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# Current exposure to phthalates and DINCH in European children and adolescents – Results from the HBM4EU Aligned Studies 2014 to 2021

Nina Vogel [a,*], Phillipp Schmidt [a], Rosa Lange [a], Antje Gerofke [a], Amrit K. Sakhi [b], Line S. Haug [b], Tina Kold Jensen [c], Hanne Frederiksen [d,e], Tamás Szigeti [f], Zsófia Csákó [f], Lubica Palkovicova Murinova [g], Miroslava Sidlovska [h], Beata Janasik [i], Wojciech Wasowicz [i], Janja Snoj Tratnik [j], Darja Mazej [j], Catherine Gabriel [k,l], Spyros Karakitsios [k,l], Fabio Barbone [m], Valentina Rosolen [n], Loïc Rambaud [o], Margaux Riou [o], Aline Murawski [a], Daan Leseman [p], Gudrun Koppen [q], Adrian Covaci [r], Sanna Lignell [s], Anna Karin Lindroos [s], Martin Zvonar [t], Lenka Andryskova [t], Lucia Fabelova [g], Denisa Richterova [g], Milena Horvat [j], Tina Kosjek [j], Denis Sarigiannis [k,l,u], Marios Maroulis [k,l], Susana Pedraza-Diaz [v], Ana Cañas [v], Veerle J. Verheyen [q], Michiel Bastiaensen [r], Liese Gilles [q], Greet Schoeters [q,w], Marta Esteban-López [v], Argelia Castaño [v], Eva Govarts [q], Holger M. Koch [x], Marike Kolossa-Gehring [a]

[a] German Environment Agency (UBA), Berlin, Germany
[b] Norwegian Institute of Public Health, Oslo, Norway
[c] IST - Clinical Pharmacology, Pharmacy and Environmental Medicine, Odense, Denmark
[d] Department of Growth and Reproduction, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[e] International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[f] National Public Health Center, Budapest, Hungary
[g] Slovak Medical University, Faculty of Public Health, Bratislava, Slovakia
[h] Constantine the Philosopher University in Nitra, Slovakia
[i] Nofer Institute of Occupational Medicine, Lodz, Poland
[j] Jozef Stefan Institute, Department of Environmental Sciences, Ljubljana, Slovenia
[k] Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki, Greece
[l] HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Thessaloniki-Thermi, Greece
[m] Department of Medicine—DAME, University of Udine, Udine, Italy
[n] Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Trieste, Italy
[o] Santé publique France, Environmental and Occupational Health Division, Saint-Maurice, France
[p] National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
[q] VITO Health, Flemish Institute for Technological Research (VITO), Mol, Belgium
[r] Toxicological Center, University of Antwerp, Wilrijk, Belgium
[s] Swedish Food Agency, Uppsala, Sweden
[t] RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic
[u] Environmental Health Engineering, Institute of Advanced Study, Pavia, Italy
[v] National Centre for Environmental Health, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain
[w] University of Antwerp, Dept of Biomedical Sciences and Toxicological Centre, Antwerp, Belgium
[x] Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany

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ABSTRACT

Phthalates are mainly used as plasticizers for polyvinyl chloride (PVC). Exposure to several phthalates is associated with different adverse effects most prominently on the development of reproductive functions. The HBM4EU Aligned Studies (2014–2021) have investigated current European exposure to ten phthalates (DEP,

* Corresponding author.
*E-mail address:* nina.vogel@uba.de (N. Vogel).

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BBzP, DiBP, DnBP, DCHP, DnPeP, DEHP, DiNP, DiDP, DnOP) and the substitute DINCH to answer the open policy relevant questions which were defined by HBM4EU partner countries and EU institutions as the starting point of the programme. The exposure dataset includes ~5,600 children (6–11 years) and adolescents (12–18 years) from up to 12 countries per age group and covering the North, East, South and West European regions. Study data from participating studies were harmonised with respect to sample size and selection of participants, selection of biomarkers, and quality and comparability of analytical results to provide a comparable perspective of European exposure. Phthalate and DINCH exposure were deduced from urinary excretions of metabolites, where concentrations were expressed as their key descriptor geometric mean (GM) and 95th percentile (P95). This study aims at reporting current exposure levels and differences in these between European studies and regions, as well as comparisons to human biomonitoring guidance values (HBM-GVs). GMs for children were highest for ∑DEHP metabolites (33.6 μg/L), MiBP (26.6 μg/L), and MEP (24.4 μg/L) and lowest for∑DiDP metabolites (1.91 μg/L) and ∑DINCH metabolites (3.57 μg/L). In adolescents highest GMs were found for MEP (43.3 μg/L), ∑DEHP metabolites (28.8 μg/L), and MiBP (25.6 μg/L) and lowest for ∑DiDP metabolites (= 2.02 μg/L) and ∑DINCH metabolites (2.51 μg/L). In addition, GMs and P95 stratified by European region, sex, household education level, and degree of urbanization are presented. Differences in average biomarker concentrations between sampling sites (data collections) ranged from factor 2 to 9. Compared to the European average, children in the sampling sites OCC (Denmark), InAirQ (Hungary), and SPECIMEn (The Netherlands) had the lowest concentrations across all metabolites and ESTEBAN (France), NAC II (Italy), and CROME (Greece) the highest. For adolescents, comparably higher metabolite concentrations were found in NEB II (Norway), PCB cohort (Slovakia), and ESTEBAN (France), and lower concentrations in POLAES (Poland), FLEHS IV (Belgium), and GerES V-sub (Germany). Multivariate analyses (Survey Generalized Linear Models) indicate compound-specific differences in average metabolite concentrations between the four European regions. Comparison of individual levels with HBM-GVs revealed highest rates of exceedances for DnBP and DiBP, with up to 3 and 5%, respectively, in children and adolescents. No exceedances were observed for DEP and DINCH. With our results we provide current, detailed, and comparable data on exposure to phthalates in children and – for the first time – in adolescents, and – for the first time – on DINCH in children and adolescents of all four regions of Europe which are particularly suited to inform exposure and risk assessment and answer open policy relevant questions.

**Abbreviations**

3xG 3xG Study (Belgium)
5-cx-MEPP Mono(2-ethyl-5-carboxypentyl) phthalate
5-OH-MEHP Mono(2-ethyl-5-hydroxyhexyl) phthalate
5-oxo-MEHP Mono(2-ethyl-5-oxohexyl) phthalate
$\Sigma PhthalateX_m$ sum of metabolites of phthalate X
BEA Biomonitoring in adolescents (Spain)
CELSPAC Central European Longitudinal Study of Parents and Children: Teenagers
CHMS Canadian Health Measures Survey
CROME Cross-Mediterranean Environment and Health Network (Greece)
crt creatinine
cx-MiDP Mono(2,7-methyl-7carboxy-heptyl) phthalate
cx-MiNP Mono(2,7-methyl-7carboxy-heptyl) phthalate
cx-MINCH Cyclohexane-1,2-dicarboxylic acid-mono-(carboxy-iso-octyl) ester
EC European Commission
ESTEBAN Environment, Health, Biomonitoring, physical Activity, Nutrition (France)
FLEHS IV FLemish Environment and Health Study 2016–2020 (Belgium)
GerES V-sub German Environmental Survey 2014–2017 sub-study
GM geometric mean
$GM_{Eu}$ geometric mean of European sample
$HBM\text{-}GV_{GenPop}$ HBM-GVs for the general population
HBM-GVs human biomonitoring guidance values
HBM4EU European Human Biomonitoring Initiative
IARC International Agency for Research on Cancer
InAirQ Transnational Adaption Actions for Integrated Indoor Air Quality Management (Hungary)
IPCHEM Information Platform for Chemical Monitoring
LOD limit of detection
LOQ limit of quantification
MCHP Mono-cyclo-hexyl phthalate
MEHP Mono(2-ethylhexyl) phthalate
MEP Mono-ethyl phthalate
MBzP Mono-benzyl phthalate
MiBP Mono-isobutyl phthalate
MnBP Mono-n-butyl phthalate
MnOP Mono-n-octyl phthalate
MnPeP Mono-n-pentyl phthalate
n sample size
NAC II Northern Adriatic Cohort II (Italy)
NEB II Norwegian Environmental Biobank, Part II
NHANES Health and Nutrition Examination Survey
OH-MiNP Mono(4-methyl-7-hydroxyoctyl) phthalate
OH-MINCH Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyl-iso-nonyl) ester
OH-MiDP Mono-hydroxy-isodecyl phthalate
OCC Odense child cohort (Denmark)
P percentile
PCB cohort (and follow-up) PCBs and early childhood development in Slovakia
POLAES Polish aligned environmental study
QA/QC quality assurance/quality control
RAC Committee for Risk Assessment
Riksmaten Adolescents Sweden Riksmaten ungdom 2016-17
sd standard deviation
SLO CRP Exposure of Children and Adolescents to Selected Chemicals Through Their Habitat Environment (Slovenia)
SPECIMEn-NL Dutch arm of the HBM4EU pesticide study SPECIMEn (The Netherlands)

