# Hexamoll(R) 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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# 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

Gerda Schwedler[a,*], André Conrad[a], Enrico Rucic[a], Holger M. Koch[b], Gabriele Leng[c], Christine Schulz[a], Maria I.H. Schmied-Tobies[a], Marike Kolossa-Gehring[a]

[a] German Environment Agency (UBA), Berlin, Germany
[b] Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-University Bochum (IPA), Bochum, Germany
[c] Currenta GmbH Co. OHG, Institute of Biomonitoring, Leverkusen, Germany

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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 (Giovanoulis 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 |
| BMU | German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety |
| CAS | Chemical Abstract Service |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence intervall |
| DEHP | di-(2-ethylhexyl) phthalate |
| DIDP | di-iso-decyl phthalate |
| DINCH | di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate |
| DiNP | di-iso-nonyl phthalate |
| DPHP | di-(2-propylheptyl) phthalate |
| ECHA | European Chemicals Agency |
| EEA | European Environment Agency |
| EFSA | European Food Safety Authority |
| ESB | German Environmental Specimen Bank |
| GerES | German Environmental Survey |
| 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 |
| LOD | limit of detection |
| LOQ | limit of quantification |
| max | maximum |
| N | sample size |
| NHANES | National Health and Nutrition Examination Survey |
| P | percentiles |
| PVC | polyvinyl chloride |
| REACH | European chemicals legislation concerning the registration, evaluation, authorisation and restriction of chemicals |
| RKI | Robert Koch-Institute, Germany |
| SVHC | substance of very high concern |
| UBA | German Environment Agency |
| VCI | German Chemical Industry Association |

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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 (Blaszkiewicz 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 (µg/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 (G-EQUAS).

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 $X^2$ 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 anlysed 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.

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 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).

**Table 5**

Urinary levels of DINCH (Σ of OH-MINCH + cx-MINCH) in subpopulations of the GerES V participants in μg/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 - ≤100,000 | 142 | 1.03 | 3.25 | 13.5 | 18.9 | 24.6 | 46.0 | 5.30 | 3.26 | 2.77–3.84 |
| ≥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 ≤ 0.05, **p ≤ 0.01, ***p ≤ 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 μg/g creatinine for 3–5 years old children versus GM of 0.34 μg/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 μg/L versus 0.64 μg/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 (Schmidtkunz 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
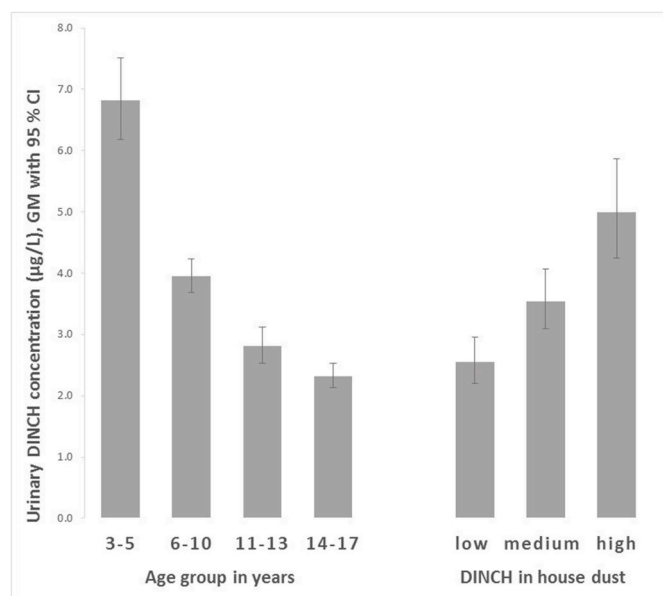
**Fig. 1.** Urinary DINCH (Σ OH-MINCH + cx-MINCH) concentrations in GerES V participants by age group and concentration of DINCH in house dust.
DINCH level categories in house dust were: low: < 11.3 μg/g, medium: 11.3–25.8 μg/g, high: > 25.8 μg/g.

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 μg/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 μg/L) of their methodology compared to our (0.05 μg/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 μg/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 μg/L in 2009 to 0.7 μg/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 μg/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 μg/L compared to 0.500 μg/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 μg/L in children 3–5 years, 2.59 versus 1.15 μg/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 μg/L for the 3–17 years old German and GM of 2.14 μg/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 μg/L) (Fromme et al., 2016), c) in 40–59 months old Swedish preschool children (GM of 2.2 μg/L) (Larsson et al., 2017), and d) in 5–14 years old children from Australia (AMs from 1.8 to 3.5 μg/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 µg/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 - ≤100,000 | 31 | 0.28 | 0.38 | 1.84 | 6.44 | | 18.3 | 0.95 | 0.48 | 0.35–0.66 |
| ≥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 wayANOVA (differences of GM). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 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 (µg/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) | 2009–2012 | 20–41 years, women, N = 178 | Trend: AM 2009: 0.2, AM 2014: 0.7 (oxo-MINCH) | | |
| Norway (Giovanoulis 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 | – | – |

## Acknowledgements

## 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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