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Phthalate metabolites in urine of children and adolescents in Germany. Human biomonitoring results of the German Environmental Survey GerES V, 2014–2017

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ABSTRACT

During the population representative German Environmental Survey of Children and Adolescents (GerES V, 2014–2017) 2256 first-morning void urine samples from 3 to 17 years old children and adolescents were analysed for 21 metabolites of 11 different phthalates (di-methyl phthalate (DMP), di-ethyl phthalate (DEP), butylbenzyl phthalate (BBzP), di-iso-butyl phthalate (DiBP), di-n-butyl phthalate (DnBP), di-cyclohexyl phthalate (DCHP), di-n-pentyl phthalate (DnPeP), di-(2-ethylhexyl) phthalate (DEHP), di-iso-nonyl phthalate (DiNP), di-iso-decyl phthalate (DiDP) and di-n-octyl phthalate (DnOP)).

Metabolites of DMP, DEP, BBzP, DiBP, DnBP, DEHP, DiNP and DiDP were found in 97%–100% of the participants, DCHP and DnPeP in 6%, and DnOP in none of the urine samples. Geometric means (GM) were highest for metabolites of DiBP (MiBP: 26.1 µg/L), DEP (MEP: 25.8 µg/L), DnBP (MnBP: 20.9 µg/L), and DEHP (cx-MEPP: 11.9 µg/L). For all phthalates but DEP, GMs were consistently higher in the 3–5 years old children than in the 14–17 years old adolescents. For DEHP, the age differences were most pronounced. All detectable phthalate biomarker concentrations were positively associated with the levels of the respective phthalate in house dust.

In GerES V we found considerably lower phthalate biomarker levels than in the preceding GerES IV (2003–2006). GMs of biomarker levels in GerES V were only 18% (BBzP), 23% (MnBP), 23% (DEHP), 29% (MiBP) and 57% (DiNP) of those measured a decade earlier in GerES IV.

However, some children and adolescents still exceeded health-based guidance values in the current GerES V. 0.38% of the participants had levels of DnBP, 0.08% levels of DEHP and 0.007% levels of DiNP which were higher than the respective health-based guidance values. Accordingly, for these persons an impact on health cannot be excluded with sufficient certainty.

The ongoing and substantial exposure of vulnerable children and adolescents to many phthalates confirms the need of a continued monitoring of established phthalates, whether regulated or not, as well as of potential substitutes. With this biomonitoring approach we provide a picture of current individual and cumulative exposure developments and body burdens to phthalates, thus providing support for timely and effective chemicals policies and legislation.

1. Introduction

Phthalates (alkyl or aryl esters of phthalic acid) are synthetic organic chemicals with an annual consumption of several million tons worldwide (Micromarket Monitor, 2015). They are used as plasticisers in a variety of industrial applications, as well as in consumer goods and personal care products (Calafat et al., 2015; Koch and Calafat, 2009; Wang et al., 2019). Since phthalates are not chemically bound to the materials to which they are added, they can be found as widespread contaminants in indoor air, house dust and food. Subsequently, humans are primarily exposed to phthalates by ingestion, inhalation and dermal contact (Becker et al., 2009; CDC, 2009; Choi et al., 2017; Den Hond et al., 2015; Heudorf et al., 2007; Koch et al., 2017; Salthammer et al., 2018; Saravanabhavan et al., 2013).

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Abbreviations

BE	biomonitoring equivalent
CAS	Chemical Abstract Service
CHMS	Canadian Health Measures Survey
CI	confidence intervall
EU	European Union
DEMOCOPHES	Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale
ESB	German Environmental Specimen Bank
GerES	German Environmental Survey
GerES IV	German Environmental Survey on Children
GerES V	German Environmental Survey on Children and Adolescents 2014–2017
GM	geometric mean
G-EQUAS	German External Quality Assessment Scheme
HBM	human biomonitoring
HBM-I-value	human biomonitoring value I
HBM4EU	European Human Biomonitoring Initiative
KiGGS Wave 2	German Health Interview and Examination Survey for Children and Adolescents, Wave 2
KoNEHS	Korean National Environmental Health Survey
LOQ	limit of quantification
m	months
N	sample size
NC	not calculated
NHANES	United States National Health and Nutrition Examination Survey
P	percentile
PVC	polyvinyl chloride
REACH	European chemicals legislation concerning the registration, evaluation, authorisation and restriction of chemicals
RfD	reference dose
RKI	Robert Koch-Institute, Germany
SES	socioeconomic status
SVHC	substance of very high concern
TDI	tolerable daily intake
UBA	German Environment Agency
USEPA	United States Environmental Protection Agency
y	years

Several phthalates have shown a variety of adverse health effects in humans and in animals (Koch and Calafat, 2009; Mariana et al., 2016), of which the most prominent are the endocrine disrupting and reprotoxic effects (summarised by Benjamin et al., 2017; Heudorf et al., 2007; Koch et al., 2017; Lioy et al., 2015; Radke et al., 2018). In addition, results of epidemiological studies also suggest associations between phthalate exposure and overweight, insulin resistance, asthma, attention deficit and attention deficit hyperactivity disorder (Engel et al., 2010; Franken et al., 2017; Hatch et al., 2010; Wang et al., 2015).

Because of their reproductive toxicity butylbenzyl phthalate (BBzP), di-iso-butyl phthalate (DiBP), di-n-butyl phthalate (DnBP), di-(2-ethylhexyl) phthalate (DEHP), di-cyclohexyl phthalate (DCHP), and di-n-pentyl phthalate (DnPeP) were classified as substances of very high concern (SVHC) and therefore included in the candidate list of SVHC for authorisation under the European chemical regulation REACH (registration, evaluation, authorisation and restriction of chemicals) (Annex XIV, EC, 1907/2006) (EU, 2006). DEHP, BBzP, DiBP, DnBP and in future DnPeP must not be used within the European Union (EU) without authorisation. Further restrictions for these substances will be implemented in July 2020 (EU, 2018). In addition, di-iso-nonyl phthalate (DiNP), di-iso-decyl phthalate (DiDP) and di-n-octyl phthalate (DnOP) are also restricted to different degrees in children's toys and childcare articles (Annex XVII EC, 1907/2006) (EU, 2006). Several phthalates are also restricted in cosmetics products (EC/1223/2009) (EU, 2009) and in materials intended to come into contact with food (EC/10/2011) (EU, 2011). Similarly, use restrictions, authorisation obligations, and bans were enacted also by the United States (CPSC, 2014) and Canada (Health Canada, 2016).

