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Time trend of exposure to the phthalate plasticizer substitute DINCH in Germany from 1999 to 2017: Biomonitoring data on young adults from the Environmental Specimen Bank (ESB)

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ABSTRACT

DINCH (cyclohexane-1,2-dicarboxylic acid-diisononyl ester) is a phthalate plasticizer substitute introduced into the market in 2002. It is increasingly used especially in the production of toys, food contact materials and medical devices. In this measurement campaign on 24-h urine samples of young adults (20–29 years) from the German Environmental Specimen Bank (ESB) collected in 2010, 2011, 2013, 2015 and 2017 (in total 300 samples, 60 samples/year) we analyzed three specific, oxidized DINCH metabolites (OH-MINCH: cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester; cx-MINCH: cyclohexane-1,2-dicarboxylic acid-mono(carboxy-isooctyl) ester, oxo-MINCH: cyclohexane-1,2-dicarboxylic acid-mono(oxo-isononyl) ester). We merged these data with earlier data of the ESB from the years 1999–2012 and are now able to report levels and time trends of internal DINCH exposure from 1999 to 2017.

After first detections of the major oxidized DINCH metabolite OH-MINCH in 2006 (6.7%) detection rates rapidly increased to 43.3% in 2009, 80% in 2010 and 98.3% in 2011 and 2012. From the year 2013 on we could detect OH-MINCH in every urine sample analyzed. The median concentrations of OH-MINCH rapidly increased from 0.15 µg/L in 2010 to twice the concentration in 2011 (0.31 µg/L) with further increases in 2013 (0.37 µg/L), 2015 (0.59 µg/L) and 2017 (0.70 µg/L). Similar increases, albeit at lower detection rates and concentration levels, could be observed for cx-MINCH and oxo-MINCH. All metabolites strongly correlate with each other.

For the ESB study population, DINCH exposures are still far below health based guidance values such as the German Human Biomonitoring Value (HBM-I; 4,500 µg/L for the sum of OH-MINCH and cx-MINCH) or the tolerable daily intake (TDI) of EFSA (1 mg/kg bw/d). The median daily DINCH intake (DI) calculated for 2017 was 0.23 µg/kg bw/d, thus 4,310-times lower than the TDI. The maximum DI calculated for one individual in 2012 (42.60 µg/kg bw/d) was a factor of more than 20 below the TDI.

The ongoing increase in DINCH exposure needs to be closely monitored in the future, including populations with potentially higher exposures such as children. This close monitoring will enable timely exposure and risk reduction measures if exposures reached critical levels, or if new toxicological data lead to lower health based guidance values. DINCH belongs to the European Human Biomonitoring Initiative (HBM4EU) priority substances for which policy relevant questions still have to be answered.

1. Introduction

Cyclohexane-1,2-dicarboxylic acid-diisononyl ester (DINCH, Hexamoll® DINCH, ELATUR® CH), hereinafter referred to as DINCH, is a substitute for endocrine disrupting and/or regulated high molecular weight phthalate plasticizers (e. g. DEHP: di-(2-ethylhexyl) phthalate; DiNP: di-isononyl phthalate) in the production of plastics, particularly in sensitive applications such as toys, food contact material or medical devices (Janssen and Bremmer, 2009; Testai et al., 2016).

DINCH was first introduced into the European market in 2002. The main producer BASF increased the production capacity from 25 ktons in 2002 to 200 ktons in 2014 (BASF, 2017a). DINCH consumption in

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Western Europe (including Germany) has steadily increased from 9 ktons in 2002 to 55 ktons in 2014 with estimated 62 ktons in 2019 (Malveda et al., 2015; HBM4EU, 2018). For the U.S., generally lower, but also increasing consumptions from 3.5 ktons in 2013 to 6.1 ktons in 2019 are estimated (Malveda et al., 2015). These numbers illustrate that increasing population exposures to DINCH have to be expected. Biomonitoring data have been shown to provide useful insights in the extent of exposure reflecting ongoing market changes and substitutions of classical phthalate plasticizers with alternatives (Silva et al., 2013; Schütze et al., 2014, Schütze et al., 2015; Zota et al., 2014; Gyllenhammar et al., 2017; Koch et al., 2017; Lessmann et al., 2017; Schoeters et al., 2017; Sackmann et al., 2018).

