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Hexamoll® DINCH and DPHP 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

The production and use of the plasticisers Hexamoll® DINCH (di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate) and DPHP (di-(2-propylheptyl) phthalate) have increased after both chemicals were introduced into the market in the early 2000s as substitutes for restricted high molecular weight phthalates.

During the population representative German Environmental Survey (GerES) of Children and Adolescents (GerES V, 2014–2017), we collected urine samples and measured the concentrations of DINCH and DPHP metabolites in 2228 and in a subsample of 516 participants, respectively.

We detected DINCH and DPHP metabolites in 100% and 62% of the 3–17 years old children and adolescents, respectively.

Geometric means of DINCH metabolites were 2.27 µg/L for OH-MINCH, 0.93 µg/L for oxo-MINCH, 1.14 µg/L for cx-MINCH and 3.47 µg/L for DINCH (Σ of OH-MINCH + cx-MINCH). Geometric means of DPHP metabolites were 0.30 µg/L for OH-MPHP, 0.32 µg/L for oxo-MPHP and 0.64 µg/L for DPHP (Σ of OH-MPHP + oxo-MPHP). The 3–5 years old children had almost 3-fold higher DINCH biomarkers levels than adolescents (14–17 years). Higher concentrations of DPHP biomarkers among young children only became apparent after creatinine adjustment. Urinary levels of DINCH but not of DPHP biomarkers were associated with the levels of the respective plasticisers in house dust.

When compared to HBM health-based guidance values, we observed no exceedance of the HBM-I value of 1 mg/L for DPHP (Σ of OH-MPHP + oxo-MPHP). However, 0.04% of the children exceeded the health based guidance value HBM-I of 3 mg/L for DINCH (Σ of OH-MINCH + cx-MINCH). This finding shows that even a less toxic replacement of restricted chemicals can reach exposures in some individuals, at which, according to current knowledge, health impacts cannot be excluded with sufficient certainty.

In conclusion, we provide representative data on DINCH and DPHP exposure of children and adolescents in Germany. Further surveillance is warranted to assess the substitution process of plasticisers, and to advise exposure reduction measures, especially for highly exposed children and adolescents. Providing the results to the European HBM Initiative HBM4EU will support risk assessment and risk management not only in Germany but also in Europe.

1. Introduction

Plasticisers are chemical additives that provide durable elasticity and flexibility of polymeric products (Bui et al., 2016; Wilkes et al., 2005). They have been used for decades in industrial applications, consumer goods and personal care products (Calafat et al., 2015; Koch

and Calafat, 2009). Because plasticisers are not chemically bound to the polymer to which they are added, they can be released into the environment during use or disposal of the products. Subsequently, they can be found as widespread contaminants in indoor air, house dust and food (Giovannoulis et al., 2018; Nagorka et al., 2011; Schossler et al., 2011; Weiss et al., 2018) leading to an almost ubiquitous human

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Abbreviations			
AM	arithmetic mean	G-EQUAS	German External Quality Assessment Scheme
BMU	German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety	HBM	human biomonitoring
CAS	Chemical Abstract Service	HBM-I-value	human biomonitoring value I
CDC	Centers for Disease Control and Prevention	HBM4EU	European Human Biomonitoring Initiative
CI	confidence intervall	KiGGs Wave 2	German Health Interview and Examination Survey for Children and Adolescents, Wave 2
DEHP	di-(2-ethylhexyl) phthalate	LOD	limit of detection
DIDP	di-iso-decyl phthalate	LOQ	limit of quantification
DINCH	di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate	max	maximum
DiNP	di-iso-nonyl phthalate	N	sample size
DPHP	di-(2-propylheptyl) phthalate	NHANES	National Health and Nutrition Examination Survey
ECHA	European Chemicals Agency	P	percentiles
EEA	European Environment Agency	PVC	polyvinyl chloride
EFSA	European Food Safety Authority	REACH	European chemicals legislation concerning the registration, evaluation, authorisation and restriction of chemicals
ESB	German Environmental Specimen Bank	RKI	Robert Koch-Institute, Germany
GerES	German Environmental Survey	SVHC	substance of very high concern
GerES V	German Environmental Survey on Children and Adolescents 2014–2017	UBA	German Environment Agency
GM	geometric mean	VCI	German Chemical Industry Association

exposure (Becker et al., 2009; CDC, 2019; Choi et al., 2017; Den Hond et al., 2015; Heudorf et al., 2007; Koch et al., 2017; Saravanabhavan et al., 2013).

Some of the most prominent plasticisers – butylbenzyl phthalate (BBzP), di-isobutyl phthalate (DiBP), di-n-butyl phthalate (DnBP) and di-(2-ethylhexyl) phthalate (DEHP) - were classified as substances of very high concern (SVHC) under the European chemical regulation REACH because of their reproductive toxicity (summarised by Heudorf et al., 2007). Use restrictions, authorisation obligations, and bans were enacted *inter alia* in the European Union (summarised by Koch et al., 2017), the United States (CPSC, 2014) and Canada (Health Canada, 2016). As a consequence, industry has been looking for alternatives and substitutes to replace the regulated phthalates.

Hexamoll® DINCH (di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate) was introduced in the European market in 2002 as a substitute for the restricted high molecular weight phthalates DEHP and di-iso-nonyl phthalate (DiNP). DINCH is used mainly for manufacturing of polyvinyl chloride (PVC) goods and is authorised to be used in sensitive applications such as toys, food contact materials and medical devices (SCENIHR, 2008; Koch et al., 2013). Current toxicological data suggest that DINCH is neither a reproductive toxicant nor an endocrine disruptor. However, adverse health effects were observed at relatively high doses in rats, namely thyroid hyperplasia and renal toxicity (EFSA, 2006; Koch et al., 2013). In consequence, an oral reference dose of 0.7 mg/kg/d was derived for humans for chronic DINCH exposure (Bhat et al., 2014b).