First human biomonitoring (HBM) studies on phthalates revealed that the general population is ubiquitously and simultaneously exposed to several phthalates (Blount et al., 2000; Koch et al., 2003b; Silva et al., 2004). Since then, phthalates are routinely determined in many HBM studies and national HBM programmes for example in the United States National Health and Nutrition Examination Survey (NHANES) (Calafat, 2012; CDC, 2019), the Canadian Health Measures Survey (CHMS) (Haines et al., 2017), the Korean National Environmental Health Survey (KoNEHS) (Choi et al., 2017), the German Environment Survey (GerES) (Kolossa-Gehring et al., 2012b), and the European DEMOCOPHES Study (Demonstration of a Study to Coordinate and Perform Human Biomonitoring on an European Scale) (Den Hond et al., 2015). The DEMOCOPHES succeeding European Human Biomonitoring Initiative HBM4EU (www.hbm4eu.eu), which is coordinating human biomonitoring in Europe in order to support policy making (Ganzleben et al., 2017), identified phthalates as substances of priority interest for which various policy relevant questions have to be answered by tailored research.

In Germany, urinary phthalate measurements have been carried out in local studies (Kasper-Sonnenberg et al., 2012, 2014; Koch et al., 2011) as well as in the German Environmental Survey on Children, GerES IV (Becker et al., 2004, 2009; Koch et al., 2007a; Schulz et al., 2012; Wittassek et al., 2007) and the German Environmental Specimen Bank (ESB) (Koch et al., 2017; Kolossa-Gehring et al., 2012a).

GerES is part of a health-related environmental surveillance system in Germany (Kolossa-Gehring et al., 2012a, 2012b). The main instruments of GerES are HBM, ambient monitoring of drinking water, house dust, indoor air, noise, and the collection of information on exposure via questionnaires. The target population of GerES V (German Environmental Survey on Children and Adolescents), carried out between 2014 and 2017, were participants aged 3–17 years (Schulz et al., 2017).

In the present paper we describe the urinary levels of 21 phthalate metabolites of 11 parent phthalates in children and adolescents in Germany in a population representative sample, and the associations with some potential predictors of exposure. We compare the results with those of the preceding GerES IV. Our data are used as a basis to calculate and update reference values for these chemicals in Germany. The results also contribute to the overarching goal of HBM4EU to gain current HBM data on the exposure of the European population to chemicals of concern in order to enhance chemical safety.

2. Material and methods

2.1. Study population and sample collection

From January 2015 to June 2017, a population representative sample was recruited in GerES V, which was conducted in close cooperation with the German Health Interview and Examination Survey for Children and Adolescents (KiGGS Wave 2) of the Robert Koch-Institute (RKI) (Mauz et al., 2017). RKI recruited a population representative sample in 167 sampling locations in Germany (Kamtsiuris et al., 2007; Kurth et al., 2008). Out of these, the 3–17 years old GerES V participants were randomly selected as a subsample in the course of the KiGGS Wave 2 examination (Mauz et al., 2017).

In GerES V various environmental contaminants were measured in blood, morning urine, tap water, indoor air and house dust samples. Additionally, questionnaires were used to obtain information on exposure relevant conditions, habits, and behaviors of the participants

(Schulz et al., 2017).

A visit at the homes of the participants was the essential component of the GerES V fieldwork. Kantar Health Munich conducted the fieldwork on behalf of the German Environment Agency (UBA). During the home visits, the fieldworkers inter alia received first void urine, collected dust bags in a subsample of the participants, and conducted interviews either with the participants or their parents.

The first void urine samples were taken either in polypropylene vessels or in narrow-necked polyethylene containers, depending on sex and age of the participant. The samples were kept cold, aliquoted in polypropylene tubes, frozen at the same day, and kept frozen (−20 °C) until analysis. None of the pretested containers had detectable levels of the investigated phthalate metabolites. Samples were analysed in a randomised sequence to avoid observer bias.

The project was approved by the Ethics Committee of the Berlin Chamber of Physicians (Eth-14/14) and the Federal Officer for Data Protection and Freedom of Information (III-425/009#0018).

2.2. Chemical analysis

Analysis of phthalate metabolites in urine was performed by the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance at the Ruhr-University Bochum, Germany. It was executed by on-line high performance liquid chromatography coupled to tandem mass spectrometry, using internal isotope-labelled standards according to previously published methods (Koch et al., 2003a, 2007b, 2012, 2017; Preuss et al., 2005). Creatinine of the urine samples was quantified by the Analytisch-Biologisches Forschungslabor München, Germany, using the Jaffé method (Blaszkiewicz and Liesenhoff-Henze, 2010).

Internal quality control measures for phthalate metabolites were performed throughout the entire period by analysing control urines with known concentrations. These quality control samples were always measured within the ± 3σ range. Additionally, blinded repeated measurements of samples in different analytical cycles always resulted in concentrations within the range of the respective confidence intervals and no metabolite was ever determined in field blanks. The quality of determined creatinine was confirmed by similar internal quality control measures. External quality assurance was confirmed within regular, biannual participation in ring trial program of the German External Quality Assessment Scheme (G-EQUAS) for creatinine, for the metabolites of DEHP, as well as for MnBP, MiBP and MBzP. For the other analytes no external quality assurance was offered. The limits of quantification (LOQ), and the Chemical Abstract Service (CAS) numbers of the measured phthalate metabolites are listed in Table 1.

For phthalate analyses in house dust, the 63 µm dust fraction was analysed with gas or liquid chromatography/mass spectrometry based on Nagorka et al. (2011). The Fraunhofer Institute for Process Engineering and Packaging IVV, Freising, Germany seived and extracted the dust samples either with toluene for gas chromatography or with acetonitrile for liquid chromatography. Quality controls were carried out with inter-laboratory comparisons and constant cross-control measurements of DEHP with gas and liquid chromatography.

2.3. Statistical analysis

In order to adjust the collected sample of GerES V with data from the official demographic statistics of the German population from 2013 to 2015 (Microzensus, 2019), weighting variables based on the key variables age, sex, community size and region were calculated by the RKI (Hoffmann et al., 2018). Subsequently, weighted samples were used in all statistical evaluations whereby the sample and subsample characteristics were calculated from the respective case weighted samples.

Characteristics of the urinary phthalate metabolite distributions were calculated (sample size (N), percentage above the LOQ of the respective phthalate metabolite as listed in Table 1 (% > LOQ), geometric mean (GM), confidence intervals (CI) and percentiles (P)). Additionally, weight sums of metabolites were built for the individual phthalates, e.g. Σ(MiBP + OH-MiBP) for DiBP and Σ(MEHP + OH-MEHP + oxo-MEHP + cx-MEPP) for DEHP. Volume-based as well as creatinine-adjusted concentrations were presented. Concentrations below the LOQ of the respective analytical method were assigned a value equal to half of the LOQ for calculation purposes. Due to the skewed (approximately log-normal) distribution of the metabolite concentrations, GM is a parameter more suitable for assessment than the arithmetic mean.

In the basic evaluation the urinary biomarker levels were described for the total sample as well as for the standard stratification variables: sex, age group, community size, socioeconomic status, region of residence in former East or West Germany, and migration background. In addition, urinary levels for subgroups of substance-specific variables were also described, which are suspected either by scientific knowledge or by biological plausibility to be associated with the metabolite

Table 1
Phthalates measured in GerES V. Parent substances, CAS numbers, metabolites measured, and the respective limits of quantification (LOQ).