## 1. Introduction

Phthalates are a large group of chemicals, mainly used as plasticizers. They are added to polyvinyl chloride (PVC) to give this inherently hard and brittle plastic elastic properties. They are used in a variety of consumer products, such as cosmetics, personal care products, floor coverings, food contact materials, toys, and wall papers. As they are not chemically bound to the plastic material, they can migrate into the environment. Humans can be exposed to phthalates via the air, the food or through dermal contact. Indeed, phthalates have been found in various human matrices including breastmilk (Arbuckle et al., 2016), in pregnant women (Arbuckle et al., 2016; Buckley et al., 2022; Enke et al., 2013; Sathyanarayana et al., 2016), in new-borns and infants (Enke et al., 2013; Frederiksen et al., 2022; Navaranjan et al., 2020), and in children (Den Hond et al., 2013), often at high detection frequencies.

In the EU, several phthalates have been identified as substances of very high concern and are thus subject to extensive regulations under REACH. Already in 1999, six phthalates have been temporarily banned from toys and child care articles (1999/815/EEC). In 2006 (Directive, 2005/84/EC) this became a permanent restriction for diethylhexyl phthalate (DEHP), di-n-butyl phthalate (DnBP), and butylbenzyl phthalate (BBzP)[1] in all toys and childcare articles (entry 51 of Annex XVII to REACH regulation (EC) No 1907/2006) and for diisononyl phthalate (DiNP), di-n-octyl phthalate (DnOP), and diisodecyl phthalate (DiDP) in toys and child care articles that can be placed in children's mouth (Annex XVII, entry 52 of REACH regulation (EC) No 1907/2006). The restriction on DEHP, DnBP and BBzP was expanded to diisobutyl phthalate (DiBP) and extended to all plastic products after the year 2020 (Commission Regulation (EU) 2018/2005). From 2015 (DEHP, DnBP, DiBP, BBzP) and 2020 (di-n-pentyl phthalate, DnPeP) on, certain phthalates may only be placed onto the EU market or used if an authorization has been granted (Annex XIV to REACH regulation (EC) No 1907/2006), effectively banning these phthalates from the European market, with only few authorized exceptions. DEHP can be still marketed in the EU if authorisation applications are still pending. Besides, the approval for authorisation does not affect imported products, meaning that products containing DEHP could be legally imported until summer 2020 when the restriction in any plasticised material came into effect as these also apply to imported goods.

In the EU, several phthalates are classified as toxic to reproduction (DEHP, DnBP, DiBP, BBzP, DnPeP and dicyclohexyl phthalate, DCHP) and to have endocrine disrupting properties (DEHP, DnBP, DiBP, BBzP, DCHP) (ECHA, 2022). Prenatal exposure in rodents can result in malformations of the reproductive organs, particular of the testis. Reduction in foetal testicular testosterone and insulin-3 hormone production during the critical time window for reproductive tract development has been identified as a crucial step in initiating those effects (for review see EFSA, 2019; Howdeshell et al., 2008; NRC, 2008; US, 2014). Associations of detrimental effects of phthalates on development and reproduction have also been reported for humans in various epidemiological studies (Radke et al., 2018, 2019; Sathyanarayana et al., 2016). As the developing organism is most sensitive to the toxicity of the phthalates, it is important to assess current exposures in vulnerable subpopulations, i.e. children and adolescents. To evaluate if current exposures to plasticizers are of health concern, human biomonitoring guidance values (HBM-GVs) were derived and consolidated for five phthalates (DEHP, DnBP, DiBP, BBzP, and bis(2-propylheptyl) phthalate, DPHP) and the substitute DINCH (cyclohexane-1,2-dicarboxylic acid-diisononyl ester) within HBM4EU (Lange et al., 2021). These guidance values represent the concentration of the respective phthalate metabolite(s) in urine at or below which, according to current knowledge, no risk is expected. Urinary metabolite concentrations can be directly compared to these HBM-GVs enabling a simple and quick risk assessment (Apel et al., 2020a).

Although various national and regional HBM programs are conducted in Europe, the direct comparison between these studies is complicated by the unique set-up of each study with respect to target population, sampling design, choice of biomarkers, questionnaires, analysing laboratories using individual analytical methodologies, data bases, data protection and availability, statistical analyses, and the health-based interpretation. A first European HBM project that has intended to overcome such obstacles has been the COPHES/DEMOCOPHES project (COnsortium to Perform Human biomonitoring on a European Scale/DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale project; Den Hond et al., 2015). This HBM program included analyses of five phthalates in morning or spot urine samples collected in 2011–12 from 120 mother-child pairs in 17 countries. To obtain more recent exposure data, the HBM4EU Aligned Studies were launched within the European Human Biomonitoring Initiative (HBM4EU; Ganzleben et al., 2017) to collect new and provide existing European HBM data for selected prioritized substances as harmonised as possible (Gilles et al., 2021). Overall, these HBM4EU Aligned Studies comprise more than 10,000 individuals (about 4,100 young adults, and 3,600 children and 3,100 adolescents) from 25 different studies and provide HBM data on various substances, including phthalates and DINCH (Gilles et al., 2022; Govarts et al., in review in this special issue).

The aim of this study was to answer open policy relevant questions as defined by HBM4EU partner countries and EU institutions by supplying recent data on the exposure of children and adolescents in Europe to phthalates and the substitute compound DINCH, using data harmonised under the HBM4EU Aligned Studies protocol. Additionally, our study aimed at investigating European biomarker concentrations (also stratified by sex, education, degree of urbanisation), to show similarities and differences between European regions, and sampling sites. To assess the health impact of the described exposure levels we have compared them to HBM-GVs to assess if current plasticizer exposures are still of concern.

## 2. Methods

### 2.1. Study population and sample collections

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 biomarker data reflective of the internal exposure for the European population across a geographic spread. The process of gathering and harmonising data collections from European countries in the HBM4EU Aligned Studies and their characteristics are described elsewhere (Gilles et al., 2022; Gilles et al., 2021; Govarts et al., in review in this special issue). Briefly, data protection and ethical approval to provide individual data were requested beforehand from each individual study. Specifically, among phthalates and DINCH, 2 to 4 countries per European region were asked to provide data on 300 samples each for children (6–11 years) and adolescents (12–18 years) collected between 2014 and 2021, either from an existing national HBM study or from newly collected samples. The children group also included 3% (n = 89) 12-year-olds from three studies. This circumstance was due to delay between recruitment and urine sampling (ESTEBAN, FR: n = 18; GerES V-sub, DE: n = 19; PCB cohort, SK: n = 52). Studies targeting hotspots, or institutionalized, patient or occupational populations were excluded. Studies providing data on phthalates and DINCH metabolites for children were: NEB II (Norway), OCC (Denmark), InAirQ (Hungary), PCB cohort (Slovakia), POLAES (Poland), CROME (Greece), NAC II (Italy), SLO CRP (Slovenia), 3 × G (Belgium), ESTEBAN (France), GerES V-sub unweighted (Germany), SPECIMEn-NL (The Netherlands). For adolescents, the following studies participated in the phthalates and DINCH program: NEB II (Norway), Riksmaten Adolescents 2016–2017

[1] There are different nomenclatures, including BBP (e.g. by European Commission), BzBP (benzyl butyl phthalate, e.g. by International Union of Pure and Applied Chemistry, IUPAC) and BBzP (butyl benzyl phthalate).