Once ingested, DINCH is rapidly metabolized to its respective hydrolytic and/or oxidative monoesters, which are excreted in urine after (partial) glucuronidation (Silva et al., 2012; Koch et al., 2013; Völkel et al., 2016; Schütze et al., 2017). Urinary biomarkers of DINCH exposure include the oxidation products of the alkyl side chain of the monoester cyclohexane-1,2-dicarboxylic acid-mono(isononyl) ester (MINCH): cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester (OH-MINCH), cyclohexane-1,2-dicarboxylic acid-mono(carboxy-isooctyl) ester (cx-MINCH) and cyclohexane-1,2-dicarboxylic acid-mono(oxo-isononyl) ester (oxo-MINCH). Similar to the high molecular weight phthalates (Koch et al., 2013), for the general population dietary intake is the predominant route of exposure and contributes to about 90% of the internal exposure whereas dust ingestion contributes to about 10%. Dermal and inhalation uptakes are minor uptake routes (Giovanoulis et al., 2018). Because of its use in toys and medical devices, additional routes of exposure can be relevant for children, e.g. mouthing of toys and increased dust ingestion (Fromme et al., 2016; Ginsberg et al., 2016; Lioy et al., 2015; Weiss et al., 2018), or medical patients, e.g. leaching/migration from medical devices (BASF, 2017b; Bernard et al., 2015; Pinguet et al., 2019; Malarvannan et al., 2019).

In contrast to some high molecular weight phthalates, for DINCH there is currently no evidence for developmental or reproductive toxicity from animal studies (EFSA, 2006). Furthermore, there is no evidence of endocrine disrupting potency (Furr et al., 2014; Engel et al., 2018). In 2006, the European Food and Safety Authority (EFSA) established a tolerable daily intake (TDI) of DINCH at 1 mg/kg body weight (bw)/d for renal toxicity (EFSA, 2006). An oral reference dose (RfD) of 0.7 mg/kg bw/d was derived from a human equivalent of the Benchmark Dose Lower Confidence Limit, 10% ($BMDL_{10}$) of 21 mg/kg bw/d for thyroid hypertrophy/hyperplasia seen in adult F_1 rats exposed in utero (Bhat et al., 2014). Based on the EFSA TDI, the German Human Biomonitoring Commission established urinary human biomonitoring (HBM-I) values for the sum of the DINCH metabolites OH-MINCH + cx-MINCH for adults (4.5 mg/L) and children (3.0 mg/L) (Apel et al., 2017). At levels below these HBM-I values there is no risk expected for adverse health effects and no need of action (Apel et al., 2017). Within the EU, DINCH is approved for the use in plastic materials for food packaging (Regulation(EU) No 1935/2004) and has also been listed in Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food without a specific migration limit (Regulation (EU) No 10/2011) (FCM substance No. 775).

The European Joint Program Human Biomonitoring for EU - HBM4EU www.hbm4eu.eu (Ganzleben et al., 2017), a joint effort among 28 HBM4EU 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 EFSA)), was initiated in 2017. The major goal of this program is implementing comparable EU-wide human biomonitoring data to provide evidence for chemical policy making. The HBM4EU consortium has identified DINCH as a substance of priority interest as a relevant alternative to regulated phthalate plasticizers.

The German Environmental Specimen Bank (ESB) collects and stores inter alia human specimens (urine, whole blood and blood plasma) since 1981 (Kolossa-Gehring et al., 2012). For all steps of the pre-analytical phase standard operation procedures have been developed and applied to safeguard comparability of the samples. Continuously collected and cryo-preserved 24-h urine samples enabled to retrospectively investigate internal exposures to DINCH and to follow possible time trends of exposure. In a first measurement campaign on samples from 1999 to 2012 the first detection and rapidly increasing exposures to DINCH were shown (Schütze et al., 2014). With the second measurement campaign, presented here, the timeline was extended to 2017 now covering a time-span of 19 years.