Phthalate	Name of parent substance	CAS Number	Metabolite	Name of metabolite	LOQ (µg/L)
DMP	**Di-methyl phthalate**	131-11-3	MMP	Mono-methyl phthalate	1.0
DEP	**Di-ethyl phthalate**	84-66-2	MEP	Mono-ethyl phthalate	0.5
BBzP	**Butylbenzyl phthalate**	85-68-7	MBzP	Mono-benzyl phthalate	0.2
DiBP	**Di-iso-butyl phthalate**	84-69-5	MiBP	Mono-iso-butyl phthalate	1.0
			OH-MiBP	Mono-hydroxy-iso-butyl phthalate	0.25
DnBP	**Di-n-butyl phthalate**	84-74-2	MnBP	Mono-n-butyl phthalate	1.0
			OH–MnBP	Mono-hydroxy-n-butyl phthalate	0.25
DCHP	**Di-cyclohexyl phthalate**	84-61-7	MCHP	Mono-cyclohexyl phthalate	0.2
DnPeP	**Di-n-pentyl phthalate**	131-18-0	MnPeP	Mono-n-pentyl phthalate	0.2
DEHP	**Di-(2-ethylhexyl) phthalate**	117-81-7	MEHP	Mono(2-ethylhexyl) phthalate	0.5
			OH-MEHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate	0.2
			oxo-MEHP	Mono(2-ethyl-5-oxohexyl) phthalate	0.2
			cx-MEPP	Mono(2-ethyl-5-carboxypentyl) phthalate	0.2
DiNP	**Di-iso-nonyl phthalate**	28553-12-0;	OH-MiNP	Mono(4-methyl-7-hydroxyoctyl) phthalate	0.2
		68515-48-0	oxo-MiNP	Mono(4-methyl-7-oxooctyl) phthalate	0.2
			cx-MiNP	Mono(4-methyl-7-carboxyheptyl) phthalate	0.2
DiDP	**Di-iso-decyl phthalate**	26761-40-0;	OH-MiDP	Mono-hydroxy-isodecyl phthalate	0.2
		68515-49-1	oxo-MiDP	Mono-oxo-iso-decyl phthalate	0.2
			cx-MiDP	Mono(2,7-methyl-7carboxy-heptyl) phthalate	0.2
DnOP	**Di-n-octyl phthalate**	117-84-0	MnOP	Mono-n-octyl phthalate	0.2
Various			MCPP[a]	Mono(3-carboxypropyl) phthalate	0.5

[a] Metabolite of several phthalates (currently known: DnBP, DnPeP, DnOP, DiNP, DiDP).

concentrations: carpets with or without plastic backing or underlay, polyvinylchloride (PVC) flooring, wearing of plastic or rubber shoes without socks, habit of chewing on plastic objects, consumption of fast food or ready meals before urine sampling, and concentration of the specific phthalate in the house dust. Excepting phthalate concentration in house dust, all stratification variables were collected by questionnaires. Phthalate levels in house dust were chemically quantified. Bivariate statistical analyses were performed for each variable selected for stratification and when at least 50% of the measured concentrations were equal or above LOQ. Thereby differences of the GM of the subgroups were tested for significance by one-way ANOVA, based on log-transformed data. Significance levels of $p \leq 0.05$ (*), $p \leq 0.01$ (**), and $p \leq 0.001$ (***) were marked for any differences within the categories of the stratification variables.

No significance tests were applied for MCHP, MnPeP and MnOP as they were only detected in very low frequency.

All statistical analyses were performed with the SPSS statistical package (versions 20 and 25).

3. Results and discussion

In GerES V, 2294 children and adolescents participated with complete data, amounting to 75.7% of the eligible persons. From those, 2256 provided sufficient urine volume to determine phthalate metabolite concentrations. Due to chromatographic interferences, some phthalate metabolites could not be determined quantitatively in all samples, resulting in 2247–2256 datasets available for individual phthalate biomarkers. The characteristics of the weighted study population as well as the distribution of several variables, which might be associated with the exposure to phthalates, are shown in Table 2. As the study population was adjusted for the key variables age, sex, community size and region by weighting variables, it can be concluded that the phthalate metabolites were determined in samples representing the 3–17 years old population in Germany.

3.1. Urinary concentrations

Table 3 summarises descriptive statistics for urinary levels of the 21 phthalate metabolites measured. We found metabolites of DMP, DEP, BBzP, DiBP, DnBP, DEHP, DiNP and DiDP at levels > LOQ in 97–100% of the participants' urine samples. In contrast, only 6% of the participants had DCHP and DnPeP and none had DnOP biomarker concentrations > LOQ. The simultaneous detection of DEP, BBzP, DiBP, DnBP, DEHP, DiNP metabolites in almost all urine samples are in line with the results in GerES IV, ESB, NHANES, CHMS, KoNEHS and DEMOCOPHES, where metabolites of these phthalates, when analysed, were also found in almost all urine samples (Becker et al., 2009; Choi et al., 2017; Den Hond et al., 2015; Haines et al., 2017; Koch et al., 2017; Zota et al., 2014). The only exceptions were DMP and DiNP, which were detected in CHMS (2007–2011) less frequently (DMP) or even not at all (DiNP) (Haines et al., 2017). However, this may be due to the higher limits of detection in CHMS.

The highest urinary metabolite concentration was found for MiBP with a GM of 26.1 µg/L urine, followed by MEP (GM of 25.8 µg/L urine), MnBP (GM of 20.9 µg/L urine) and cx-MEPP (GM of 11.9 µg/L urine). Lower concentrations were found for OH-MiNP (GM of 6.9 µg/L urine), MMP (GM of 6.4 µg/L urine), MBzP (GM of 3.1 µg/L urine), and OH-MiDP (GM of 1.5 µg/L urine). Taking the sums of biomarkers for each phthalate, the ranking order of measurable GMs was DiBP > DEHP > DEP > DnBP > DiNP > DMP > DiDP > BBzP. A direct comparison between urinary metabolite levels in terms of exposure to the respective phthalate however is not possible, as urinary excretion fractions differ considerably between the different phthalates and their metabolites. To extrapolate exposure from urinary concentration, urinary metabolite conversion factors, daily urine volume and other anthropometric factors are necessary (Koch et al., 2017).

Table 2
Characterization of the weighted study population for phthalates in GerES V and frequency of various environmental factors, suspected to be related with phthalate exposure.