In a joint effort between 28 partner countries and the EU policy board consisting of five General Directorates and the three EU agencies European Environment Agency (EEA), European Chemicals Agency (ECHA) and European Food Safety Authority (EFSA), the European Human Biomonitoring Initiative HBM4EU (www.hbm4eu.eu) (Ganzleben et al., 2017) identified DINCH as a substance of priority interest for which various policy relevant questions have to be answered by tailored research. The German Human Biomonitoring Commission derived a human biomonitoring value (HBM-I-value) of 3.0 mg/L for children's urinary DINCH metabolite (Σ of OH-MINCH + cx-MINCH) levels (Apel et al., 2017; HBM Commission, 2014); the same value was derived by HBM4EU as the HBM health-based guidance value for children of the general population.

DPHP (di-(2-propylheptyl) phthalate), trade name Palatinol®, is primarily used as a plasticiser in PVC and vinyl chloride copolymers for technical applications like cables, carpet backing, roofing membranes and car interiors. It is not approved for food contact, toys and medical products and has not been evaluated by the EFSA (Gries et al., 2012; Leng et al., 2014). DPHP is also used as a substitute of DEHP and DiNP with increasing global consumption (Schütze et al., 2015). No developmental or testicular effects were observed in rats, however, adverse effects on thyroid, pituitary and adrenal glands were seen. An oral reference dose for humans was derived of 0.1 mg/kg/day for DPHP exposure (Bhat et al., 2014a) and an HBM-I-value of 1.0 mg/L for children's urinary DPHP (Σ of OH-MPHP + oxo-MPHP) levels was determined by the German Human Biomonitoring Commission (Apel et al., 2017; HBM Commission, 2015).

Concurrent with the introduction of DINCH and DPHP in the market and the constant increase of production volume and applications, appropriate biomarkers and analytical methods to determine human body burden to DINCH and DPHP were developed in a cooperation project between the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) and the German Chemical Industry Association (VCI), which is scientifically operated by the German Environment Agency (UBA) (Gries et al., 2012; Koch et al., 2013; Kolossa-Gehring et al., 2017; Leng et al., 2014; Schütze et al., 2012). In the meantime, similar HBM approaches have been published by other research groups (Fromme et al., 2016; Klein et al., 2018; Shih et al., 2018; Silva et al., 2012, 2013).

In view of the widespread use of DINCH and DPHP and associated human exposure, the quantification of both compounds in a population representative survey is needed to understand the extent of exposure in the general population and in its subgroups.

The German Environmental Survey (GerES) is part of a health-related environmental surveillance system in Germany. It is a population representative cross-sectional study on the human exposure to environmental chemicals and their sources (Kolossa-Gehring et al., 2012a, 2012b) and has been carried out since 1985. The main instruments of GerES are human biomonitoring (HBM), ambient monitoring and the collection of information on exposure via questionnaires. Whereas GerES I to GerES III focused mainly on the adult population (Schulz et al., 2007), GerES IV exclusively addressed children aged 3–14 years

(Schulz et al., 2012). Following this, the target populations of GerES V were children and adolescents, aged 3–17 years (Schulz et al., 2017).

Here we describe the urinary levels of the metabolites of the plasticisers DINCH and DPHP in children and adolescents in Germany in a population representative sample. Our data build the baseline to derive reference values for these chemicals in Germany, to assess exposure over time and to monitor effects of market and regulation changes on the exposure of the German population to these plasticisers. Furthermore, the elucidation of the exposure to DINCH and DPHP in Germany can be used in the context of the European HBM initiative HBM4EU and, thus, contribute to the overarching goal to exploit HBM data for EU chemicals policy (Ganzleben et al., 2017).

2. Material and methods

2.1. Study population and sample collection

From January 2015 to June 2017, a population representative sample was collected 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). In the cross-sectional component of KiGGS Wave 2 the recruitment of children and adolescents was carried out in two steps: first, 167 sampling locations were chosen, reflecting the grade of urbanisation and geographic distribution of the population in Germany. Second, children and adolescents were randomly selected from the respective inhabitant registries, which are resident registrations kept by the local public administrations (Kamtsiuris et al., 2007; Kurth et al., 2008). Out of these, the 3–17 years old participants of GerES V were recruited as a random subsample in the course of the KiGGS Wave 2 examination.

The fieldwork of GerES V was conducted with a visit at the homes of the participants as the essential component. Kantar Health Munich conducted the fieldwork on behalf of the UBA. Prior to fieldwork the fieldworkers underwent extensive training. During the home visits, the fieldworkers received first void urine as well as tap water samples from all participants. Blood samples were already taken during the KiGGS Wave 2 examinations. During the home visits, fieldworkers also conducted interviews with the parents of the children or with the adolescents themselves, performed noise measurements and determined indoor ultrafine particle concentration. In a subsample of the participants, they additionally received dust bags to determine contaminants in house dust, hang up samplers to measure volatile organic compounds in indoor air or set up measuring devices to examine particulate matter in indoor and outdoor air. The quality of fieldwork was assured by internal controls by Kantar Health and UBA.

The first void urine samples were taken either in polypropylene

receptacles or in narrow-necked polyethylene containers, depending on sex and age of the participant. The samples were kept cold, aliquoted in polypropylene vials, frozen (-20°C) the same day, and kept frozen until analysis. None of the pre-tested containers had detectable levels of the investigated DINCH or DPHP metabolites. Samples were analysed in a randomised sequence to avoid observer bias.

All parents and all adolescents themselves provided written informed consent. 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) had approved the project.

2.2. Chemical analysis

The methods for the determination of DINCH and DPHP metabolites in urine were developed in the context of the German BMU/VCI-cooperation (Kolossa-Gehring, 2017).

The three secondary DINCH metabolites cyclohexane-1,2-dicarboxylic acid-mono(hydroxyl-iso-nonyl) ester (OH-MINCH), cyclohexane-1,2-dicarboxylic acid-mono(oxo-iso-nonyl) ester (oxo-MINCH) and cyclohexane-1,2-dicarboxylic acid-mono-(carboxy-iso-octyl) ester (cx-MINCH) were determined by the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance at the Ruhr-University Bochum, Germany, by online enrichment and high-performance liquid chromatography coupled to tandem mass spectrometry according to Schütze et al. (2012). Stable isotope-labeled standards were available for all metabolites except for oxo-MINCH. The results for oxo-MINCH should therefore be regarded as semi-quantitative.