2. Materials and methods

2.1. Analytical procedure

DINCH metabolites in urine were determined after enzymatic hydrolysis with *E. coli* β-glucuronidase K12 (arylsulfatase-free) and online enrichment by means of stable isotope dilution analysis using HPLC-MS/MS according to (Schütze et al. (2012, 2017), identical to the first measurement campaign (Schütze et al., 2014). In short, urine samples were matrix depleted and enriched on a Capcell PAK (5u C18-MG-II Guard Cartridge (10 × 4 mm), Phenomenex) and chromatographically resolved on an Atlantis dC18 (2.1 × 150 mm; 3 µm; Waters) applying a water-acetonitrile gradient in 0.05% acetic acid. The injection volume was 25 µL. Limits of quantification (LOQ) of 0.05 µg/L were obtained for all three DINCH metabolites (OH-MINCH, cx-MINCH and oxo-MINCH) based on the 9-fold signal-to-noise ratio in urine. D4-OH-MINCH and D2-cx-MINCH were used as stable isotope-labeled internal standards. No stable isotope-labeled internal standard was available for the metabolite oxo-MINCH. Instead, we used the stable isotope-labeled standard D4-OH-MINCH. The results for oxo-MINCH should, therefore, be regarded as semi-quantitative. The precision of the method was determined by processing and analyzing two native pooled urines (one with high and one with low concentration). For within series precision, these pooled quality controls were analyzed eight times in a row. For day-to-day precision the quality controls were processed and analyzed on eight different days. For the within series precision we obtained a variation coefficient of < 5% and for the day-to-day precision of < 10%. To determine accuracy (relative recovery), eight individual urines were processed and analyzed non-spiked and after spiking at 2 or 10 µg/L. Accuracy was between 84 and 108% (Q low) and 88–106% (Q high). The samples of the first and second measurement campaign (Schütze et al., 2014) were analyzed under the same analytical conditions and in the same laboratory with continuous quality assurance.

2.2. Study population

The Institute for Prevention and Occupational Medicine (IPA) was provided by the ESB with 24-h urine samples from the years 2010, 2011, 2013, 2015 and 2017 (30 males and 30 females per year, a total of 300 samples). Samples from 2010 to 2011 were chosen to ensure a good overlap with the previous study by Schütze et al., (2014) (ending with samples from 2012) and a 2 year interval (from 2011 to 2017) instead of a 3 year interval was chosen to be able to follow the rather rapid changes in exposure more closely. The concept and sampling criteria of the ESB, as well as storage conditions, are described in detail elsewhere (Kolossa-Gehring et al., 2012; Schütze et al., 2014; Lermen et al., 2014). Participants were students from the University of Münster, aged 20–29 years. All urine samples were randomized before measurement, and blinded to the analyzing laboratory. The complete decoding of the urine samples for further evaluation was carried out by the German Environment Agency (UBA) after the results of the analysis were sent to the UBA. The Ethics Commission of the Medical Association of Westphalia-Lippe and the Medical Faculty of the Westfälische Wilhelms-Universität Münster and (since 2012) the ethical committee of the Medical Association of the Saarland examined and approved the

Table 1
Anthropometric data of the study population (data for the new measurement campaign in bold).

Year of sampling	n (male/female)	Age [years] mean (min-max)	Body weight [kg] mean (min-max)	24h urine volume [mL] mean (min-max)	Creatinine [g/L] mean (min-max)
1999	60 (30/30)	24.3 (21–29)	71.8 (46–175)	1595 > (550–4000)	1.05 (0.28–2.66)
2003	60 (30/30)	23.0 (20–28)	70.2 * (49–105)	1757 (410–3500)	1.10 (0.23–3.41)
2006	60 (30/30)	24.0 (20–29)	69.4 (47–95)	1897 (719–4250)	0.89 (0.29–2.11)
2009	60 (30/30)	23.2 (20–28)	69.4 (50–102)	2074 (540–3660)	0.83 (0.27–2.19)
2010	**60 (30/30)**	**23.3 (20-28)**	**72.0 (50-101)**	**1985 (749-5168)**	**0.85 (0.28-2.19)**
2011	**60 (30/30)**	**23.2 (20-29)**	**73.5 (52-102)**	**1823 (393-3049)**	**0.89 (0.25-2.12)**
2012	60 (30/30)	24.2 (20–30)	70.6 (48–105)	2108 (574–3027)	0.70 (0.21–2.18)
2013	**60 (30/30)**	**23.7 (20-29)**	**69.4 (50-112)**	**1894 (502-3194)**	**0.79 (0.29-1.71)**
2015	**60 (30/30)**	**23.2 (20-29)**	**67.9 (49-95)**	**1937 (271-4601)**	**0.72 (0.15-2.20)**
2017	**60 (30/30)**	**23.5 (20-29)**	**71.6 (46-110)**	**2102 (561-3211)**	**0.76 (0.17-2.34)**
Total of the two campaigns					
All participants	600 (300/300)	23.6 (20–30)	70.6 (46–175)	1910 (271–5168)	0.86 (0.15–3.41)
Male	300	23.8 (20–30)	78.6 (52–175)	1967 (410–5168)	1.00 (0.25–3.41)
Female	300	23.3 (20–30)	62.5 ** (46–105)	1852 (271–4601)	0.72 (0.15–2.24)