(Sweden), PCB cohort follow-up (Slovakia), CELSPAC: Teenagers (Czech Republic), POLAES (Poland), BEA (Spain), CROME (Greece), SLO CRP (Slovenia), ESTEBAN (France), FLEHS IV (Belgium), GerES V-sub unweighted (Germany).

Only for the group of ten phthalates (BBzP, DEP, DiBP, DnBP, DEHP, DiDP, DiNP, DnOP, DnPeP, DCHP) and the substitute DINCH both the population of children and adolescents were prioritized for HBM4EU Aligned Studies stressing the importance to assess exposure to plasticizers in these age windows. Exposure to the ten phthalates and DINCH was assessed by analysing 17 different urinary metabolites (see Supplementary Table 1). The quality and comparability of analytical results from different analytical laboratories analysing phthalate and DINCH metabolites in urine samples were assured via the HBM4EU QA/QC program (Esteban López et al., 2021; Mol et al., 2022). The laboratories participating in the HBM4EU analysed the test materials using their own method. They reported the concentration in ng/mL through a web tool and provided details of their methods (regarding deconjugation, extraction, instrumental analysis, use of internal standards, method of quantification, and identification parameters). The results and extended information of the phthalates and DINCH exercises are described in Mol et al. (2022). All studies used liquid chromatography-tandem mass spectrometry (LC-MS/MS). For the current analyses, only phthalate/-DINCH metabolite data which were rated "quality assured by HBM4EU QA/QC program" or "generated before HBM4EU QA/QC program but deemed comparable by HBM4EU Quality Assurance Unit (QAU)" were included. Deemed comparable means that data was generated outside (before) the HBM4EU QA/QC program but the analysing laboratory proved its competence for the biomarkers certified by passing the HBM4EU QA/QC.

In order to control the dilution of the urine samples, creatinine and specific gravity were also measured. These parameters were not included in the QA/QC programme.

### 2.2. Statistical analysis

Values below limits of quantification (LOQ) or limits of detection (LOD) were imputed for each biomarker in each data collection by single random imputation from a truncated lognormal distribution (Hengingsen and Toomet, 2011) if at least 30% of values were detected. Sum parameters were only calculated if all biomarkers needed to calculate the sum were measured and if at least 60% of values were detected for at least one of the biomarkers that constitute the sum. For the sum parameters, metabolite concentrations below LOD or LOQ were replaced by LOD/2 or LOQ/2. This method was used because in some cases not enough values were quantified for all metabolites constituting the sum to estimate a truncated lognormal distribution to allow random imputation. Sums (μg/L) of metabolites were available for DEHP (OH-MEHP, oxo-MEHP, and cx-MEPP), DiDP (cx-MiDP, OH-MiDP), DiNP (OH-MiNP, cx-MiNP), and DINCH (OH-MINCH, cx-MINCH) which will be presented as ∑DEHPm, ∑DiDPm, ∑DiNPm, and ∑DINCHm, respectively, for simplification reasons in this study. To be able to use sums, studies not having measured all metabolites for the sums were excluded.

All statistical analyses were performed in RStudio (RStudio Team, 2008) with pooled data from all data collections, and run separately for the metabolites or summed metabolites. We calculated sample proportion equal to or exceeding LOQ, geometric mean (GM, based on log-transformed data) and 95th percentile (P95) and their 95th confidence interval (CI), median (50th percentile, P50) and 90th percentile (P90) for the pooled data and stratified by sex, region, degree of urbanization, and household education level (for data protection reasons only presented for subgroups of $n \geq 50$). Since higher similarity can be assumed within a study, survey methods were applied when pooling individual data from data collections (per suggestion in HBM4EU) to account for the nesting of individuals within studies (applied technically by using a survey design with data collection as identifier). We also checked with multiple linear regression models separately for each sum parameter or metabolite whether there are differences between children and adolescents and whether there is an association across age in years in a pooled data set. Data were compared to urinary biomarker concentrations (GMs and P95) for both children (6–11 years old) and adolescents (12–19 years old) from two national surveys in North America in the overlapping time frame: U.S. National Health and Nutrition Examination Survey (NHANES; cycle 2015–2016; CDC, 2019) and the Canadian Health Measures Survey (CHMS; cycle 2016–2017; Health Canada, 2019). To compare exposure biomarker concentrations expressed as GMs of each HBM4EU Aligned Study to the European geometric mean ($GM_{Eu}$) heat maps were created separately for each age group (cf. Den Hond et al., 2015) and metabolite. We calculated the Log2 Fold Change (Log2FC) by dividing each of the countries GMs by $GM_{Eu}$ for each substance and taking the logarithm to the base 2. This method generates an easily interpretable presentation of the relative differences between studies and the European mean exposure. The order of the countries is based on the mean Log2 Fold Change across all substances from low to high. Generalized Linear Models (GLM) with survey method as described above were run to check differences in exposure between European regions, while controlling for basic covariates (sex, education, sampling year) which were only included in the model if significant with $p \geq 0.05$ in a model for any metabolite or summed metabolites. To evaluate potential health risks, we compared the urinary metabolite (or summed metabolite) concentrations with toxicologically-derived healthbased guidance values for the general population. In HBM4EU, a consolidated methodology to derive the so-called human biomonitoring guidance values (HBM-GVs) has been established (Apel et al., 2020b). HBM-GVs for the general population ($HBM\text{-}GV_{GenPop}$) are defined as the concentration of a substance or its specific metabolite(s) in human biological media (e.g. urine) at or below which according to current knowledge no risk of health impairment can be anticipated (Apel et al., 2020b). $HBM\text{-}GV_{GenPop}$ are equivalent to HBM-I values derived by the German HBM Commission, and similar to the biomonitoring equivalent values (BE) of Summit Toxicology if the referred biomarker concentration in the biological media is consistent with toxicity reference values (TRV, external exposure guidance values, such as the tolerably daily intake by EFSA). For health-based risk assessments of BBzP, DiBP, DnBP, DEHP, and the non-phthalate substitute DINCH in this research, consolidated HBM-GVs derived under HBM4EU were used (Lange et al., 2021). Except for BBzP the $HBM\text{-}GV_{GenPop}$ for phthalates and DINCH were calculated by converting existing external TRVs into internal values by using a simple mass balance approach. For BBzP, instead the $HBM\text{-}GV_{GenPop}$ was based on a point of departure (POD) identified in experimental animal studies. More details can be found in Lange et al. (2021). For the DEP metabolite MEP, a biomonitoring equivalent (BE) value was used instead. The BE for DEP is based on the oral reference dose (RfD) (Aylward et al., 2009).

## 3. Results and discussion

Phthalate and DINCH metabolites provided by each of the studies for children (n = 2,880) and adolescents (n = 2,799) can be found in Supplemetary Table S1 and Table S2. Most of the chemical analyses was performed within the project time of HBM4EU and thus quality assured by the HBM4EU QA/QC. 11% (adolescents) and 13% (children) were phthalate metabolite data generated before the HBM4EU QA/QC. These data were included only if the analysing laboratory had received the HBM4EU certificates for the respective biomarkers (biomarker data generated before HBM4EU QA/QC program but deemed comparable). On average, MCHP, MnOP, and MnPeP were only found in 1–5% of all urine samples (with differing levels of detection, however) indicating only low-level exposures to DCHP, DnPeP and DnOP. Because of the low detection frequencies these three biomarkers were not included as imputed concentrations in further statistical analyses. Metabolites of DEP, BBzP, DiBP, DnBP, DEHP, DiDP, DiNP, and DINCH had very high detection frequencies, ranging from 65% for cx-MiNP in children to

100% for metabolites of DEP, BBzP, DiBP, DnBP, DEHP, and DINCH in most studies. The high detection frequencies indicate that despite various (strict) regulations, phthalates are still ubiquitous. Given the short elimination half-lives, it is likely that children and adolescents are exposed to phthalates and DINCH on a regular basis.