The three secondary DPHP metabolites mono (2-propyl-6-hydroxyheptyl) phthalate (OH-MPHP), mono (2-propyl-6-oxo-heptyl) phthalate (oxo-MPHP) and mono (2-propyl-6-carboxyhexyl) phthalate (cx-MPHP) were quantified at the Institute of Biomonitoring of the Currenta GmbH, Leverkusen, Germany, by capillary gas chromatography coupled to high resolution mass spectrometry (Gries et al., 2012; Leng et al., 2014). This method specifically detects DPHP metabolites, chromatographically separating interferences of di-iso-decyl phthalate (DiDP) isomers (Leng and Gries, 2017).

Urinary creatinine was quantified by Analytisch-Biologisches Forschungslabor München, Germany, using Jaffé method (Blaszkiwicz and Liesenhoff-Henze, 2010).

Because no external quality control schemes were available for DINCH and for DPHP metabolites, internal quality control measures were performed by analysing urine samples with known concentrations. Concentrations in these quality control samples were always within the $\pm 3\sigma$ range. Additionally, blinded repeated measurements of samples in different analytical cycles resulted always in concentrations within the range of the respective confidence intervals; no metabolite

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

Parent substance	Full name of parent substance	CAS Number	Metabolite	Full name of metabolite	LOQ ($\mu\text{g/L}$)
DINCH	Di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate	166412-78-8 ^a 474919-59-0 ^b	OH-MINCH	Cyclohexane-1,2-dicarboxylic acid-mono (hydroxyl-iso-nonyl) ester	0.05
			oxo-MINCH	Cyclohexane-1,2-dicarboxylic acid-mono (oxo-iso-nonyl) ester	0.05
			cx-MINCH	Cyclohexane-1,2-dicarboxylic acid-mono (carboxy-iso-octyl) ester	0.05
DPHP	Di-(2-propylheptyl) phthalate	53306-54-0	OH-MPHP	Mono (2-propyl-6-hydroxyheptyl) phthalate	0.3
			oxo-MPHP	Mono (2-propyl-6-oxo-heptyl) phthalate	0.25
			cx-MPHP	Mono (2-propyl-6-carboxyhexyl) phthalate	0.15

Abbreviation: CAS: Chemical Abstract Service.

^a Europe and Asia.

^b USA.

was ever detected in field blanks.

Similar internal quality control measures confirmed the quality of creatinine determination. Additionally, external quality assurance for creatinine was confirmed within biannual participation in the ring trial program of the German External Quality Assessment Scheme (GEQUAS).

The measured DINCH and DPHP metabolites, the Chemical Abstract Service (CAS) numbers, acronyms and respective limits of quantification (LOQ) are summarised in Table 1.

For DINCH and DPHP measurements in house dust, the 63 µm dust fraction was analysed with liquid chromatography/mass spectrometry based on Nagorka et al. (2011).

2.3. Statistical analysis

In order to adjust the realised sample of GerES V with data from the official demographic statistics of the German population from 2013 to 2015 (Microzensus, 2019), weighting variables were calculated by the RKI (Hoffmann et al., 2018). Subsequently, weighted samples were used in all statistical evaluations whereby the sample and subsample sizes were calculated as a sum of case weights.

Characteristics of the biomarker distributions were calculated (sample size (N), % > LOQ, maximum (max), arithmetic mean (AM), geometric mean (GM), confidence intervals (CI) and percentiles (P)). Volume based as well as creatinine adjusted concentrations are presented for the measured metabolites and for sums of metabolites. Concentrations below each LOQ 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 AM.

In the basic evaluation the levels of substances 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. Beyond this, 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 concentrations: carpets with or without plastic backing or underlay, 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, concentration of the specific plasticiser in the house dust.

Bivariate statistical analyses were performed for each variable selected for stratification. When more than 50% of the measured concentrations were equal or above LOQ, differences of the GM of the subgroups were tested for significance by t-tests or by one-way ANOVA. When less than 50% of the measured concentrations were above LOQ, the proportions above and below LOQ were compared and significance was tested by χ^2 test of independence.

All statistical analyses were performed with the SPSS statistical package (version 25).

3. Results and discussion

In GerES V, 2294 children and adolescents aged 3–17 years participated. From those, 2228 provided urine samples of sufficient volume to be analysed for the DINCH metabolites OH-MINCH, cx-MINCH and oxo-MINCH. The DPHP metabolites OH-MPHP, oxo-MPHP and cx-MPHP were measured in a subsample of 516 children and adolescents. The characteristics of the weighted study populations analysed for DINCH and DPHP metabolites are shown in Table 2. The distributions of the variables age, sex, community size, region, socioeconomic status and migration background of the DPHP-subsample only slightly

differed from that of the DINCH-sample. As the DINCH-sample comprised almost the whole study population, it is concluded that DINCH and the DPHP metabolites were determined in samples representing the target population.

The distribution of variables suspected to be associated with exposure to DINCH and DPHP metabolites is shown in Table 3. Once again, variable distribution only slightly differed between the study samples. Clear differences, however, were observed for the distribution of DINCH and DPHP levels in house dust, which may reflect their different application pattern.

Table 4 summarises descriptive statistics for OH-MINCH, oxo-MINCH and cx-MINCH as well as for the sum of the DINCH metabolites OH-MINCH and cx-MINCH. Table 4 also shows the descriptive statistics for OH-MPHP, oxo-MPHP, cx-MPHP, and the sum of the DPHP metabolites OH-MPHP and oxo-MPHP.