*n = 59; **n = 299; bold: data from the second measurement campaign.

complete study protocol for collecting human samples. All participants provided their informed written consent. Information on total 24-h urine volume, body weight, height, age and sex were collected by the ESB. Further information of the study population is depicted in Table 1.

2.3. Statistical analyses

Metabolite concentrations determined in this measurement campaign (for the years 2010, 2011, 2013, 2015 and 2017) were combined with the results of the previous measurement campaign (for the years 1999, 2003, 2006, 2009 and 2012) reported by Schütze et al. (2014). Metabolite concentrations below the LOQ were included in all calculations using LOQ/2 (0.025 µg/L). Because the concentrations were not normally distributed we calculated differences between male and female participants with the non-parametric Mann-Whitney *U* test.

Correlation analyses were performed using the non-parametric Spearman rank correlation analysis. For time trend investigations, correlation analysis between the metabolite concentrations and the years of sampling were examined by adjusting the concentrations to distance-weighted least squares. A linear regression requires that the residuals are equally distributed over the complete range of the independent variable. If this is not the case (as for the respective metabolite concentrations) the use of this method is more appropriate. Secondly, the values must have a normal distribution and therefore, we used logarithmically transformed metabolite concentrations. The sum of the squared deviations of the observed and predicted values is used as a loss function of the estimation with choosing a stiffness parameter of 0.25. With this analysis, outliers will get lower weights than values within the normal distribution. The results are smoothed correlation curves. Furthermore, we tested exposure differences of the metabolites ΣOH-MINCH + cx-MINCH across the sampling years with the Kruskal-Wallis and Jonckheere-Terpstra tests.

The sum of the two metabolites OH-MINCH + cx-MINCH was calculated by summation of the volume-related metabolite concentrations (in µg/L).

From the 24-h urine samples the daily intake (DI) was calculated for ΣOH-MINCH + cx-MINCH based on the urinary concentrations by the product of the respective urinary metabolite concentrations (sum UC in µmol/L), the 24-h urine volume (UV 24h in L) and the molar mass of DINCH (M_{DINCH} in µg/µmol), divided by the product of the urinary excretion factor (sum FUE), and the individual body weight (bw):

$$DI\ [\mu g/kg\ bw/d] = (UC\ OH\text{-}MINCH\ [\mu mol/L] + UC\ cx\text{-}MINCH\ [\mu mol/L]) \times UV\ 24h\ [L] \times M_{DINCH}\ [\mu g/\mu mol]/(\Sigma FUE) \times bw\ [kg]$$

The FUEs represent the percentage of metabolites excreted in urine in relation to the applied dose on a molar basis to calculate the DI with FUEs (OH-MINCH = 10.73%; cx-MINCH = 2.03%; $\Sigma FUE = FUE_{OH\text{-}MINCH} + FUE_{cx\text{-}MINCH}$) reported by Koch et al. (2013) and Schütze et al. (2017). DIs at the geometric mean (GM), median and 95th percentile are only presented if a sufficient number of samples within a given year had OH-MINCH levels above the LOQ (> 60% for GM and median; > 10% for 95th percentile). In all other cases, DI values are set to N.A. (not applicable). The statistical analyses were performed with SAS 9.4 Institute Inc. and Statistica (data analysis software system) v13, TIBCO Software Inc. (2018) (for distance-weighted least square and Spearman correlation analyses).