Since not all studies provided data on both children and adolescents (NEB II in Northern Europe, POLAES and PCB cohort/PCB cohort follow-up in Eastern, SLO CRP and CROME in Southern, and ESTEBAN and GerES V-sub in Western Europe), comparisons between children and adolescents might be confounded with possibly different study characteristics in each age group. Therefore, all results are reported separately for children and adolescents and comparisons between these age groups need to be interpreted with caution. Descriptive statistics for children's and adolescents' samples with quality assured phthalate metabolites data can be found in Table 1. Children were on average 8.7 years, adolescents 14.2 years old. The majority of participants in each age group were from households with high education and more participants lived in Eastern and Western Europe than in Northern or Southern Europe. For more details on the targeted study populations, obtained study samples and participating data collections see Govarts et al. (in review in this special issue) and Gilles et al. (2022).

Regression analyses of pooled data separately for each metabolite or summed metabolites with age group as the predictor indicate that lower concentrations are found in adolescents compared to children for MBzP (by 31.6%), ∑DEHPm (16%) and ∑DINCHm (41.9%), whereas higher levels were observed in adolescents for MEP (77.2%), MnBP (16.7%), and ∑DiNPm (22.2%) ($p < 0.05$). No differences between age groups were found for MiBP and ∑DiDPm. A follow-up check using age in years instead of the dichotomous age group variable as predictor revealed a linear trend with the above-mentioned direction across age years. Using this evaluation, ∑DiDPm showed a decrease with increasing age, while MiBP concentrations showed a non-linear (accelerated) decrease (vs. no difference between age groups in both phthalates). In sum, children had higher concentrations in MBzP, ∑DEHPm, ΣDiDPm, MiBP, and ∑DINCHm, and adolescents had higher concentrations in MEP, MnBP, and ∑DiNPm. This could be an indication towards different exposure sources for the age groups, where adolescents for example use more cosmetics and other personal care products, a possible source of DEP and DnBP (Zota et al., 2014). A separate manuscript investigating the role of exposure determinants with HBM4EU Aligned Studies data collections is currently being prepared.

**Table 1**
Descriptive characteristics of participants and samples in the children's and adolescents' data collections.

| | Children (n = 2,880) | Adolescents (n = 2,799) |
|---|---|---|
| Participants | | |
| Sex: % female | 50 | 50 |
| Age: mean (sd; range) | 8.7 (1.7; 6–12) | 14.2 (1.5; 12–18) |
| Education of household (%) | | |
| Low | 35 | 37 |
| Medium | 4 | 6 |
| High | 60 | 56 |
| Region (%) | | |
| North | 21 | 17 |
| East | 30 | 31 |
| South | 21 | 20 |
| West | 28 | 32 |
| BMI | | |
| Mean (sd) | 17.2 (7.4) | 20.8 (13.0) |
| Range | 7.4–39.2 | 13.0–52.0 |
| Degree of urbanisation (%) | | |
| Cities | 46 | 39 |
| Towns or suburbs | 23 | 32 |
| Rural area | 25 | 30 |
| Samples | | |
| $N_{total}$ | 33,436 | 34,214 |
| $n_{biomarker}$ | | |
| Mean (sd) | 2,388 (324) | 2,444 (379) |
| Range | 1,557–2,879 | 1,631–2,799 |
| Year of sampling | | |
| Mean (sd) | 2017.1 (1.7) | 2017.2 (1.5) |

Notes. Ranges of sampling year: 2014 to 2021. Education of household measured with ISCED (International Standard Classification of Education (ISCED); UNESCO Institute for Statistics (2011)). ISCED was missing for 62 children and 71 adolescents. Degree of urbanisation measured with DEGURBA. $N_{total}$ is the total number of data points analysed, $n_{biomarker}$ is the number of available samples per biomarker.

### 3.1. GM and P95

Table 2 shows the GM and P95 for all parent compounds (expressed as their metabolite or summed metabolites concentrations; volume-based, μg/L) for children and adolescents. Highest GM and P95 concentrations in children were observed for ∑DEHPm (33.6 and 127 μg/L), MiBP (26.6 and 122 μg/L) and MEP (24.4 and 214 μg/L), and in adolescents for MEP (43.3 and 387 μg/L), ∑DEHPm (28.8 and 116 μg/L), and MiBP (25.6 and 112 μg/L). Lowest GM and P95 values both in children and adolescents were found for ∑DiDPm (children: 1.91 and 8.61 μg/L; adolescents: 2.02 and 8.8 μg/L) and ∑DINCHm (children: 3.57 and 23.7; adolescents: 2.51 and 17 μg/L).

Volume based GMs and P95s for all substances can be found in Table 2, crt-adjusted and sg-adjusted concentrations in the Supplementary Tables S3 and S4

Table 3 shows exemplary, more detailed data for the DiBP biomarker MiBP, including GM and P95 with their CIs, P50, and P90 for the total sample of children and adolescents, and stratified by sex, European region, degree of urbanisation, and education. Detailed data on each of the 14 quantifiable biomarkers and their sums are presented in Supplementary Tables S5–S22.

Interestingly, highest concentrations are still found for metabolites of DiBP, DnBP and DEHP. Regulation of these phthalates in the EU has started as early as 1999 in toys and childcare products and REACH authorization demands starting in 2015. Compared to DEMOCOPHES data from children of the same age group (see Table 2 and Fig. 1) collected for Europe in 2011/2012, metabolite levels of these phthalates were clearly lower (COPHES GMs: MnBP, 35.8 μg/L; MiBP, 47.5 μg/L; ∑DEHPm (= ∑ of MEHP, 5OH-MEHP, 5oxo-MEHP), 48.6 μg/L; see Supplementary Table 3 in Den Hond et al., 2015) indicating a success of regulatory measures, but also to other sources of exposure not directly impacted by the current regulation (e.g. broader environmental exposures, dust exposures, imported goods etc.). Also, the majority of data from the HBM4EU Aligned Studies did not collect data from very recent years (2021) and the potential decrease of exposure as a result from the extensive ban in plastic consumer articles from 2020 on is not yet reflected in the here presented data (ECHA, 2017; Koch et al., 2013). To investigate the effect of regulations on exposure, European-scale time trend studies with continuously collected samples are needed (Vogel et al., 2023, this issue).

We chose to focus our data evaluation on the GM and P95 concentrations as they are the key descriptors of exposure used in HBM studies worldwide.

European exposure levels dropped compared to DEMOCOPHES studies in 2011/2012 (Den Hond et al., 2015) for all phthalates (Fig. 1). For the substitute ∑DINCHm, exposures increased. Comparisons of the GMs in HBM4EU Aligned Studies with NHANES (cycle 2015–2016; CDC, 2019) and CHMS (cycle 2016–2017; Health Canada, 2019) for children indicate roughly similar urinary metabolite concentrations between North America and Europe for MnBP, MEP, and DEHP metabolites. Higher concentrations in North America can be seen for MBzP, while the opposite was seen for MiBP. Also, higher concentrations in the U.S. study compared to HBM4EU Aligned Studies can be found for cx-MiNP, cx-MiDP, while the exposure level was lower for DINCH metabolites OH-MINCH & cx-MINCH. For all but MBzP and cx-MiDP, CHMS has similar or lower concentrations compared to HBM4EU Aligned Studies.