	N (%)
Children and adolescent	**2256**
Sex	
boys	1164 (52)
girls	1092 (48)
Age group	
3–5 years	402 (18)
6–10 years	736 (33)
11–13 years	457 (20)
14–17 years	662 (29)
Community size	
< 50,000 inhabitants	593 (26)
50,000 - ≤100,000 inhabitants	143 (6)
≥100,000 inhabitants	1520 (67)
Socio-economic status[a]	
low	465 (21)
medium	1320 (58)
high	405 (18)
Region of residence	
West Germany (including West Berlin)	1898 (84)
East Germany (including East Berlin)	358 (16)
Migration background[b]	
no migration background	1561 (69)
one-sided migration background[c]	230 (10)
two-sided migration background[d]	416 (18)
Carpets, carpet tiles, rugs [e]	
with plastic underlay	912 (40)
without underlay	1115 (49)
PVC flooring	
yes	588 (26)
no	1665 (74)
Wearing of plastic or rubber shoes without socks in summer	
yes	1119 (50)
no	1137 (50)
Habit of chewing on plastic objects	
yes	570 (25)
no	1684 (75)
Consumption of fast food or convenience food before urine sampling	
1 day before	506 (22)
2 days before	332 (15)
more than 2 days/never before	1400 (62)
Phthalate level in house dust	
categorized as low, medium, high [f]	various [g]

Note: Due to rounding to nearest whole numbers, the sum of stratified sample sizes not always exactly corresponds to the total sample size. Further differences are due to missing values in stratification criteria.

[a] Socioeconomic status was generated from the dimensions education, occupation and income as provided by the parents. Low, middle or high socioeconomic status were classified as the first (low), second to fourth (medium) or fifth (high) quintile of an index, built by the equally weighted subscales of education, occupation and income (Lampert et al., 2018).

[b] Migration background was based on the country of birth of the child or adolescent and the parents and of the parents' nationality.

[c] One-sided migration background: defined as having one parent not born in Germany or without German citizenship.

[d] Two-sided migration background: includes children and adolescents who themselves migrated to Germany and have at least one parent who was not born in Germany. Children and adolescents belong also to this group, when both parents were born in a country other than Germany or when they are non-German nationals (Frank et al., 2018).

[e] Participants who reported to have no carpets at all were filtered (N = 229).

[f] Categories of low, medium and high phthalate levels were chosen to comprise approximately one third of the participants each. The limits for the medium categories were for: DMP: 0.41–0.48 µg/g, DEP: 0.47–0.83 µg/g, BBzP: 1.67–5.10 µg/g, DiBP: 5.7–11.3 µg/g, DnBP: 5.1–10.5 µg/g, DCHP 1.4–2.7 µg/g, DEHP 108–212 µg/g, DiNP: 135–402 µg/g, DiDP: 19.5–41.0 µg/g. Low levels were below, high levels were above these values for the respective phthalate.

[g] Phthalate levels in house dust were determined in a subsample of 639–646 participants. For N for the specific phthalate see Table 4 and Supplementary Tables 1–50.

Table 3
Phthalates measured in GerES V. Frequency of quantification, percentiles, maximum, arithmetic mean and geometric mean with 95 %-confidence interval of urinary metabolite levels (in µg/L) of the GerES V participants.

Phthalate	Metabolite	N	% ≥ LOQ	P10	P50	P90	P95	GM	95 %CI GM
DMP	MMP	2256	97	1.9	5.9	23.1	43.2	6.4	6.1–6.7
DEP	MEP	2256	100	7.0	23.1	113	219	25.8	24.6–27.0
BBzP	MBzP	2256	99	0.9	2.9	11.2	18.7	3.1	2.9 - 3.2
DiBP	MiBP	2256	100	9.4	26.2	75.0	110	26.1	25.2–27.0
	OH-MiBP	2256	100	3.1	8.8	26.9	37.5	8.9	8.6–9.3
	Σ MiBP + OH-MiBP			12.7	35.4	100	150	35.3	34.1–36.5
DnBP	MnBP	2256	100	8.3	21.0	53.5	69.6	20.9	20.3–21.6
	OH–MnBP	2256	99	0.8	2.5	6.3	8.5	2.4	2.3 - 2.5
	Σ MnBP + OH–MnBP			9.2	23.4	59.6	77.0	23.4	22.7–24.2
DCHP	MCHP	2256	6	< LOQ	< LOQ	< LOQ	0.3	< LOQ	
DnPeP	MnPeP	2255	6	< LOQ	< LOQ	< LOQ	0.2	< LOQ	
DEHP	MEHP	2256	86	< LOQ	1.5	4.7	6.7	1.4	1.4 - 1.5
	OH-MEHP	2256	100	4.3	11.1	29.1	40.9	11.0	10.6–11.4
	oxo-MEHP	2253	100	2.7	7.7	21.5	29.0	7.6	7.3–7.8
	cx-MEPP	2256	100	4.4	12.0	34.0	46.1	11.9	11.5–12.3
	Σ OH- + oxo-MEHP	2253		7.1	18.8	49.0	70.2	18.6	18.0–19.3
	Σ MEHP + OH-MEHP + oxo-MEHP + cx-MEPP			12.4	32.4	86.9	123	32.5	31.5–33.6
DiNP	OH-MiNP	2249	100	2.4	6.9	19.7	30.2	6.9	6.7–7.2
	oxo-MiNP	2256	99	0.9	2.7	8.6	14.2	2.8	2.7 - 2.9
	cx-MiNP	2250	100	1.9	5.4	19.0	30.2	5.9	5.6–6.1
	Σ OH-MiNP + oxo-MiNP + cx-MiNP			5.5	15.7	47.1	71.9	16.0	15.4–16.6
DiDP	OH-MiDP	2256	98	0.5	1.5	4.9	7.5	1.5	1.5 - 1.6
	oxo-MiDP	2256	88	< LOQ	0.7	2.3	3.6	0.6	0.6 - 0.7
	cx-MiDP	2256	97	0.3	0.9	2.6	4.2	0.9	0.9 - 0.9
	Σ OH-MiDP + oxo-MiDP + cx-MiDP			1.0	3.1	9.6	16.0	3.2	3.1–3.3
DnOP	MnOP	2256	0	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	
Various	MCPP	2256	92	0.5	1.4	4.1	6.4	1.5	1.4 - 1.5

Abbreviations: N: sample size, LOQ: limit of quantification, P10, P50, P90. P95: percentiles, GM: geometric mean, 95% CI GM: 95% confidence interval for GM. Values below LOQ were set LOQ/2 for calculation purposes. No 95% CI GM is given if GM < LOQ.

The urinary concentrations of phthalate metabolites were also evaluated for the subgroups illustrated in Table 2. In Table 4 we exemplarily show the distributions and statistical parameters for the phthalate metabolite MiBP. The tables for all other metabolites and metabolite sums are compiled in Supplementary Tables 1–26 in µg/L urine and in Supplementary Tables 27–50 in µg/g creatinine.

The most striking result of the bivariate analyses was the age dependence of urinary phthalate metabolite concentration. The GMs of MBzP and the sums of DiBP, DnBP, DEHP DiNP and DiDP urinary metabolite levels, constantly decreased with age, being highest for the 3–5 years old and lowest for the 14–17 years old participants. MEP showed an opposite age effect, the GMs of MEP levels increased with age. As MCHP, MnPeP and MnOP were only detected sporadically, no subgroup differences became apparent. The GMs of phthalate urine levels of 3–5 years old children and 14–17 years old adolescents are illustrated in Fig. 1. Excepting DEP (i.e. MEP), the proportions of GMs of the 3–5 compared to the 14–17 years old participants varied between about 1.3-fold for DMP to about 1.9-fold for DEHP.