3. Results

3.1. Measurement campaign 2010–2017

The results of the current measurement campaign, summarized for the years 2010–2017, separated for males and females, and as total, are depicted in Table 2 in µg/L. Creatinine adjusted results are given in Table 3. For all three DINCH metabolites we obtained median concentrations above the LOQ, showing the increased detection rates of DINCH in the more recent years compared to the first measurement campaign covering the years 1999–2012 (Schütze et al., 2014). Detection rates were 95.7% for OH-MINCH, 85.3% for oxo-MINCH and 66.3% for cx-MINCH. Similar to detection rates, also in terms of urinary concentrations, OH-MINCH was the dominant metabolite (median 0.42 µg/L, maximum 72.4 µg/L), followed by oxo-MINCH (median 0.22 µg/L, maximum 45.5 µg/L) and cx-MINCH (median 0.14 µg/L, maximum 23.3 µg/L). This finding is in agreement with human metabolism and urinary excretion of DINCH metabolites after oral dosage (Schütze et al., 2017; Völkel et al., 2016; Koch et al., 2013).

For both the volume-related and the creatinine-adjusted concentrations, women had slightly higher metabolite levels in the medians, GMs and 95th percentiles in comparison to men. For cx-MINCH, this difference was statistically significant at $p \leq 0.05$ (median: 0.16 µg/L vs. 0.10 µg/L) and, similarly, this trend was also detected with OH-MINCH although not statistically significant (median: 0.43 µg/L vs. 0.39 µg/L; $p \leq 0.1$). For the creatinine-adjusted concentrations, differences were statistically significant for all metabolites with p-values ≤ 0.001 (median: OH-MINCH 0.74 vs. 0.44 µg/g; cx-MINCH 0.36 vs. 0.22 µg/g; oxo-MINCH 0.26 vs. 0.12 µg/g) (Table 3).

All three urinary metabolites were highly correlated with each other as shown in Fig. 1, confirming the reliability, robustness and specificity of all three metabolites as biomarkers of DINCH exposure.

With this second measurement campaign we are able to fill the gaps (years 2010 and 2011) of the first measurement campaign (years 1999–2012) and extended the timeline for the years 2013, 2015 and

Table 2
Summary statistics of the metabolite concentrations from the second measurement campaign 2010–2017 (levels below LOQ were included in calculations using LOQ/2).

	OH-MINCH [µg/L]	cx-MINCH [µg/L]	oxo-MINCH [µg/L]*
Females			
GM	0.47	0.14	0.26
Median	0.43	0.16	0.26
P95	4.39	1.33	2.67
Min-Max	< LOQ-34.8	< LOQ-9.58	< LOQ-17.4
n	150	150	150
n > LOQ	145	110	135
% > LOQ	96.7	73.3	90.0
Males			
GM	0.41	0.11	0.18
Median	0.39	0.10	0.19
P95	3.48	1.35	2.16
Min-Max	< LOQ-72.4	< -LOQ-23.3	< LOQ-45.5
n	150	150	150
n > LOQ	142	89	121
% > LOQ	94.7	59.3	80.7
Total			
GM	0.44	0.12	0.22
Median	0.42	0.14	0.22
P95	4.28	1.34	2.61
Min-Max	< LOQ-72.4	< LOQ-23.3	< LOQ-45.5
n	300	300	300
n > LOQ	287	199	256
% > LOQ	95.7	66.3	85.3

* semi-quantitative; GM: geometric mean; P95: 95th percentile; Min: minimum; Max: maximum; LOQ: limit of quantification (0.05 µg/L).

Table 3
Summary statistics of the creatinine-adjusted metabolite concentrations (µg/g crea) of the second measurement campaign (GM, median, P95 were calculated where 50% of samples had levels above LOQ, minimum values (< LOQ) were set to N.A.