**Table 2**
Exposure biomarker concentrations for quantifiable metabolites and summed metabolites of phthalates and DINCH in the HBM4EU Aligned Studies expressed as GM and P95 with their 95% CI.

| Children | | | | | | | Adolescents | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Substance | Biomarker | N | GM (95% CI) | P95 (95% CI) | P50 | P90 | N | GM (95% CI) | P95 (95% CI) | P50 | P90 |
| DEP | MEP | 2,580 | 24.4 (13.9, 43.0) | 214 (138, 396) | 22.7 | 130 | 2,499 | 43.3 (31.4, 59.8) | 387 (260, 615) | 37.9 | 214 |
| BBzP | MBzP | 2,279 | 3.64 (2.22, 5.95) | 28.6 (17.3, 47.6) | 3.60 | 17.4 | 2,799 | 2.76 (1.71, 4.47) | 27.9 (14.9, 45.6) | 2.71 | 14.7 |
| DiBP | MiBP | 2,279 | 26.6 (20.1, 35.2) | 122 (96.2, 172) | 26.7 | 83.2 | 1,631 | 25.6 (20.5, 32.1) | 112 (87.7, 141) | 24.4 | 71.6 |
| DnBP | MnBP | 2,579 | 21.1 (17.1, 26.1) | 80.5 (65.4, 103) | 21.4 | 59.8 | 2,499 | 24.8 (16.7, 36.9) | 163 (59.0, 443) | 24.8 | 93.1 |
| DEHP | MEHP | 2,280 | 1.21 (0.816, 1.80) | 7.00 (5.28, 10.1) | 1.36 | 4.71 | 2,799 | 1.77 (1.40, 2.23) | 9.23 (6.00, 14.8) | 1.77 | 6.00 |
| | OH-MEHP | 2,579 | 11.2 (8.47, 14.7) | 46.3 (37.8, 56.0) | 11.2 | 32.9 | 2,799 | 10.4 (7.35, 14.8) | 54.7 (24.7, 159) | 9.99 | 34.7 |
| | cx-MEPP | 2,579 | 14.4 (11.0, 18.8) | 54.5 (46.2, 69.5) | 14.3 | 40.8 | 2,799 | 10.6 (8.43, 13.4) | 40.6 (32.8, 52.3) | 10.9 | 29.5 |
| | oxo-MEHP | 2,577 | 7.41 (5.53, 9.94) | 29.6 (26.0, 35.9) | 7.43 | 22.4 | 2,798 | 6.11 (4.98, 7.50) | 24.7 (20.9, 30.8) | 6.11 | 17.9 |
| | ΣDEHPm | 2,577 | 33.6 (25.7, 43.9) | 127 (110, 152) | 33.5 | 95.8 | 2,798 | 28.8 (23.3, 35.6) | 116 (82.4, 181) | 28.4 | 82.2 |
| | ΣDEHPm_COPHES | 2,278 | 19.5 (14.5, 26.2) | 77.8 (66.4, 94.3) | 19.6 | 57.3 | 2,798 | 19.1 (14.3, 25.5) | 89.3 (51.3, 167) | 18.6 | 58.5 |
| DiDP | OH-MiDP | 2,418 | 1.12 (0.759, 1.67) | 5.88 (4.36, 8.77) | 1.16 | 3.89 | 2,062 | 1.22 (0.876, 1.69) | 6.03 (4.61, 8.17) | 1.22 | 4.00 |
| | cx-MiDP | 1,557 | 0.746 (0.533, 1.04) | 3.05 (2.10, 6.67) | 0.744 | 2.22 | 1,881 | 0.728 (0.490, 1.08) | 2.89 (1.90, 4.41) | 0.800 | 1.90 |
| | ΣDiDPm | 1,557 | 1.91 (1.26, 2.90) | 8.61 (5.93, 18.8) | 1.87 | 5.96 | 1,881 | 2.02 (1.54, 2.63) | 8.80 (6.41, 12.5) | 1.94 | 5.63 |
| DiNP | OH-MiNP | 2,280 | 3.77 (2.25, 6.29) | 22.6 (15.1, 44.7) | 3.90 | 14.6 | 2,212 | 4.63 (3.58, 5.99) | 27.3 (18.5, 38.1) | 4.49 | 15.7 |
| | cx-MiNP | 1,980 | 4.34 (2.43, 7.77) | 27.0 (15.5, 55.5) | 4.70 | 16.8 | 2,618 | 5.44 (3.65, 8.13) | 34.8 (21.7, 52.9) | 5.16 | 19.6 |
| | ΣDiNPm | 1,980 | 8.31 (5.18, 13.3) | 43.1 (26.5, 105) | 8.50 | 28.9 | 2,031 | 10.2 (7.19, 14.3) | 57.9 (34.3, 116) | 9.45 | 32.8 |
| DINCH | OH-MINCH | 2,879 | 2.34 (1.80, 3.05) | 16.5 (11.8, 22.3) | 2.22 | 9.01 | 2,499 | 1.59 (1.19, 2.11) | 12.0 (8.39, 19.2) | 1.49 | 6.86 |
| | cx-MINCH | 2,579 | 1.25 (0.909, 1.72) | 8.29 (5.37, 13.0) | 1.22 | 4.88 | 2,317 | 0.932 (0.719, 1.21) | 5.99 (3.83, 10.7) | 0.930 | 3.57 |
| | ΣDINCHm | 2,579 | 3.57 (2.70, 4.70) | 23.7 (16.1, 37.9) | 3.38 | 13.2 | 2,317 | 2.51 (2.00, 3.16) | 17.0 (12.1, 26.1) | 2.35 | 9.93 |

Notes: Unit: volume based (μg/L). Sums: ΣDEHPm = OH-MEHP + cx-MEPP + oxo-MEHP; ΣDEHPm_COPHES reflects the sum of metabolites investigated in DEMOCOPHES: MEHP + OH-MEHP + oxo-MEHP; ΣDiDPm = OH-MiDP + cx-MiDP; ΣDiNPm = OH-MiNP + cx-MiNP; ΣDINCH = OH-MINCH + cx-MINCH.

**Table 3**
Volume based MiBP (DiBP) concentrations (μg/L) by GM, P95, median, and P90 and by major factors in children and adolescents.

| | | Children | | | | | Adolescents | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | GM (95% CI) | P95 (95% CI) | P50 | P90 | N | GM (95% CI) | P95 (95% CI) | P50 | P90 |
| Europe | All | 2,279 | 26.6 (20.1, 35.2) | 122 (96.2, 172) | 26.7 | 83.2 | 1,631 | 25.6 (20.5, 32.1) | 112 (87.7, 141) | 24.4 | 71.6 |
| Sex | Female | 1,124 | 27.2 (20.5, 36.0) | 126 (95.9, 188) | 27.3 | 90.1 | 838 | 25.5 (19.5, 33.3) | 109 (83.2, 155) | 24.7 | 71.1 |
| | Male | 1,152 | 26.1 (19.3, 35.1) | 121 (83.4, 184) | 26.0 | 77.8 | 793 | 25.8 (21.4, 31.2) | 112 (78.7, 149) | 24.3 | 71.5 |
| Region | North | 600 | 19.1 (17.7, 20.6) | 97.6 (75.8, 116) | 18.8 | 61.6 | 181 | 32.2 (28.3, 36.7) | 217 (101, 315) | 29.2 | 99.9 |
| | South | 609 | 30.0 (28.1, 32.1) | 106 (95.3, 143) | 31.0 | 76.8 | 546 | 21.9 (20.5, 23.5) | 90.3 (69.8, 111) | 21.9 | 58.7 |
| | West | 808 | 30.1 (28.3, 32.0) | 128 (117, 160) | 29.0 | 96.7 | 904 | 26.9 (25.4, 28.5) | 113 (96.3, 140) | 26.0 | 74.3 |
| | East | 262 | 29.3 (25.7, 33.3) | 148 (110, 207) | 29.3 | 106 | | | | | |
| Urbanisation | Cities | 1,020 | 23.0 (14.2, 37.4) | 101 (67.2, 217) | 23.3 | 73.7 | 579 | 23.9 (19.5, 29.2) | 95.5 (74.2, 121) | 23.5 | 66.2 |
| | Towns | 710 | 28.5 (23.9, 33.9) | 129 (101, 189) | 27.7 | 92.2 | 563 | 25.2 (20.8, 30.7) | 109 (84.6, 133) | 24.1 | 70.9 |
| | Rural areas | 549 | 31.7 (25.9, 38.9) | 139 (115, 159) | 30.6 | 98.0 | 488 | 28.5 (21.2, 38.2) | 141 (89.9, 204) | 26.6 | 77.6 |
| Education | Low | 104 | 21.2 (11.0, 40.9) | 96.7 (53.2, 168) | 23.3 | 63.6 | 127 | 28.4 (20.1, 40.1) | 108 (86.3, 122) | 30.0 | 86.3 |
| | Medium | 707 | 25.4 (16.5, 39.1) | 121 (80.1, 234) | 25.0 | 82.0 | 500 | 26.9 (20.4, 35.5) | 122 (74.5, 214) | 26.1 | 73.2 |
| | High | 1,413 | 27.5 (22.7, 33.4) | 125 (104, 149) | 27.4 | 85.2 | 969 | 24.5 (19.9, 30.1) | 110 (82.8, 132) | 23.0 | 69.4 |

Notes: Unit: volume based (μg/L). Countries per region (Children): North: Denmark, Norway; South: Greece, Italy, Slovenia; West: Belgium, France, Germany, The Netherlands; East: Hungary. Countries per region (Teenagers): North: Norway; South: Greece, Slovenia, Spain; West: Belgium, France, Germany; East: . Urbanisation is classified by the Degree of Urbanisation (DEGURBA). Education is classified by the International Standard Classification of Education (ISCED): Low education (ISCED 0–2), Medium education (ISCED 3–4), High education (ISCED ≥ 5).