DINCH metabolites were detected in the urine samples of almost all participants. Nearly 100% of the participants had OH-MINCH levels, 97% oxo-MINCH levels and 99% cx-MINCH levels > LOQ in their

Table 2
Characteristics of the weighted study population.

	analysed for	
	DINCH N (%)	DPHP N (%)
Children and adolescents	2228	516
Sex		
boys	1145 (51)	266 (52)
girls	1083 (49)	250 (48)
Age group		
3–5 years	389 (17)	99 (19)
6–10 years	731 (33)	166 (32)
11–13 years	452 (20)	102 (20)
14–17 years	656 (29)	149 (29)
Community size		
< 50,000 inhabitants	581 (26)	168 (33)
50,000 - ≤100,000 inhabitants	142 (6)	31 (6)
≥100,000 inhabitants	1505 (68)	317 (61)
Socioeconomic status^a		
low	457 (21)	103 (20)
medium	1304 (60)	309 (60)
high	400 (19)	82 (16)
Region of residence		
West Germany (including West Berlin)	1878 (84)	434 (84)
East Germany (including East Berlin)	351 (16)	82 (16)
Migration background^b		
no migration background	1540 (71)	358 (69)
one-sided migration background ^c	227 (10)	59 (11)
two-sided migration background ^d	413 (19)	83 (16)

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 its 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).

Table 3
Frequency of various exposure factors stratified for in the statistical descriptions of levels of DINCH and DPHP metabolites in the urine of GerES V participants.

Exposure factors	Reported by participants analysed for	
	DINCH N (%)	DPHP N (%)
Carpets, carpet tiles, rugs^a		
with plastic underlay	901 (45)	205 (45)
without underlay	1101 (55)	249 (55)
PVC flooring		
yes	581 (26)	135 (26)
no	1644 (74)	380 (74)
Wearing of plastic or rubber shoes without socks in summer		
yes	1105 (50)	238 (46)
no	1123 (50)	277 (54)
Habit of chewing on plastic objects		
yes	559 (25)	123 (24)
no	1668 (75)	392 (76)
Consumption of fast food or convenience food before urine sampling		
1 day before	500 (22)	111 (22)
2 days before	328 (15)	71 (14)
more than 2 days before/never	1381 (63)	328 (64)
	House dust analysed for	
	DINCH N (%)	DPHP N (%)
Analyte level in house dust^b		
low	209 (35)	47 (37)
medium	187 (31)	12 (10)
high	203 (34)	67 (53)

Note: Due to rounding to nearest whole numbers, the sum of stratified sample sizes not always exactly corresponds to the total sample size (N = 2228 analysed for DINCH, N = 516 analysed for DPHP). Further differences are due to missing values in stratification criteria.

^a Participants who reported to have no carpets at all were filtered (N = 226 analysed for DINCH and N = 62 analysed for DPHP).

^b House dust levels of DINCH and DPHP were determined in a subsample of the respective participants (N = 598 for DINCH, N = 126 for DPHP). Measured house dust levels were categorised with the following limits for DINCH levels: low: < 11.33 µg/g, medium: 11.33–25.8 µg/g, high: > 25.8 µg/g and with the following limits for DPHP levels: low: < 8.01 µg/g, medium: 8.01–8.9 µg/g, high: > 8.9 µg/g.

Table 4

Frequency of quantification, percentiles, maximum, arithmetic mean and geometric mean with 95 %confidence interval of urinary metabolite levels (in µg/L urine) of DINCH and DPHP metabolites of the GerES V participants.

Substance	N	N < LOQ	% ≥ LOQ	P10	P50	P90	P95	P98	MAX	AM	GM	95 %CI GM
DINCH												
OH-MINCH	2228	4	100	0.57	2.20	9.57	15.8	28.5	2540	5.68	2.27	2.16–2.38
oxo-MINCH	2227	67	97	0.18	0.96	4.69	7.61	13.8	594	2.41	0.93	0.88–0.99
cx-MINCH	2225	21	99	0.31	1.08	4.38	7.61	13.8	893	2.56	1.14	1.08–1.19
DINCH(Σ of OH-MINCH + cx-MINCH)^a	2224			0.90	3.35	13.9	24.1	42.6	3430	8.25	3.47	3.31–3.63
DPHP												
OH-MPHP	516	259	50	< LOQ	< LOQ	0.87	1.34	2.73	17.9	0.51	0.30	
oxo-MPHP	516	198	62	< LOQ	0.31	1.10	1.84	3.93	27.6	0.60	0.32	0.30–0.35
cx-MPHP	516	512	1	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.83	< LOQ	< LOQ	
DPHP (Σ of OH-MPHP + oxo-MPHP)^b	516			0.28	0.58	1.92	3.59	6.80	44.3	1.11	0.64	0.59–0.69

Abbreviations: N: sample size, LOQ: limit of quantification, P10, P50, P90, P95, P98: percentiles, MAX: maximum value, AM arithmetic mean, GM: geometric mean, 95% CI GM: 95% confidence interval for GM.

Values below LOQ were set LOQ/2 for calculation purposes.

^a HBM-I-value for DINCH (Σ of OH-MINCH + cx-MINCH) for children: 3 mg/L (HBM Commission, 2014).

^b HBM-I-value for DPHP (Σ of OH-MPHP + oxo-MPHP) for children: 1 mg/L (HBM Commission, 2015).

urine. The maximum levels found were 2540 µg/L for OH-MINCH, 594 µg/L for oxo-MINCH, 893 µg/L for cx-MINCH and 3430 µg/L for DINCH (Σ of OH-MINCH + cx-MINCH). The GMs were determined as 2.27 µg/L for OH-MINCH, 0.93 µg/L for oxo-MINCH, 1.14 µg/L for cx-MINCH and 3.47 µg/L for DINCH (Σ of OH-MINCH + cx-MINCH).

The DPHP metabolites were quantifiable to a lesser extent. 50% of the participants had OH-MPHP levels, 62% had oxo-MPHP levels and 1% had cx-MPHP levels > LOQ in their urine. Maximum levels were 17.9 µg/L for OH-MPHP, 27.6 µg/L for oxo-MPHP, 0.83 µg/L for cx-MPHP and 44.3 µg/L for DPHP (Σ of OH-MPHP + oxo-MPHP). GMs were 0.30 for OH-MPHP, 0.32 µg/L for oxo-MPHP, < LOQ for cx-MPHP, and 0.64 µg/L for DPHP (Σ of OH-MPHP + oxo-MPHP).

