buekers et al., 2018).

1) Result indicators were directly derived from internal exposure concentrations. These indicators show differences in exposure between e.g., age groups, sexes, geographical regions, and time points when comparing median exposure levels. If differences are observed for one group or the other, the reasons for the differences can be investigated and then policy measures or risk management options can be implemented.
2) Impact indicators support health risk assessment by comparing exposure levels with health-based guidance values, such as the HBM-GVs (Apel et al., 2020a).

HBM-indicators for phthalates and DINCH have been derived based on HBM4EU Aligned Studies data and for the comparison of time points also based on DEMOCOPHES data. Their applicability, current shortcomings and solution strategies have been reported (Gerofke et al., 2023). The derived indicators allow a direct and simple interpretation of the HBM data and can help policy makers to answer policy-relevant research questions. Thereby, they enable policy makers to set priorities for further actions on the way to a toxic free environment (Ganzleben et al., 2017).

3.4.2.3. European HBM dashboard. The European HBM Dashboard (see 2.3.7) enables the visualization of results and a comparison with health-based guidance values, such as the HBM-GVs.

3.4.3. *Direct input into policy processes and impact of HBM4EU results*

The scientific results of HBM4EU for phthalates served, among others, as a direct input for public consultations of the European Commission and the European Food Safety Authority (EFSA). The input into policy processes at the European level is presented in Table S4 in the Supplementary Material. Project results have been fed into national and European political processes. Examples and guidance on the use of HBM in RA and its application to different regulatory schemes, based on work from the HBM4EU initiative and including phthalates, have been published (Santonen et al., 2023). As it will take some time to incorporate the project results and implement them in political measures and regulations, quantification of the actual impact of HBM4EU results on phthalates and substitutes is only likely to be possible in the medium to longer term.

4. Conclusion and outlook

HBM4EU succeeded with a concerted approach of simultaneously answering policy-relevant questions on phthalates/substitutes and building a pan European scientific network. Scientific partners grew together as a strong and sustainable scientific network uniting different scientists from the diverse fields of exposure to risk assessment, including chemical analyses, statistical analyses, toxicology, and epidemiology. Not all of the involved groups necessarily needed to be experts on phthalates/substitutes from the onset of the project. Several networks were built, e.g., for HBM analytical laboratories but also for planning and conducting field studies in almost all affiliated countries.

The phthalates/substitutes group included both data rich and data poor representatives. A variety of policy-relevant questions was answered. The approach can be used for other substance groups. Successful concepts such as HBM-GVs, HBM indicators or mixture RA approaches, can quickly be derived or adapted for a growing number of old or new chemicals to ensure a quick and transparent science-to-policy transfer supporting timely and targeted policy measures.

HBM4EU findings suggest that phthalate substitutes used instead of the strictly regulated reprotoxic phthalates should be immediately included in HBM studies, once introduced on the market. They are likely used in similarly large quantities and enter the human body by the same routes, but they are less well studied regarding their toxicological effects. Further elucidation of exposure determinants is needed. A timely HBM enables rapid regulatory intervention, if the trajectory of cumulative exposures (by known or unknown exposure pathways and sources) points to potentially critical exposure levels in the future. This risk assessment is supported by the provision of up to date HBM-GVs for the health-based interpretation of the measurement results, which take into account the current state of knowledge.

Despite observed decreasing trends, exposure of European children and teenagers to phthalates remains a health concern. In addition, specific occupational groups like recycling workers may still be exposed to restricted phthalates for a long time after a ban. Therefore, continuous human biomonitoring for both regulated and non-regulated phthalates is needed to allow further assessment of the effectiveness of existing regulations and, if necessary, to highlight the need for additional measures to protect the population from health effects caused by phthalate exposure. Targeted studies, such as food duplicate studies, could contribute to this.

HBM4EU has shown that despite strict regulation, a significant proportion of children and teenagers in Europe are still exposed to phthalates at levels that health effects cannot be ruled out with sufficient certainty. This is especially true when cumulative exposure (i.e., simultaneous exposure to several phthalates) is considered in a MRA. RAs for mixtures are essential because of the additive effects of phthalates and simultaneous exposure to other antiandrogenic substances. Further development, testing, and implementing of real-world mixing effects methodology into the regulatory process are of utmost importance. Conventions for the integration of mixture effects into regulatory RAs are essential, e.g., through a MAF.

Further work on AOPs could help to understand the underlying toxicological mechanisms between exposure and biological effects that could justify regulation of a larger group of compounds based on an expanded mechanistic understanding. Targeted human longitudinal studies to assess the link of exposure and health effects could confirm causality between exposure to substances like phthalates (substitutes) and health effects but also for any other substance class and even mixtures.

While HBM4EU has been able to renew the science-policy interface in the field of chemicals management and environmental health, there still lies much work ahead. Much more cross talk is needed between risk assessors and risk managers, which could be achieved e.g., by the development of a broader network in the social sciences and humanities for environment and health, e.g., in the follow-up project PARC. The presented achievements lay the groundwork for future work in PARC.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix B. Supplementary data

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