For all of these comparisons not only the regional differences, but also the differences in sampling years have to be kept in mind. Some of the differences in concentration can be due to the differing sampling years and known time trends of phthalate/DINCH exposure (Kasper-Sonnenberg et al., 2019; Koch et al., 2017). The respective comparisons of P95 and for adolescents can be found in Supplementary Figs. S1 and S2.

### 3.2. Comparisons between studies and regions

Relative levels for summed phthalate and DINCH metabolites of each study in comparison to the European geometric mean ($GM_{Eu}$) can be found in Fig. 2 for children (top panel) and adolescents (bottom panel). Across all compounds the studies OCC (DK), InAirQ (HU), and SPECIMEn (NL) have on average (mean of the Log2FC of all available substances for each country) the lowest urinary concentrations in children compared to $GM_{Eu}$ (darker blue). OCC, being the only study showing all concentrations for phthalates below the $GM_{Eu}$ indicates a rather rapid phase out of phthalates and use of the substitute DINCH instead. The studies with the highest overall concentration (darker pink) were ESTEBAN (FR), NAC II (IT), and CROME (GR), where the French ESTEBAN study shows almost exclusively levels above the $GM_{Eu}$.

Values of GMs, factor differences between studies, and factor differences with the $GM_{Eu}$ can be seen in Supplementary Fig. 3. On the biomarker concentration level, countries differ from each other by a factor of 2–9. For example, ESTEBAN's children's (FR) concentration in ∑DiNPm was nine times higher than FLEHS's IV (BE) concentration (top panel). The lowest concentrations for children (top panel) are found for ∑DiNPm in 3 x G (BE) with ~20% of the $GM_{Eu}$, and for MEP GMs in OCC (DK) which were about one third of the $GM_{Eu}$. The highest concentrations in children were observed for MBzP in ESTEBAN (France) which was about three times higher than $GM_{Eu}$, and MEP in CROME (GR) and NAC II (IT), and for ∑DiNPm in ESTEBAN (FR) which were all about 2.5 times higher than $GM_{Eu}$. For adolescents, deviations of the studies' urinary concentrations from the $GM_{Eu}$ were smaller than those for children (Fig. 2, bottom panel), and the quantified factor of differences between studies was two to seven. The highest levels compared to the $GM_{Eu}$ were found in ESTEBAN (FR), PCB cohort (SK), and NEB II (NO), and the lowest for FLEHS IV (BE), POLAES (PL), FLEHS IV (BE),

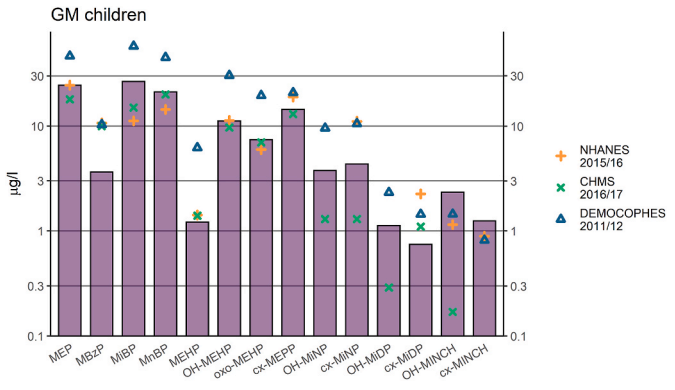


**Fig. 1.** GMs (µg/L) of children (6–11) from HBM4EU Aligned Studies (2014–2021) compared to GMs from comparable age groups in NHANES (2015–2016), CHMS (2016–2017), and DEMOCOPHES (mean of available country GMs, 2011–2012) by phthalate and DINCH metabolites.

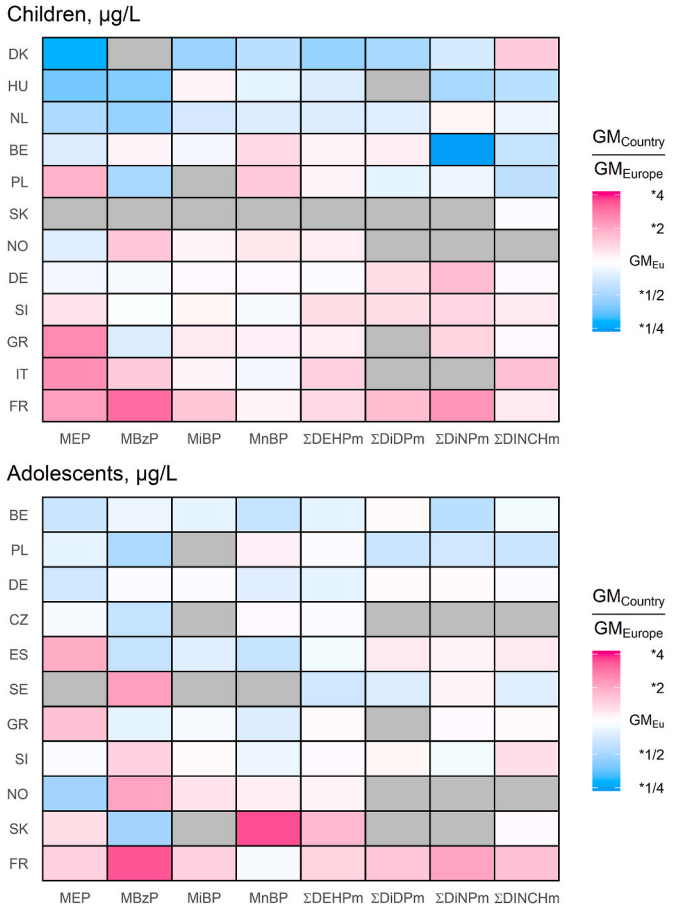


**Fig. 2.** Heatmap of comparisons of each study's GM (µg/L) to the European GMs ($GM_{Eu}$; µg/L; in white). The darker pink cells indicate relatively higher metabolite concentrations of a specific phthalate/DINCH compared to the $GM_{Eu}$ and the darker blue cells indicate relatively lower metabolite concentrations of a specific phthalate/DINCH compared to the $GM_{Eu}$, while the white cells indicate similar metabolite concentrations of a specific phthalate/DINCH in the present study as the $GM_{Eu}$. Grey cells show missing data (e.g. no quality-assured data). ∑DEHPm is the sum of OH-MEHP, oxo-MEHP, and cx-MEPP; ∑DiNPm the sum of OH-MiNP and cx-MiNP; ∑DiDPm the sum of OH-MiDP and cx-MiDP; and ∑DINCHm the sum of OH-MINCH and cx-MINCH. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and GerES V-sub (DE). When looking at compounds separately, ESTEBAN (FR) had more than three times the $GM_{Eu}$ of MBzP, and PCB cohort (SK) and NEB II (NO) had about half of the $GM_{Eu}$ of MBzP and MEP, respectively. Heatmaps showing comparisons based on creatinine-adjusted concentrations are presented in Supplementary Figs. 4 and 5.