Table 5 presents the distribution and the statistical parameters for DINCH (Σ of OH-MINCH + cx-MINCH) levels in the subgroups listed in Tables 2 and 3. The respective data for the individual DINCH metabolites are shown in Supplementary Tables 1–3 (in µg/L) and in Supplementary Tables 4–7 adjusted for creatinine (µg/g creatinine). As Table 5 and Supplementary Tables 1–3 show, no statistically significant differences in DINCH biomarker urine levels were found in the subgroups stratified for the variables sex, community size, region of residence, socioeconomic status and migration background. There was, however, a significant difference between the four age groups. Urinary DINCH metabolite levels were highest in the youngest children and decreased with age. Whereas adolescents aged 14–17 years had the lowest GM with 2.32 µg/L, children aged 3–5 years had the highest GM with 6.82 µg/L, being almost 3-fold higher. From the other variables suspected to be associated with DINCH exposure only the concentration of DINCH in house dust and the habit of chewing on plastic objects were positively associated with DINCH levels in urine. The habit of chewing on plastic objects, however, did not remain significant when adjusted for age. Associations of the variables sex and fast food with creatinine adjusted DINCH levels in urine (Supplementary Tables 4–7) also disappeared upon age adjustment. The remaining significant associations between DINCH exposure and the age of the participants or the DINCH concentration in house dust are illustrated in Fig. 1.

Table 6 summarises the distribution and statistical parameters of DPHP (Σ of OH-MPHP + oxo-MPHP) in GerES V participants. Supplementary Tables 8–10 show levels of individual DPHP metabolites in µg/L urine and Supplementary Tables 11–13 in µg/g creatinine. Although statistical testing revealed significant differences of DPHP

Table 5
Urinary levels of DINCH (Σ of OH-MINCH + cx-MINCH) in subpopulations of the GerES V participants in $\mu\text{g/L}$.

	N	P10	P50	P90	P95	P98	MAX	AM	GM	95% CI GM
Total	2224	0.90	3.35	13.9	24.1	42.6	3430	8.25	3.47	3.31–3.63
Sex										
boys	1143	0.86	3.23	14.3	23.2	39.9	252	6.80	3.34	3.13–3.57
girls	1082	0.93	3.50	13.5	25.0	44.8	3430	9.77	3.61	3.38–3.85
Age group***										
3–5 years	389	2.21	6.19	26.4	40.3	53.7	3430	18.8	6.82	6.18–7.52
6–10 years	729	1.34	3.61	13.3	21.0	44.7	153	6.90	3.95	3.68–4.24
11–13 years	450	0.77	2.56	13.1	19.8	36.3	252	6.16	2.81	2.53–3.12
14–17 years	656	0.62	2.20	9.79	13.8	29.5	535	4.90	2.32	2.13–2.53
Community size (inhabitants)										
< 50,000	578	0.92	3.13	12.8	19.8	43.8	172	6.31	3.30	3.02–3.60
50,000 - \leq 100,000	142	1.03	3.25	13.5	18.9	24.6	46.0	5.30	3.26	2.77–3.84
\geq 100,000	1504	0.89	3.50	14.6	27.4	44.6	3430	9.27	3.56	3.36–3.77
Socioeconomic status										
low	457	0.91	3.53	13.1	21.4	33.3	67.5	6.03	3.37	3.04–3.73
medium	1302	0.92	3.43	13.6	23.6	42.4	3430	9.40	3.51	3.30–3.72
high	400	0.89	3.17	16.1	27.1	61.7	218	7.41	3.51	3.14–3.93
Region of residence										
West Germany (including West Berlin)	1874	0.92	3.37	14.3	25.0	43.6	3430	8.68	3.51	3.34–3.69
East Germany (including East Berlin)	351	0.82	3.27	12.5	21.0	40.9	172	5.96	3.25	2.91–3.62
Migration background										
no migration background	1537	0.89	3.42	14.5	24.9	43.9	3430	9.16	3.53	3.34–3.73
one-sided migration background	227	0.78	3.49	11.4	17.2	33.3	67.5	5.48	3.22	2.81–3.69
two-sided migration background	413	0.93	3.25	12.9	32.4	53.7	74.9	6.64	3.33	2.97–3.73
Carpets, carpet tiles, rugs										
with plastic underlay	897	1.00	3.70	14.5	21.4	39.4	252	7.06	3.70	3.45–3.97
without plastic underlay	1101	0.92	3.40	14.3	27.2	43.8	3430	9.73	3.50	3.27–3.74
PVC flooring										
yes	579	0.86	3.66	15.2	21.4	39.6	535	6.94	3.64	3.33–3.97
no	1642	0.92	3.28	13.2	24.9	44.6	3430	8.72	3.41	3.23–3.60
Wearing of plastic or rubber shoes without socks in summer										
yes	1104	0.91	3.38	13.0	24.3	52.7	3430	10.0	3.50	3.27–3.74
no	1120	0.90	3.35	14.4	24.6	40.5	535	6.49	3.44	3.23–3.66
Habit of chewing on plastic objects***										
yes	557	1.04	4.11	16.7	27.2	38.9	153	7.66	4.27	3.91–4.66
no	1665	0.85	3.09	12.9	21.2	43.1	3430	8.44	3.23	3.06–3.41
Consumption of fast food or convenience food before urine sampling										
1 day before	500	0.89	3.39	15.2	23.1	32.4	535	6.84	3.38	3.05–3.74
2 days before	328	1.03	3.23	13.6	29.5	62.7	138	6.79	3.53	3.16–3.96
more than 2 days/never before	1377	0.89	3.44	13.9	25.0	45.0	3430	9.15	3.50	3.30–3.71
House dust level of DINCH***										
low	209	0.69	2.51	12.4	13.7	18.8	93.7	4.69	2.55	2.19–2.96
medium	186	1.04	3.47	14.9	23.1	45.2	218	6.28	3.55	3.09–4.07
high	203	1.45	4.99	27.1	37.5	54.7	153	10.2	4.99	4.25–5.86

For abbreviations see Table 4. For description of subpopulations see Tables 2 and 3. 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). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

biomarker levels in various categories of the variables age group, socioeconomic status, and migration background, no concurrent increase or decrease were observed (Table 6). However, when adjusted for creatinine, age group became significant. Again, young children had higher levels of DPHP (Σ of OH-MPHP + oxo-MPHP) than adolescents (Supplementary Table 11: GM of 0.99 $\mu\text{g/g}$ creatinine for 3–5 years old children versus GM of 0.34 $\mu\text{g/g}$ creatinine for 14–17 years old adolescents). No further consistent associations were found (compare results of Table 6 and Supplementary Table 11).