No consistent picture can be drawn from the additional socioeconomic and geographic variables suspected to be associated with phthalate exposure. Sex differences were found for some phthalate metabolites, mainly when comparing creatinine-adjusted levels (Supplementary Tables 27–50). Whereas boys had a higher GM for MMP, higher GMs for girls were found for MEP, MnBP, DiNP and DiDP metabolites. Socioeconomic status (SES) was associated with MMP, MEP, MBzP as well as with DiBP, DEHP, and DiNP metabolite levels in urine (see Supplementary Tables 1-3, 5, 16, 20). Whereas GMs of MMP increased with increasing SES, GMs of MEP, MBzP, DiBP, DEHP, and DiNP metabolites were conversely associated and declined with increasing SES. Migration background was associated with higher GMs of MEP, DEHP, and DiNP metabolite concentrations (Supplementary Tables 2, 16, 20). For MBzP GMs of urinary levels also differed with community size (Supplementary Table 3), being smaller in larger communities. Participants living in former East Germany had higher GMs of MMP, DiBP, and DnBP metabolite levels than participants living in former West Germany (Supplementary Tables 1, 5, 8).

When considering variables of living environment and habits, high phthalate concentrations in house dust were associated with the respective phthalate metabolite levels in urine (see Fig. 2 and Supplementary Tables 1-3, 5, 8, 16, 20, 24). With high phthalate concentration in house dust, the participants had 1.6- to 2.0-fold higher GMs of urinary MMP, MEP, MBzP, and DiBP metabolites and 1.2- to 1.3-fold higher GMs of urinary DEHP, DiNP, and DiDP metabolites than with low concentrations of the respective phthalate in house dust. Moreover, PVC flooring and carpets with plastic underlay were mostly positively associated with phthalate concentrations, namely with MMP, MBzP, DnBP, DEHP, and DiNP metabolites, either volume- or creatinine-adjusted or both (Supplementary Tables 1, 3, 8, 16, 20, 27, 29, 35, 41, 45). Levels of DiDP metabolites were only associated with plastic carpet underlays, but not with PVC flooring (see Supplementary Tables 24 and 49). MEP levels were not associated with PVC flooring, which is probably due to its main use in personal care products. Surprisingly, MEP levels were positively associated with plastic underlays (Supplementary Tables 2 and 28). For many phthalate concentrations, positive associations were also found with the habit of chewing on plastic objects, the consumption of fast or convenience food, and wearing of plastic or rubber shoes. These associations, however, were not coherent and could not be substantiated when adjusted for age.

The age dependency of urinary phthalate metabolite levels as revealed in GerES V can be found in many studies (for example Becker

Table 4
Urinary levels of MiBP in subpopulations of the GerES V participants in µg/L urine.

	N	% > LOQ	P10	P50	P90	P95	GM	95% CI GM
Total	2256	100	9.4	26.2	75.0	110	26.1	25.2–27.0
Sex								
boys	1164	100	9.5	26.2	83.6	115	26.3	25.0–27.6
girls	1092	100	9.1	25.9	72.9	104	25.9	24.6–27.1
Age group***								
3–5 years	402	100	10.9	29.5	93.7	143	30.4	27.9–33.2
6–10 years	736	100	10.8	28.8	72.5	122	28.9	27.3–30.5
11–13 years	457	100	8.9	22.7	74.4	114	23.9	22.1–25.8
14–17 years	662	100	8.3	22.2	66.0	88.1	22.5	21.2–24.0
Community size (inhabitants)*								
< 50,000	593	100	9.7	24.5	65.4	100	25.1	23.5–26.7
50,000 - < 100,000	143	100	10.8	31.8	95.1	231	31.4	27.1–36.4
≥100,000	1520	100	9.1	26.2	77.6	110	26.0	24.9–27.1
Socioeconomic status*								
low	465	100	9.5	29.2	75.4	114	28.1	26.1–30.3
medium	1320	100	9.1	25.0	79.3	113	26.0	24.8–27.2
high	405	100	9.7	23.7	62.5	84.7	23.8	22.1–25.6
Region of residence**								
West Germany (including West Berlin)	1898	100	9.1	25.4	74.6	110	25.4	24.5–26.4
East Germany (including East Berlin)	358	100	11.5	29.7	79.0	120	29.6	27.2–32.3
Migration background***								
no migration background	1561	100	9.4	24.9	70.4	100	25.2	24.2–26.3
one-sided migration background	230	100	7.9	27.9	66.2	86.1	25.1	22.7–27.7
two-sided migration background	416	100	11.2	29.9	110	136	30.1	27.5–33.0
Carpets, carpet tiles, rugs								
with plastic underlay	912	100	9.5	27.7	80.6	113	27.0	25.6–28.6
without plastic underlay	1115	100	9.8	26.1	74.6	108	26.3	25.0–27.6
PVC flooring***								
yes	588	100	11.4	29.6	101	141	31.4	29.3–33.7
no	1665	100	9.1	24.4	69.5	95.6	24.4	23.5–25.4
Wearing of plastic or rubber shoes without socks in summer***								
yes	1119	100	8.5	24.9	69.1	107	24.6	23.4–25.8
no	1137	100	9.7	27.0	77.5	113	27.6	26.3–29.0
Habit of chewing on plastic objects*								
yes	570	100	9.7	27.8	82.8	129	28.1	26.2–30.2
no	1684	100	9.4	25.2	71.6	105	25.4	24.4–26.4
Consumption of fast food or convenience food before urine sampling								
1 day before	506	100	9.5	25.6	69.4	127	25.3	23.5–27.2
2 days before	332	100	8.5	28.1	68.2	110	26.7	24.4–29.1
more than 2 days/never before	1400	100	9.4	25.9	78.7	109	26.3	25.2–27.5
House dust levels of DiBP***								
low	188	100	7.1	16.4	43.5	58.5	17.2	15.6–19.1
medium	193	100	12.2	25.9	69.2	105	26.9	24.3–29.8
high	248	100	13.2	32.1	84.5	109	32.4	29.6–35.6

For abbreviations see Table 3. For description of subpopulations see Table 2. Variant sample sizes and sums of sample sizes are due to rounding strategy, filtering and missing values.
Significance test: One-way ANOVA (differences of GM). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. Significance levels mean differences within any of the categories of the respective variable.

et al., 2009; Correia-Sa et al., 2018; Gari et al., 2019; Kasper-Sonnenberg et al., 2014; Wittassek et al., 2007). Likewise, higher phthalate metabolite levels are reported for children when directly compared to adults, the only exception being MEP (CDC, 2019; Den Hond et al., 2015; Schwedler et al., 2017; Zota et al., 2014). This is probably due to a higher food consumption related to body weight of young children, but also to other characteristics such as mouthing habits, or increased dust intake by playing near the ground. The clearly higher burden of young children compared to adolescents and adults and the simultaneous presence of the various phthalate metabolites must be considered when assessing exposure burden.