	OH-MINCH [µg/g crea]	cx-MINCH [µg/g crea]	oxo-MINCH [µg/g crea]*
Females			
GM	0.76	0.42	0.23
Median	0.74	0.36	0.26
P95	7.71	4.50	2.56
Min-Max	N.A. - 100	N.A. - 50.2	N.A. - 27.7
n	150	150	150
Males			
GM	0.49	0.22	0.13
Median	0.44	0.22	0.12
P95	4.62	2.34	1.50
Min-Max	N.A. - 189	N.A. - 96.13	N.A. - 30.8
n	150	150	150
Total			
GM	0.61	0.31	0.17
Median	0.56	0.29	0.20
P95	7.07	4.21	2.02
Min-Max	N.A. - 189	N.A. - 96.1	N.A. - 30.8
n	300	300	300

*semi-quantitative; GM: geometric mean; P95: 95th percentile; Min: minimum; Max: maximum; crea: creatinine; N.A.: not applicable.

2017. Therefore, we are now presenting urinary DINCH metabolite data for the time between 1999 and 2017 (years 1999, 2003, 2006, 2009, 2010, 2011, 2012, 2013, 2015, and 2017), see Table 4 and Fig. 2.

As already stated by Schütze et al. (2014), we detected no DINCH metabolites (LOQ = 0.05 µg/L) in samples collected in 1999 (pre-market introduction of DINCH) and 2003 (one year after market introduction in 2002). Thereafter, detection rates of the major oxidized DINCH metabolite OH-MINCH rapidly increased from 6.7% in 2006 to 43.3% in 2009, 80% in 2010 and 98.3% in 2011 and 2012. From the year 2013 on we detected this metabolite in every 24-h urine sample of