Our data suggest that an estimated 100% and 62% of children and adolescents in Germany have been exposed to DINCH and DPHP, respectively. Both plasticisers were developed to substitute the high molecular weight phthalates and plasticisers DEHP and DiNP. GerES V data on phthalates (unpublished results) will show whether the urine levels of biomarkers of these restricted phthalates decreased in opposite

direction. Higher urinary metabolite levels for DINCH compared to DPHP (GM of 3.47 $\mu\text{g/L}$ versus 0.64 $\mu\text{g/L}$) might be explained by the different production and consumption volumes and different uses of these plasticisers. DINCH consumption is higher than DPHP consumption (Malveda et al., 2015), and DINCH is used in applications often close to the consumer such as toys and food contact materials (EFSA, 2006; Koch et al., 2013). DPHP is mostly used in not as sensitive applications with a lower probability of close human contact like tarpaulins, roofing membranes, wire and cable coatings but also car interiors (Schmidt-kunz et al., 2019). In agreement with previous findings for the phthalates DEHP and DiNP (Becker et al., 2009; Wittassek et al., 2007), the concentrations of biomarkers of DPHP and even more pronounced of DINCH increased with decreasing age. This is probably due to the increased food intake of young children in relation to their body weight, their greater body surface in relation to their body weight, but

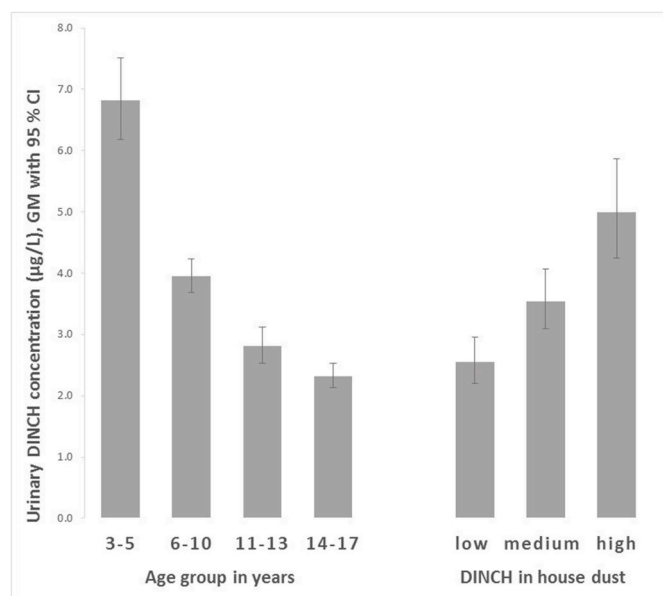


Fig. 1. Urinary DINCH (Σ OH-MINCH + cx-MINCH) concentrations in GerES V participants by age group and concentration of DINCH in house dust. DINCH level categories in house dust were: low: < 11.3 $\mu\text{g/g}$, medium: 11.3–25.8 $\mu\text{g/g}$, high: > 25.8 $\mu\text{g/g}$.

probably also due to other child specific characteristics such as mouthing habits or increased dust intake from crawling on the floor (Ginsberg et al., 2016; Ferguson et al., 2016). Therefore, the clearly higher burden of young children compared to adolescents, but probably even more pronounced compared to adults (see below), must be kept in mind when further assessing the substitution process of certain phthalates with alternative plasticisers.

Table 7 compares DINCH and DPHP biomarkers levels determined in GerES V with biomonitoring data of other national and international studies. We restricted the comparison to the metabolites OH-MINCH (representing DINCH) and oxo-MPHP (representing DPHP) as they are detected at the highest levels, and are the most common biomarkers reported in studies.

So far, only a few studies are available for children and adolescents exposures. In regard to DINCH, the omnipresent detection of DINCH biomarkers in GerES V is in line with findings from our recent time trend study of young German adults from the German Environment Specimen Bank (ESB) with first detection of DINCH metabolites in urine samples in 2006 (6.7%) and nearly omnipresent detection in 2012 (98.3%) and a GM for OH-MINCH of 0.39 $\mu\text{g/L}$ (Schütze et al., 2014). Likewise, for the USA, Silva et al. (2013) reported a steadily increasing detection of DINCH metabolites in adults, albeit with lower detection rates (19% in 2012). These lower detection rates probably relate to the higher detection limit (0.4 $\mu\text{g/L}$) of their methodology compared to our (0.05 $\mu\text{g/L}$) (Schütze et al., 2012). More recently, more than 50% detectable results have been reported for US adults older than 20 years in 2015–2016 with a median of 0.50 $\mu\text{g/L}$ for OH-MINCH (CDC, 2019). For Swedish women, the AM of oxo-MINCH (OH-MINCH has not been determined in their study) increased from 0.2 $\mu\text{g/L}$ in 2009 to 0.7 $\mu\text{g/L}$ in 2014 with a detection rate of 90% (Gyllenhammar et al., 2017). A detection rate of 84–90% for OH-MINCH was also reported in Norwegian adults in 2013–2014 (Giovanoulis et al., 2016). For the German ESB, in 2017, OH-MINCH was quantified in 100% of the students with a GM of 0.695 $\mu\text{g/L}$ (Kasper-Sonnenberg et al., 2019). These findings

confirm the rapid increase in detection frequencies and in urinary concentrations of DINCH metabolites in urine samples worldwide mirroring the increased production and use of DINCH (BASF, 2014; Malveda et al., 2015). These rapid changes over the last decade have to be kept in mind when comparing DINCH HBM data between studies.

Another important influencing factor to consider is the age of the study population. We could show the considerably higher DINCH metabolite concentrations of young children (3–5 years) compared to adolescents in our study, but children in general seem to be more exposed than adults. In NHANES 2015–2016, 6–11 year old children had a median concentration of OH-MINCH of 1.10 $\mu\text{g/L}$ compared to 0.500 $\mu\text{g/L}$ in adults (CDC, 2019).