There are no consistent results for the exposure factors sex and SES in the literature. Only MEP urinary levels were constantly higher in girls than in boys (CDC, 2019; Correia-Sa et al., 2018; Gari et al., 2019; Saravanabhavan et al., 2013). Associations of higher SES with lower urinary levels of MBzP were also found by Gari et al. (2019) in a Polish study, and by Kobrosly et al. (2012) in the NHANES population of 2001–2008. Associations of SES with other phthalate metabolite levels were inconsistent.

House dust levels of the respective phthalate were not associated with the urinary phthalate metabolite concentrations in earlier studies (Becker et al., 2004). However, in more recent studies, school dust (Larsson et al., 2017) and PVC materials at home (Den Hond et al., 2015; Koppen et al., 2019; Schwedler et al., 2017) indeed were associated with urinary phthalate metabolite concentrations, underlining the relevance of the exposure pathways via house dust and indoor air for several phthalates.

A strength of the study is the robust sampling design and the application of sampling weights in the analyses ensuring that the results are representative of the respective population. However, the single urine sample per participant and the cross-sectional study design limits the analyses of associations of urinary phthalate levels and potential predictors of exposure.

3.2. Comparison with results of GerES IV

Phthalates were also measured in GerES IV in 3–14 years old children. This allows comparison of the average urinary phthalate metabolite concentrations between GerES V and GerES IV for this age group (Fig. 3). The GMs of all phthalate metabolite levels measured in both

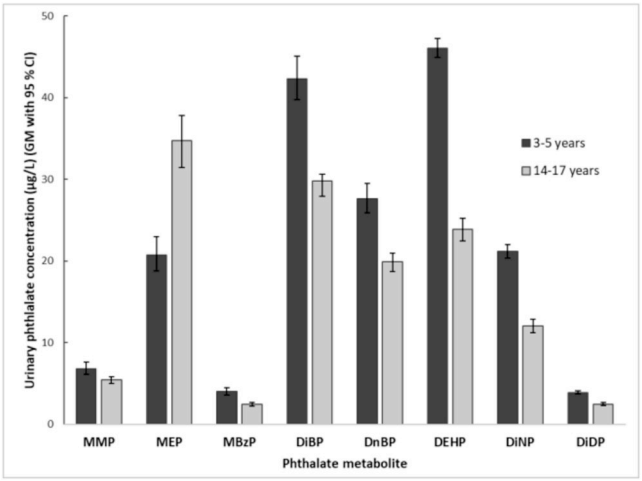

Fig. 1. Urinary phthalate concentrations in younger (3–5 years) and older (14–17 years) GerES V participants.
MMP, MEP and MBzP are the metabolites of DMP, DEP and BzPB, respectively. DIBP, DnBP, DEHP, DiNP, and DiDP are expressed as sums of the following metabolites: DiBP (Σ MiBP + OH-MiBP), DnBP (Σ MnBP + OH–MnBP), DEHP (Σ MEHP + OH-MEHP + oxo-MEHP + cx-MEPP), DiNP (Σ OH-MiNP + oxo-MiNP + cx-MiNP), DiDP (Σ OH-MiDP + oxo-MiDP + cx-MiDP). Details on all age groups are given in the Supplementary Tables 1-3, 5, 8, 16, 20, and 24.

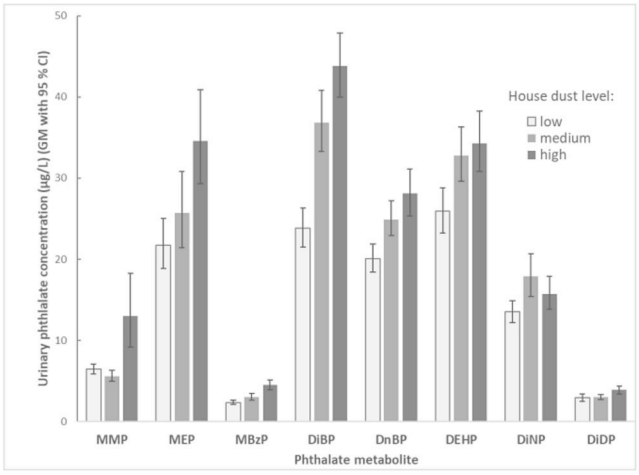

Fig. 2. Urinary phthalate concentrations in association with the respective phthalate levels in house dust.
For the definition of low, medium and high house dust levels see legend to Table 2.
For the description of phthalate and phthalate metabolites see legend to Fig. 1.

surveys were considerably lower in samples collected in the years 2015–2017 (GerES V) than in the years 2003–2006 (GerES IV). The highest difference was observed for MBzP with a GM in GerES V being only 18% of that in GerES IV. GMs of MiBP, MnBP, and DEHP concentrations amounted to only 29%, 23%, and 23% of the GMs found in GerES IV. The lowest difference was found for DiNP with a GM amounting 57% of the GM calculated for GerES IV.

Reduced urinary phthalate concentrations over the last decade were also reported for the German ESB (Koch et al., 2017), NHANES (Calafat et al., 2015; Reyes and Price, 2018b; Zota et al., 2014) and CHMS (Haines et al., 2017). The reduction may be assigned to bans and restrictions in children's toys and childcare articles, in cosmetic products and materials intended to come in contact with food (summarised by Koch et al., 2017), and also to increasing consumer awareness towards these substances (Calafat et al., 2015). The relatively slim reduction of

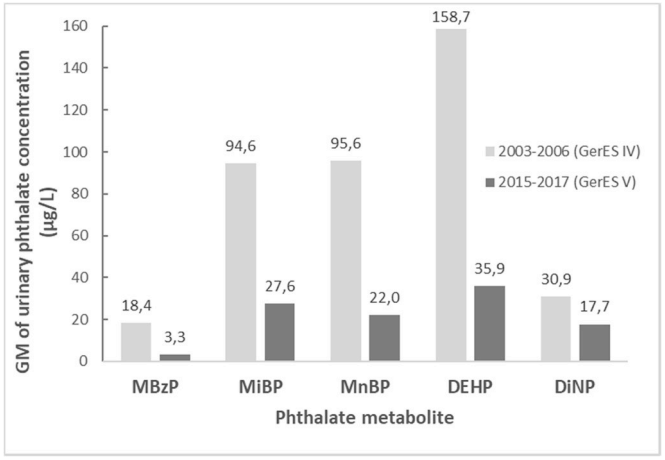

Fig. 3. Comparison of urinary phthalate biomarker levels in 3–14 years old children in Germany. Samples were collected in 2003–2006 (GerES IV) and in 2015–2017 (GerES V).
MBzP, MiBP and MnBP are the metabolites of BBzP, DiBP and DnBP, respectively DEHP and DiNP are expressed as sums of the following metabolites: DEHP (Σ MEHP + OH-MEHP + oxo-MEHP + cx-MEPP), DiNP (Σ OH-MiNP + oxo-MiNP + cx-MiNP).