Although some subsets of the HBM4EU Aligned Studies were derived from nationally representative studies (ESTEBAN, GerES V), the data collections included here were not necessarily representative of their country (e.g. targeting mostly citizens from cities, distribution of education does not reflect the country's, ESTEBAN and GerES V-sub not weighted to be nationally representative). In addition, up to 300 participants per study make it difficult to balance major demographics even in a single age group and include sufficient and representative variation in participants to be able to draw conclusions for a whole country. Thus, when comparing countries between each other, study characteristics and specifics need to be kept in mind. For more details with respect to participating data collections in HBM4EU aligned studies see Gilles et al. (2022).

A European region could be included when it consisted of at least one data collection. We observed that the effect of the European region was dependent on the substances studied. Fig. 3 shows all pair-wise differences for any two regions in the group of children. Among children, no differences in mean urinary concentrations of MnBP, MiBP, and ∑DEHPm were found between the regions, but regional differences in ∑DiNPm, MBzP, ∑DiDPm, MEP, and ∑DINCHm. For example, for ∑DiNPm, participants from Southern Europe (consisting of studies BEA from Spain, CROME from Greece, and SLO CRP from Slovenia) had higher mean urinary concentrations than those from Eastern (POLAES from Poland) and Northern (Riksmaten adolescents from Sweden) Europe. In addition, participants from Western data collections (ESTEBAN from France, FLEHS IV from Belgium, GerES V-sub from Germany) had higher mean urinary concentrations than participants from the Eastern data collection.

For adolescents (Supplementary Fig. 5), no differences between European regions were found for ∑DEHPm and ∑DINCHm. For MiBP, there was no data for Eastern Europe and only three regions could be compared. For the other sum parameters or metabolites, differences between regions differed by compound.

The example of DiBP exposure in children illustrates that although 2 to 4 studies per region provided data on phthalates, depending on the metabolites, only one study might have contributed to the observed differences for a region (e.g. in Eastern Europe). The composition of a region is important to keep in mind (see Supplementary Tables 1 and 2), also with respect to the degree of representativity participating countries (which in turn are represented by the respective studies). Further requirements for the European regions level such as the required number, characteristics, and representation weight of countries to make a region sufficiently representative might improve the meaning of regional differences. However, with the current practices HBM4EU provides the best basis to compare European regions with the highest level of alignment possible.

For the investigation of differences between European regions in exposure to phthalates and DINCH with GLM analysis only year of sampling emerged as significant covariate for some compounds and was included in the model, sex and education were excluded. Since a separate manuscript on exposure determinants of phthalates and DINCH with HBM4EU Aligned Studies is currently being prepared, we refrain from reporting and going further into the effects of the control variables, including the role of sampling year (Vogel et al., 2023, this issue). The broad time frame of the HBM4EU Aligned Studies (2014–2021) and data collections covering different time and age ranges are confounded with time trends seen in phthalates, suggesting a stricter alignment is needed in future for the comparison of European studies.

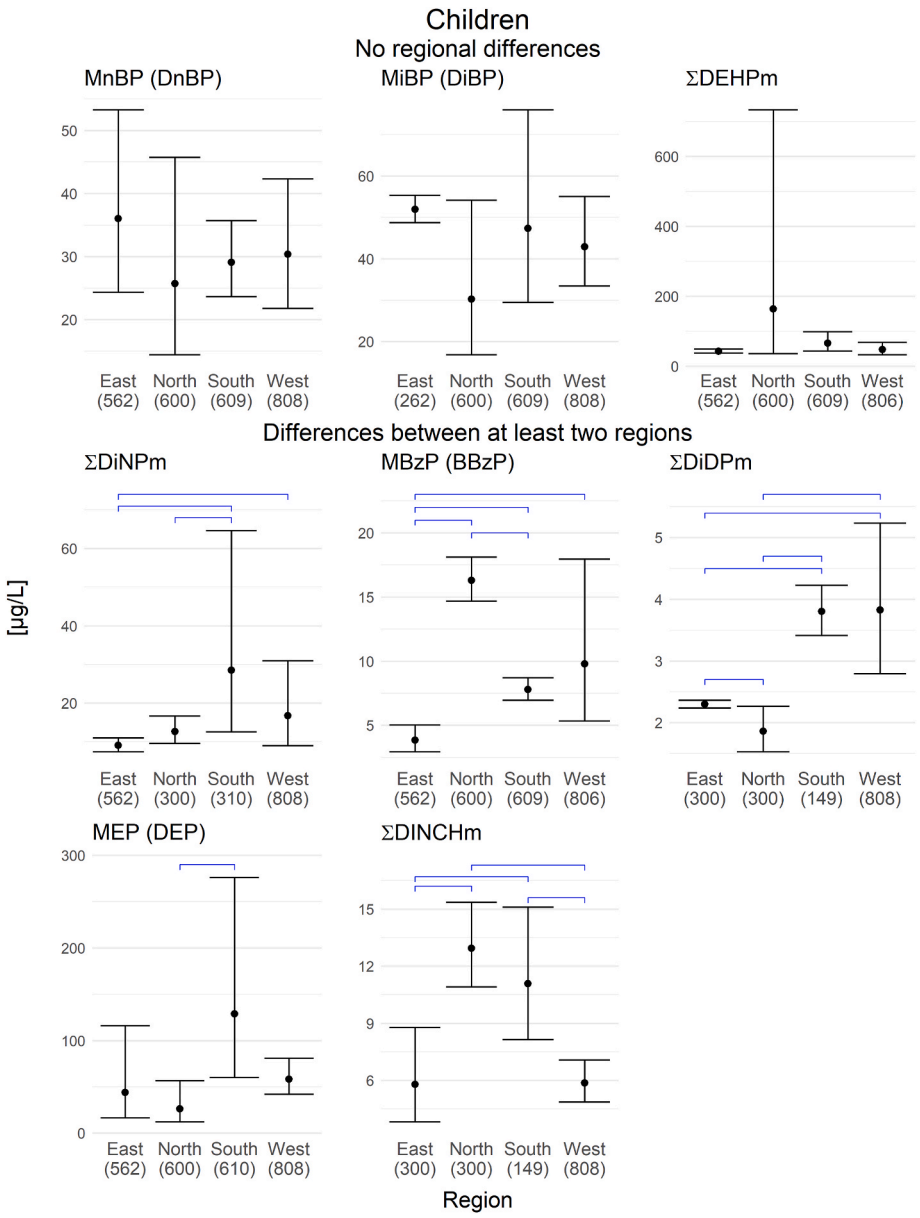


**Fig. 3.** Regional differences in children's data separate by compound. A region was included when it consisted of at least one study. The number below each region denotes the number of participants who provided measures for that compound. Results from GLM models (controlled for sampling year) testing for pair-wise differences. Predicted average and 95% confidence interval are displayed. A blue bracket between two regions indicates significant difference in their concentrations ($p < 0.05$). ∑DEHPm is the sum of OH-MEHP, oxo-MEHP, and cx-MEPP; ∑DiNPm the sum of OH-MiNP and cx-MiNP; ∑DiDPm the sum of OH-MiDP and cx-MiDP; and ∑DINCHm the sum of OH-MINCH and cx-MINCH. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### *3.3. Comparison with human biomonitoring guidance values (HBM-GVs and BE)*

There are different statistical approaches to relate urinary concentrations to HBM-GVs. To investigate exceedance in the highly exposed participants, comparisons of P95 of urinary metabolite concentration in children and respective HBM-$GV_{GenPop}$ as indicators of exposure for DiBP and DINCH can be found in Gerofke et al. (2023, this issue). With respect to individual level data, less than 0.1% of all boys exceeded the respective HBM-GV for BBzP. HBM-GVs for DEHP were exceeded by some studies between 1 and 2% of the study participants while DnBP and DiBP were exceeded more often. No participant exceeded respective values for DEP (not shown) and DINCH. Exceedance rates stratified by sex are presented in Fig. 4. Exceedances per study in each age group regardless of sex can be found in Supplementary Fig. 6. Overall, the number of exceedances were highest for DiBP and DnBP in children (DiBP: n = 72 of 2,277 (3.16%); DnBP (n = 51 of 2,577 (1.98%)) and adolescents (DiBP: n = 35 of 1,631 (2.15%); DnBP: 117 of 2,499 (4.68%)). Two studies from Slovakia and Czech Republic had remarkably high exceedance rates among adolescents: 33% for Slovakian boys and 9% in Czech boys and girls, respectively.