Urinary DINCH biomarker levels of children reported in other countries tend to be higher than in the USA even in earlier sampling years. In GerES V, comprising similar sampling years 2015–2016 as NHANES, OH-MINCH levels were up to 3 times higher than in NHANES (GM of 4.52 versus 1.36 $\mu\text{g/L}$ in children 3–5 years, 2.59 versus 1.15 $\mu\text{g/L}$ in children 6–10 years) (CDC, 2019).

In contrast, GerES V results are in better accordance with those reported in a) Portuguese children and adolescents (GM of 2.27 $\mu\text{g/L}$ for the 3–17 years old German and GM of 2.14 $\mu\text{g/L}$ for the 4–18 year old Portuguese children) (Correia-Sa et al., 2017), b) in 27–80 months old German daycare children (P50 of 1.66 $\mu\text{g/L}$) (Fromme et al., 2016), c) in 40–59 months old Swedish preschool children (GM of 2.2 $\mu\text{g/L}$) (Larsson et al., 2017), and d) in 5–14 years old children from Australia (AMs from 1.8 to 3.5 $\mu\text{g/L}$) (Gomez Ramos et al., 2016). Differences in age groups, study settings, sites, sampling protocols, and year of sampling may have contributed to some of the differences observed. Further investigations may demonstrate to which extent marketing aspects and regional peculiarities also account for the different OH-MINCH levels.

For DPHP the database is much more limited. Up to now, there are only two time trend analyses reported for young German adults from the ESB, comprising samples from 1999 to 2012 (Schütze et al., 2015) and from 1999 to 2017 (Schmidtkunz et al., 2019). With no detections before 2009, these studies report detection rates between of 15.0% and 18.3% for the years 2014 and 2017. We detected oxo-MPHP in 62% of the GerES V participants, again confirming that children and adolescents appear to be more exposed to DPHP than adults.

To assess the health relevance of DINCH and DPHP exposure, we compared the urinary metabolite levels with the respective HBM-I values derived by the German Human Biomonitoring Commission for children and adults for DINCH (Σ of OH-MINCH + cx-MINCH) based on nephrotoxic effects, and for DPHP (Σ of OH-MPHP + oxo-MPHP) based on thyroid and pituitary gland effects (HBM Commission, 2014; HBM Commission, 2015). For DINCH, 0.04% of the participating children, all in the age group of 3–5 years, exceeded the HBM-I value of 3.0 mg/L urine. Extrapolated to the reference population in Germany, this would represent 4400 children. In contrast, none of the participating children and adolescents exceeded the HBM-I value of 1.0 mg/L urine for DPHP (Table 8).

The exceedance of the health-based guidance value for DINCH indicates that even a less toxic replacement of a restricted chemical can reach levels in the human body at which, according to current knowledge, an impact on health cannot be excluded with sufficient certainty. However, regulation, discussion on chemicals safety and substitution may lead to a reduction of the overall chemical hazard burden from plasticisers for the environment as well as for human health (Sackmann et al., 2018).

Nevertheless, the detection of DINCH in all participants, the exceedance of the health based guidance value for DINCH, the increased exposure of young children and the reported exposure

Table 6
Urinary levels of DPHP (Σ of OH-MPHP + oxo-MPHP) in subpopulations of the GerES V participants in $\mu\text{g/L}$.

	N	P10	P50	P90	P95	P98	MAX	AM	GM	95% CI GM
Total	516	0.28	0.58	1.92	3.59	6.80	44.3	1.11	0.64	0.59–0.69
Sex										
boys	266	0.28	0.54	1.93	3.72	11.3	40.4	1.17	0.64	0.57–0.71
girls	250	0.28	0.58	1.89	2.90	6.29	44.3	1.05	0.65	0.58–0.72
Age group*										
3–5 years	99	0.28	0.61	3.66	6.11	12.3	18.3	1.33	0.71	0.58–0.86
6–10 years	166	0.28	0.64	1.94	3.33	4.75	40.4	1.08	0.65	0.57–0.74
11–13 years	102	0.28	0.71	2.17	2.27	14.0	25.9	1.21	0.72	0.61–0.85
14–17 years	149	0.28	0.44	1.65	2.32	7.10	44.3	0.93	0.55	0.48–0.62
Community size (inhabitants)										
< 50,000	168	0.28	0.62	1.90	3.92	6.51	44.3	1.19	0.71	0.62–0.81
50,000 - \leq 100,000	31	0.28	0.38	1.84	6.44		18.3	0.95	0.48	0.35–0.66
\geq 100,000	317	0.28	0.58	1.94	2.86	6.84	40.4	1.08	0.63	0.57–0.69
Socioeconomic status*										
low	103	0.28	0.50	1.18	1.23	2.58	40.4	0.81	0.52	0.46–0.59
medium	309	0.28	0.57	2.12	4.02	9.64	44.3	1.21	0.67	0.60–0.74
high	82	0.28	0.63	1.91	2.82	5.44	25.9	1.02	0.64	0.53–0.77
Region of residence										
West Germany (including West Berlin)	434	0.28	0.58	1.94	3.73	6.65	25.9	1.09	0.65	0.60–0.71
East Germany (including East Berlin)	82	0.28	0.49	1.91	2.65	16.9	44.3	1.22	0.59	0.49–0.72
Migration background*										
no migration background	358	0.28	0.58	1.94	3.28	10.4	44.3	1.22	0.67	0.61–0.73
one-sided migration background	59	0.28	0.28	1.21	1.90	4.07	4.27	0.63	0.47	0.39–0.56
two-sided migration background	83	0.28	0.54	2.17	4.02	5.42	5.49	0.96	0.63	0.52–0.76
Carpets, carpet tiles, rugs**										
with plastic underlay	205	0.28	0.73	2.12	3.85	6.62	18.3	1.17	0.75	0.66–0.85
without plastic underlay	249	0.28	0.47	1.85	2.28	12.0	44.3	1.15	0.59	0.53–0.66
PVC flooring**										
Yes	135	0.28	0.41	1.71	2.96	3.83	7.27	0.81	0.54	0.47–0.62
No	380	0.28	0.62	1.94	3.99	8.07	44.3	1.22	0.68	0.62–0.75
Wearing of plastic or rubber shoes without socks in summer										
yes	238	0.28	0.53	2.06	4.24	6.84	40.4	1.19	0.63	0.56–0.70
no	277	0.28	0.59	1.90	3.16	4.02	44.3	1.04	0.66	0.59–0.73
Habit of chewing on plastic objects										
yes	123	0.28	0.63	3.52	5.22	6.84	40.4	1.30	0.70	0.59–0.84
no	392	0.28	0.54	1.77	2.26	6.05	44.3	1.05	0.62	0.57–0.68
Consumption of fast food or convenience food before urine sampling										
1 day before	111	0.28	0.54	2.17	6.08	11.9	40.4	1.34	0.67	0.56–0.80
2 days before	71	0.28	0.61	2.10	5.42	7.79	18.3	1.16	0.68	0.55–0.84
more than 2 days/never before	328	0.28	0.58	1.84	3.01	4.27	44.3	1.03	0.63	0.57–0.69
House dust level of DPHP										
low	47	0.28	0.62	1.75	1.89	– ^a	7.27	0.81	0.63	0.52–0.77
medium	12	0.28	0.82	3.13	– ^a	– ^a	4.27	1.01	0.71	0.41–1.24
high	67	0.28	0.59	3.23	6.88	18.2	25.9	1.66	0.76	0.58–0.99