DiNP, a phthalate introduced in the market as a substitute for DEHP may extend in the future, as it has been restricted just recently. Additionally, current market changes and substituting chemicals must be considered. Newly developed plasticisers like DPHP (di-(2-propylheptyl) phhtalate), DEHTP (di-(2-ethylhexyl) terephthalate), and Hexamoll® DINCH (di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate) were introduced into the market and have seen a constant increase of production volume and applications. Meanwhile results of the German ESB revealed an omnipresent detection of DINCH and DEHTP in urine samples of the German ESB study population (Kasper-Sonnenberg et al., 2019; Lessmann et al., 2019) and a detection of DPHP in one of five ESB participants (Schmidtkunz et al., 2019). DINCH and DEHTP have also been detected in urine samples of the population of the United States in substantial amounts (CDC, 2019; Silva et al., 2013; Silva et al., 2019). DINCH and DPHP measurements in children and adolescents in GerES V revealed that DINCH has reached the bodies of all and DPHP of about 62% of the children and adolescents in Germany at quantifiable levels (Schwedler et al., 2019). The favourable result of reduced phthalate levels in children and adolescents in Germany therefore is contrasted by a clear and extensive exposure to supplementary chemicals. In summary, to evaluate the total body burden with phthalates and plasticisers, not only the reduction of exposure to established phthalates, whether restricted or not, but also the emerging exposure to substitutes must be considered.

3.3. Comparison with other surveys

In Table 5 we compare phthalate metabolite levels determined in GerES V with biomonitoring data of HBM studies of a similar time period and with participants of similar age. Additionally, data of 20–29 years old adults of the German ESB from 2015 (Koch et al., 2017) were included. Compared to the German ESB, the children and adolescents of GerES V throughout had higher median phthalate metabolites levels.

Compared to 6–11 years old children from NHANES (CDC, 2019), 6–10 years old GerES V participants had similar GMs of MEP and DEHP, higher GMs of DnBP, and lower GMs of MBzP, cx-MiNP, and cx-MiDP levels. The same differences were found in GerES IV (Becker et al., 2009) and may reflect country specific production and use patterns.

Similarities and differences were also observed when European studies were compared. MBzP, MiBP, MnBP, MEHP, OH-MEHP, and oxo-MEHP were measured in Czechia (Puklova et al., 2019). The 5 and

Table 5
Comparison of median phthalate levels in urine (μg/L) of GerES V children and adolescents with levels measured in different studies.

Study, region	GerES V[a] Germany	ESB[b] Germany	GerES V[a] Germany	NHANES[c] USA	Czechia[d]	REPRO_PL[e] Poland	Esteban[f] France	GerES V[a] Germany	Sweden[g]	GerES V[a] Germany	Portugal[h]
Year	2015–2017	2015	2015–2017	2015–2016	2016–2017	2014–2015	2014–2016	2015–2017	2015	2015–2017	2014–2015
Age	3–17 y	20–29 y	6–10 y	6–11 y	5 + 9 y	7 y	6–10 y	3–5 y	40–48 m	3–17 y	4–18 y
N	2249–2256	60	727–736	415	370	250		397–402	113	2249–2256	112
	P50	P50	GM	GM	GM	GM	GM	GM	GM	GM	GM
MMP	5.9	2.8	7.3			5.1	5.3	6.8		6.4	3.1
MEP	23.1	13.5	21.7	24.5		42.9	40.6	20.8	32	25.8	58.3
MBzP	2.9	1.2	3.4	10.7	3.65	5.5	9.7	4.0	9.0	3.1	2.25
MiBP	26.2	9.8	28.9	11.2	44.1	76.2	50.1	30.4		26.1	16.8
OH-MiBP	8.8	2.8	10.2	4.04		27.9		11..5		8.9	6.54
MnBP	21	8	22.9	14.4	63	55	27.6	24.2	55	20.9	12.8
OH–MnBP	2.5	0.8	2.7	1.5		7		3.2		2.4	1.67
MCHP	< LOQ	< LOQ	< LOQ			< LOQ	NC	< LOQ		< LOQ	< LOQ
MnPeP	< LOQ	< LOQ	< LOQ			< LOQ		< LOQ		< LOQ	< LOQ
MEHP	1.5	1.1	1.4	1.42	2.31	2.7	2.0	1.4	1.5	1.4	1.9
5OH-MEHP	11.1	4.2	12.7	8.81	20.5	27.1	17.0	15.4	17	11.0	10.9
5oxo-MEHP	7.7	3.2	9.0	5.97	12.8	19.9	12.9	11.0	11	7.6	7.62
5cx-MEPP	12	3.8	14.1	14.6		31.4		17.7	16	11.9	16.1
OH-MiNP	6.9	2.4	8			9.5		9.4	12	6.9	5.57
oxo-MiNP	2.7	0.9	3.1			3.1		3.6	5.9	2.8	2.23
cx-MiNP	5.4	2	6.6	11.1		7.6		7.6	17	5.9	7.42
OH-MiDP	1.5	0.8	1.8			1.8		1.9		1.5	1.31
oxo-MiDP	0.7	0.3	0.7			0.89		0.7		0.6	0.71
cx-MiDP	0.9	0.4	1.1	2.26		0.91		1.2		0.9	1.19
MnOP	< LOQ	< LOQ	< LOQ			< LOQ	NC	< LOQ		< LOQ	< LOQ
MCPP	1.4	0.3	1.8	1.79		2.2		2.1		1.4	1.03

Abbreviations: N: sample size, LOQ: limit of quantification, P50: 50th percentiles, GM: geometric mean, NC: not calculated, y: years, m: months.
[a] This study.
[b] ESB: German Environmental Specimen Bank (Koch et al., 2017).
[c] NHANES: National Health and Nutrition Examination Survey (CDC, 2019).
[d] Czechia (Puklova et al., 2019).
[e] REPRO_PL: Polish Mother and Child Cohort Study (Gari et al., 2019).
[f] Esteban, France (Balicco et al., 2019).
[g] Sweden (Larsson et al., 2017).
[h] Portugal (Correia-Sa et al., 2018).

9 years old Czech children throughout had higher GMs of urinary phthalate metabolite levels than the 6–10 years old participants of GerES V, ranging from 1.1-fold for MBzP to 2.7-fold for MnBP. The GMs of MEP, MBzP, MiBP, MnBP, MEHP, OH-MEHP, and oxo-MEHP, measured in the Esteban 2014–2016 study in France inter alia in 6–10 years old children (Balicco et al., 2019) were also 1.2–2.9-fold higher than those measured in GerES V. Only the GM of MMP was lower in the Esteban than in the GerES V study.

In a Swedish study, children aged 40–48 months were investigated for MEP, MBzP, MnBP, and for DEHP and DiNP metabolites (Larsson et al., 2017). Compared with the 3–5 years old GerES V children, the GMs for urinary DEHP metabolites were similar, whereas the Swedish children had 1.5- to 2.3-fold higher GMs for MEP, MBzP, MnBP, OH-MiNP, oxo-MiNP, and cx-MiNP.