In comparison with exceedances observed in children and their mothers investigated in the DEMOCOPHES study, results are similar. However, only exposure to three phthalates (DEP, DEHP, BBzP) could be compared with HBM-I (DEHP) or BE (DEP, BBzP) values in the DEMOCOPHES study. No exceedances were observed for DEP or BBzP, neither in children nor their mothers, which corresponds to our observations. The HBM-I value used in the DEMOCOPHES study (300 µg/L for mothers, 500 µg/L for children) were exceeded by 12 children (n = 0.6%) and 19 mothers (1%), whereas in our study the percentage of children and adolescents that exceeds HBM-$GV_{GenPop}$ for DEHP are even smaller with 0.28 and 0.25%, respectively, although HBM-$GV_{GenPop}$ are lower than the HBM-I values used in the DEMOCOPHES study. This is in line with on average lower exposure levels found in our study compared to the DEMOCOPHES study. However, caution must be taken to possibly confounding effects of sampling year when comparing the exceedances between these two studies as our data set includes a broad time span (2014–2021). Indeed, the studies in children in which HBM-GVs were exceeded (ESTEBAN in France, NEB II in Norway) sampled in earlier years (2014–2017). However, this is not the case for studies in

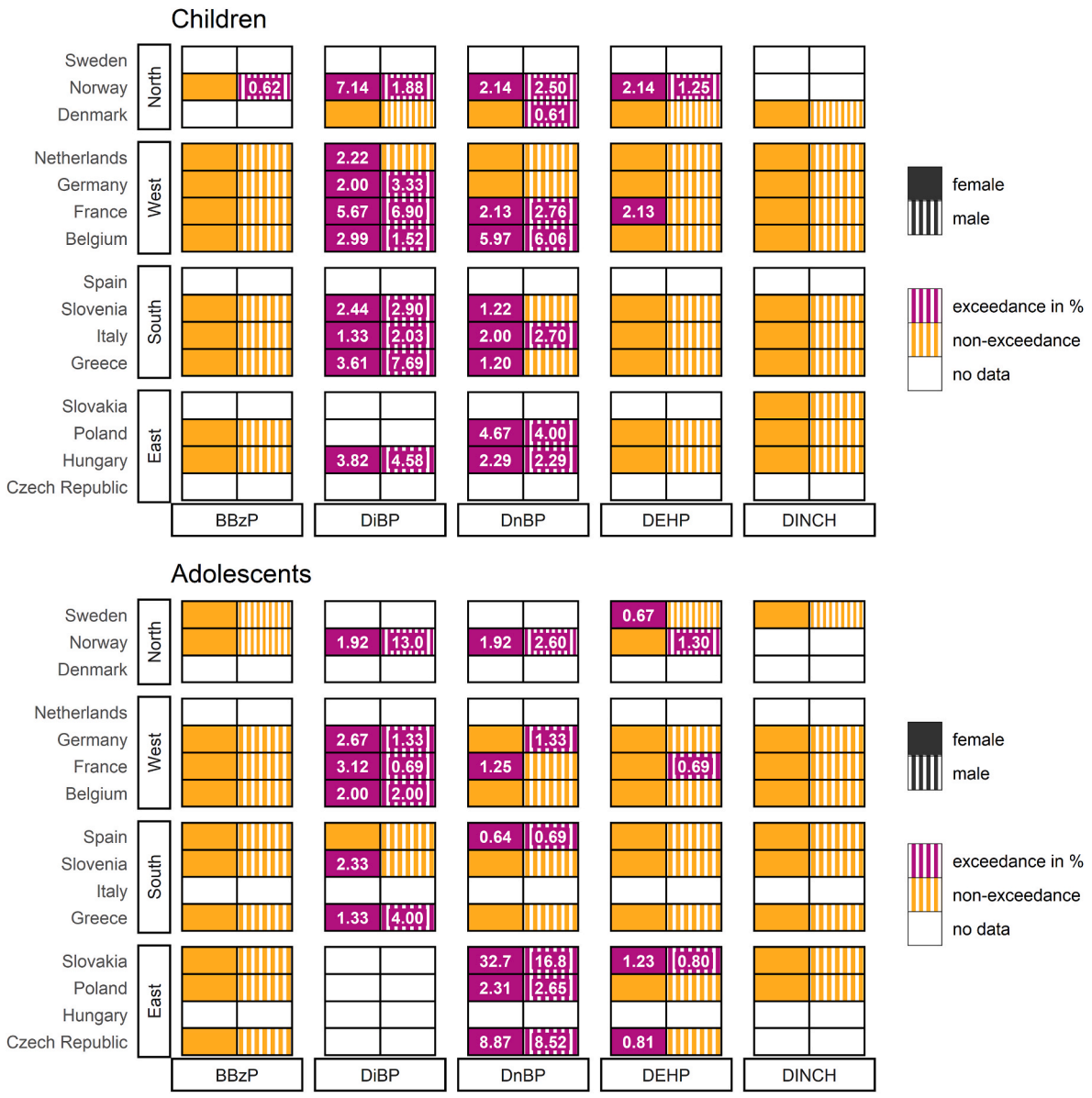


**Fig. 4.** Percentage of individuals exceeding HBM-GVs for four phthalates and DINCH in children (top panel) and adolescents (bottom panel), separately for girls (left column, filled cells) and boys (right column, striped cells). Yellow indicates that no individual exceeded the HBM-GVs in that biomarker. Violet indicates exceedance with the percentage of individuals exceeding HBM-GVs. HBM-GVs used for participants younger than 14 years old: DnBP: 120 μg/L; BBzP: 2,000 μg/L, DiBP: 160 μg/L, ∑DEHPm: 340 or 380 μg/L, depending on available metabolites; for participants older than 13 years: DnBP: 190 μg/L; BBzP: 3,000 μg/L, DiBP: 230 μg/L, ∑DEHPm: 500 or 570 μg/L, depending on available metabolites. Exceedances of BE for the metabolite of DEP not shown as there weren't any. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

adolescents.

## 4. Conclusion

In the HBM4EU Aligned Studies, metabolites of ten phthalates and DINCH were measured in urine samples of children (6–11 years old) and adolescents (12–18 years old) of two to four European countries per European region. We provide exposure levels (GM and P95), for the total of ~5,600 participants and stratified by major demographic characteristics, which can be used to compare concentrations of individuals or sample subgroups to. Our results can be used for regulatory needs, and document success, but also highlight areas of further focus. Compared to 2011/2012 (DEMOCOPHES) we see a successful reduction in exposure but exceedances of HBM-GVs indicate that further efforts are needed. Some issues seem country specific, with higher exposures and exceedances. For example, geometric mean exposure (GM) in adolescents differed slightly more between the studies than did GM in children (i.e. up to a factor of 9 vs a factor of 7), suggesting different usage and/or exposure patterns within the countries. We only covered one substitute plasticizer here (DINCH) and observed increased exposures. Although according to current knowledge currently of no concern, there is a need for further surveillance to follow up increasing time trends and enable intervention, if needed. Also, other substitutes (such as terephthalates or adipates) need to be included in the next surveillance. Even though several phthalates are subjected to strict regulation in Europe a considerable proportion of children and adolescents have exposure levels above the desirable safe level. This underlines the need for a sustainable and permanent HBM system in Europe to follow up if regulatory steps are sufficiently successful. Most exceedances of HBM-GVs were observed for DiBP and DnBP (up to 5%) indicating unacceptable exposure levels of these two substances in European children and adolescents and that further analysis of exposure determinants is needed to

inform on major exposure sources, especially for DnBP and DiBP. In addition, as HBM4EU Aligned Studies included only little data from recent exposure years (2021), more harmonised HBM at EU level is warranted to evaluate the effectiveness of recent phthalate regulation.

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## Declaration of competing interest

The authors declare no conflict of interest related to this work.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2022.114101.

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