For abbreviations see Table 4. For description of subpopulations see Tables 2 and 3 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). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

^a No distinct values calculable.

compared to other studies confirm that a continuous monitoring for DINCH and DPHP is necessary to observe exposure trends and the aggregate burden to plasticisers as well as to identify potential exposure sources. These are prerequisites to support actions to reduce exposure, especially in children and adolescents and other susceptible population groups.

4. Conclusion

The results of GerES V show that all children and adolescents in Germany are exposed to DINCH, confirming its widespread use and omnipresence in daily life. Young children are exposed to DINCH at about 3-fold higher levels than adolescents. Furthermore, the DINCH biomarker levels determined in GerES V are higher than those reported in adults, suggesting a higher DINCH burden in children and adolescents than in adults. Likewise DPHP was determined in a large

proportion of the children and adolescents, reflecting its extensive use and the exposure of the general population. The exceedance of the health-based guidance value for DINCH indicates the need for reduction measures in certain applications and ongoing monitoring of exposure, especially in young children.

The results show that continuous surveillance of DINCH and DPHP exposure is warranted. Furthermore, the evaluation of the GerES V results supports the basis to derive current reference values for this subpopulation in Germany, providing valuable information to assess whether individuals or subgroups are more exposed when compared to environmental background exposure.

Beyond that, the representative GerES V DINCH and DPHP exposure data will be shared with the European HBM initiative HBM4EU in order to build up and enhance knowledge about exposure to these chemicals. This will support the EU chemicals regulation and foster the protection of Europeans against environmental health risks.

Table 7
Comparison of levels of OH-MINCH and oxo-MPHP in urine ($\mu\text{g/L}$) in different studies.

Study, region (reference)	Sampling year	Sample: age and size	P50	GM	AM
OH-MINCH					
ESB ^a Germany (Schütze et al., 2014)	1999–2012	20–30 years, N = 60	Trend: 0–98.3% > 0.05 (LOQ) GM 2012: 0.39		
USA (Silva et al., 2013)	2000–2012	adults, N = 527	Trend: 0–19% > 0.4 (LOD)		
NHANES ^b USA (CDC, 2019)	2015–2016	20 + years, N = 1690	0.500		
Sweden (Gyllenhammar et al., 2017)	2009–2014	20–41 years, women, N = 178	Trend: AM 2009: 0.2, AM 2014: 0.7 (oxo-MINCH)		
Norway (Giovannoulis et al., 2016)	2013–2014	20–66 years, N = 61	84–90% > LOD		
ESB ¹ Germany (Kasper-Sonnenberg et al., 2019)	2017	20–30 years, N = 60	0.695		
GerES V Germany (this study)	2015–2017	3–17 years, N = 2228	2.20	2.27	5.68
GerES V Germany (this study)	2015–2017	3–5 years, N = 389	4.25	4.52	13.2
GerES V Germany (this study)	2015–2017	6–10 years, N = 731	2.37	2.59	4.69
NHANES ² USA (CDC, 2019)	2015–2016	3–5 years; N = 465	1.30	1.36	
NHANES ² USA (CDC, 2019)	2015–2016	6–11 years; N = 415	1.10	1.15	
Germany (Fromme et al., 2016)	2011–2012	27–80 months, N = 208	1.66		
Australia (Gomez Ramos et al., 2016)	2012–2013	5–14 years, 4 pools à 100			1.8, 2.7, 3.1, 3.5
Portugal (Correia-Sa et al., 2017)	2014–2015	4–18 years, N = 112		2.14	
Sweden (Larsson et al., 2017)	2015	40–58 months, N = 113		2.2	
oxo-MPHP					
GerES V Germany (this study)	2014–2017	3–17 years, N = 516	62% > 0.25 (LOQ), GM: 0.32		
ESB ¹ Germany (Schütze et al., 2015)	1999–2012	20–30 years, N = 300	Trend: 0.0–21.7% > 0.25 (LOQ)		
ESB ¹ Germany (Schmidtkunz et al., 2019)	2012,2014,2017	20–30 years, N = 180	Trend: 21.7, 15.0, 18.3% > 0.25 (LOQ)		

Abbreviations: N: sample size, LOQ: limit of quantification, LOD: Limit of detection, P50: 50th percentile, GM: geometric mean, AM arithmetic mean.

^a ESB: Environmental Specimen Bank.

^b NHANES: National Health and Nutrition Examination Survey.

Table 8
Exceedances of HBM I values for DINCH and DPHP.

HBM I value for children	Value in mg/L	% of GerES V participants exceeding HBM-I-value	Extrapolated for the population in Germany aged 3–17 years (~11 million)
Σ DINCH metabolites OH-MINCH and cx-MINCH	3	0.04	~4400 persons
Σ DPHP metabolites OH-MPHP and oxo-MPHP	1	–	–

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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.2019.09.004>.

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