The whole GerES V set of phthalate metabolites was analogously determined in 7 years old children in Poland (Gari et al., 2019) and in 4–18 years old children in Portugal (Correia-Sa et al., 2018). For MCHP, MnPeP, and MnOP, values below LOQ were obtained in all three studies. GMs of urinary DiNP and DiDP metabolite levels were in the same range in the German, Polish, and Portuguese respective age groups (GerES 6–10 years olds compared with Polish 7 years olds, GerES 3–17 years olds compared to Portuguese 4–18 years olds). GMs of the other individual phthalate metabolite levels differed not more than 2.6-fold compared with GerES V data. Polish children had lower GM of MMP and higher MEP, MBzP, DiBP, DnBP, and DEHP levels than the GerES V children. Portuguese children and adolescents had lower GMs of MMP, MBzP, DiDP, and DnBP, higher GMs of MEP, and similar GMs of DEHP levels compared to the German children and adolescents.

In summary, comparison of a similar time period predominantly revealed similarities and only slight differences in GMs of individual phthalate metabolite levels in comparable age groups. As all but one of the compared studies were located in Europe, similar phthalate restrictions and usages may explain the predominant congruence.

3.4. Comparison with health-based guidance values

Health-based guidance values are available for MEP, MBzP, MnBP, for the sum of the 3 DiNP metabolites and for different combinations of DEHP metabolites (Angerer et al., 2011; Apel et al., 2017; Aylward et al., 2009a, b; Hays et al., 2011). The proportions of children and adolescents exceeding either human biomonitoring value I (HBM-I value) derived by the German Human Biomonitoring Commission (Apel et al., 2017) or BE (biomonitoring equivalent) values, derived by Aylward et al. (2009a, 2009b) and Hays et al. (2011) are shown in Table 6. None of the children and adolescents in Germany exceeded BE values for MEP (18000 μg/L urine), BBzP (3800 μg/L urine) and the HBM-I value for DEHP (Σ OH-MEHP and oxo-MEHP) of 500 μg/L for 6–13 years old children.

However, 0.38% of the participants had concentrations of MnBP in urine above the BE value of 200 μg/L urine, exceeding the limit where adverse health effects cannot be excluded with sufficient certainty. Likewise, the BE value of 1800 μg/L for DiNP was exceeded by 0.007%, and for DEHP (260 μg/L for ΣMEHP + OH-MEHP + oxo-MEHP and 400 μg/L for ΣMEHP + OH-MEHP + oxo-MEHP + cx-MEPP) by 0.08% of the participants. Extrapolated to the reference population in Germany, this would represent about 41500, 800, and 9000 children

Table 6
German GerES V participants exceeding health-based guidance values derived for urinary phthalate metabolites.

Phthalate	Biomarkers/metabolites	Source of health based guidance value	Value	% of GerES V participants exceeding health-based guidance value	Extrapolated for the population in Germany aged 3–17 years (↑ 11 million)
DEP	MEP	BE based on USEPA subchronic RfD	18000 µg/L	0	0
BBzP	MBzP	BE based on USEPA subchronic RfD	3800 µg/L	0	0
DnBP	MnBP	BE based on EFSA subchronic TDI	200 µg/L	0.38	~41500
DiNP	OH-MiNP + oxo-MiNP + cx-MiNP	BE based on EFSA subchronic TDI	1800 µg/L	0.007	~800
DEHP	OH-MEHP + oxo-MEHP	HBM-I-value (6-13 years)	500 µg/L	0	0
	MEHP + OH-MEHP + oxo-MEHP	BE based on USEPA subchronic RfD	260 µg/L	0.08	~9000
	MEHP + OH-MEHP + oxo-MEHP + cxMEPP	BE based on USEPA subchronic RfD	400 µg/L	0.08	~9000

Abbreviations: BE: biomonitoring equivalent, EFSA: European Food Safety Authority, GerES V: German Environmental Survey for Children and Adolescents 2014–2017, HBM-I-value: human biomonitoring value I, RfD: reference dose, TDI: tolerable daily intake, USEPA: United States Environmental Protection Agency.
Health based guidance values for DEP, BBzP, DnBP: Aylward et al. (2009a), DiNP: Hays et al. (2011), DEHP: Apel et al. (2017) and Aylward et al. (2009b).

and adolescents, exceeding health-based guidance values for MnBP, DiNP, and DEHP, respectively. These results show that even though regulations of DnBP, DiNP, and DEHP are in force for several years and average phthalate concentrations were lower than in previous studies, a proportion of children and adolescents still exceeds health-based guidance values.

Several phthalates have similar toxicological profiles and there is evidence that they can produce cumulative additive adverse effects (Christiansen et al., 2009; Conley et al., 2018; Furr et al., 2014; Howdeshell et al., 2007, 2017; Reyes and Price, 2018a; Rider et al., 2010). As DnBP and DEHP are among those phthalates suspected to induce comparable endocrine disrupting and reprotoxic effects, exceedances of their health-based guidance values are of special importance.

The ongoing exposure to phthalates, whether regulated or not, confirms the need for continuous monitoring of established as well as of upcoming phthalates and their substitutes. A comprehensive picture of the actual levels and developments of aggregated body burdens and comprehensive health-based guidance values are necessary to support further actions to reduce exposure to plasticisers in the vulnerable group of children and adolescents.

4. Conclusion

The omnipresence of phthalates in daily life is reflected in the body burdens of children and adolescents in Germany. Metabolites of 8 phthalates were found in 97%–100% of the samples. With the exception of MEP, the young children in GerES V were exposed to phthalate metabolites at up to 1.9-fold higher levels than the adolescents. Compared to GerES IV reduced GMs of all measured phthalates were measured in GerES V, which is most probably due to restrictions and regulations in applications and consumer products. However, alternatives and substitutes have entered the market and have to be monitored and evaluated accordingly.

Comparison with other studies for the years 2015–2017 revealed similarities and only slight differences in GMs of individual phthalate metabolite levels. Comparable phthalate restrictions and usages may contribute to these results.

Although regulation, bans, and restrictions are in force for several phthalates and average phthalate concentrations have declined, there are still some children and adolescents with urinary levels exceeding the individual health-based guidance values for DnBP, DEHP, and DiNP.

Maintaining biomonitoring of phthalate metabolites is also necessary to reveal whether the current authorisation of BBzP, DiBP, DnBP and DEHP results in further reduction of urinary levels.

The representative GerES V data on phthalate exposure of children and adolescents will be used to calculate and update reference values for this subpopulation in Germany. Repeated monitoring is necessary to assess the extent of phthalate exposure in the population in the light of their widespread use and to observe the developments due to regulatory restrictions and replacements by substitutes. By providing the best possible exposure data, our results will also contribute to further EU chemicals regulation via the European HBM initiative HBM4EU, which aims to support and promote the protection of all Europeans against environmental health risks.

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Appendix A. Supplementary data

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