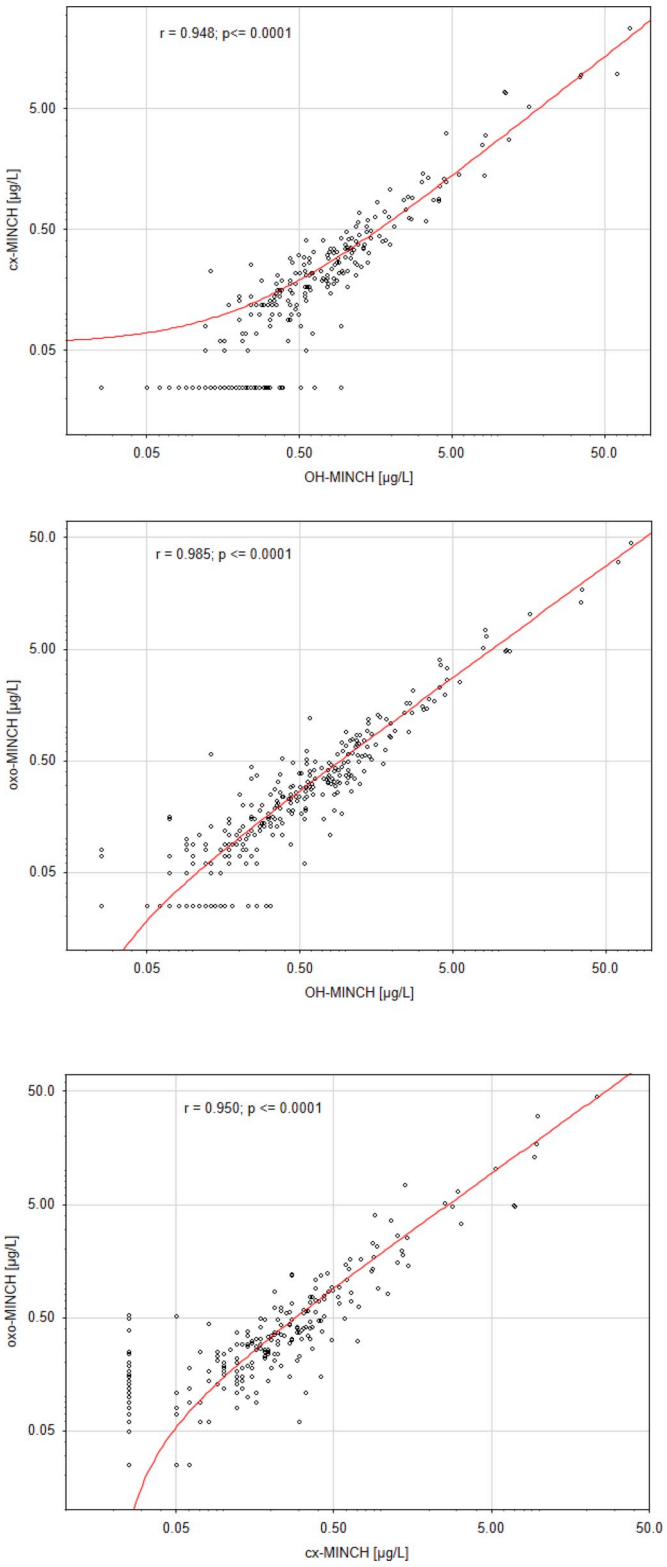

Fig. 1. Correlation analyses of the three DINCH metabolites among each other in samples from the recent measurement campaign (2010–2017). Samples with metabolite levels below LOQ were included with LOQ/2. Time trends of exposure (1999–2017).

the ESB analyzed. This increase in OH-MINCH detections is flanked by increasing detections of the other two oxidized DINCH metabolites.

The increase in metabolite detection rates is also reflected in a rapid increase in urinary metabolite concentrations. From the year 2010 on

Table 4
Metabolite concentrations (µg/L) for individual sampling years (N = 600).

	OH-MINCH					cx-MINCH					oxo-MINCH*					∑OH-MINCH + cx-MINCH			
Year	GM (95th conf. interval)	% >LOQ	P50	P95	Min-Max	GM (95th conf. interval)	% >LOQ	P50	P95	Min-Max	GM (95th conf. interval)	% >LOQ	P50	P95	Min-Max	GM (95th conf. interval)	P50	P95	Min-Max
1999	<LOQ	0	<LOQ	<LOQ	<LOQ-<LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ - <LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ-<LOQ	<LOQ	<LOQ	<LOQ	<LOQ - <LOQ
2003	<LOQ	0	<LOQ	<LOQ	<LOQ-<LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ - <LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ-<LOQ	<LOQ	<LOQ	<LOQ	<LOQ - <LOQ
2006	<LOQ	6.7	<LOQ	0.074	<LOQ - 0.42	<LOQ	3.3	<LOQ	<LOQ	<LOQ - 0.29	<LOQ	5	<LOQ	<LOQ	<LOQ - 0.22	<LOQ	<LOQ	<LOQ	<LOQ - 0.72
2009	0.063 (<LOQ - 0.090)	43.3	<LOQ	1.015	<LOQ - 8.04	<LOQ (<LOQ - 0.061)	28.3	<LOQ	1.08	<LOQ - 4.67	<LOQ (<LOQ - 0.060)	20.0	<LOQ	0.745	<LOQ - 4.59	0.111 (0.080-0.155)	<LOQ	2.23	<LOQ - 12.71
2010	0.183 (0.123 - 0.273)	80.0	0.15	3.29	<LOQ - 11.78	0.053 (<LOQ - 0.075)	28.3	<LOQ	1.27	<LOQ - 2.79	0.085 (0.059 - 0.122)	55.0	0.07	1.460	<LOQ - 4.88	0.252 (0.174-0.363)	0.17	4.33	<LOQ - 14.57
2011	0.425 (0.280 - 0.645)	98.3	0.31	9.55	<LOQ - 72.41	0.118 (0.075 - 0.183)	58.3	0.09	5.08	<LOQ - 23.26	0.225 (0.142 - 0.356)	80.0	0.18	6.210	<LOQ - 45.54	0.559 (0.369-0.849)	0.36	13.74	<LOQ - 95.67
2012	0.395 (0.281 - 0.557)	98.3	0.39	2.06	<LOQ - 236	0.180 (0.128 - 0.254)	88.3	0.17	0.85	<LOQ - 98.40	0.252 (0.171 - 0.373)	85.0	0.25	1.644	<LOQ - 211	0.583 (0.416-0.818)	0.56	2.91	<LOQ - 334
2013	0.448 (0.343 - 0.586)	100	0.37	3.40	0.070 - 34.26	0.131 (0.096 - 0.179)	78.3	0.13	0.89	<LOQ - 9.24	0.250 (0.191 - 0.328)	100	0.21	2.225	0.050-13.13	0.595 (0.456-0.778)	0.52	4.31	<LOQ - 43.50
2015	0.640 (0.482 - 0.849)	100	0.59	3.94	0.090 - 34.75	0.175 (0.125 - 0.246)	80.0	0.21	1.34	<LOQ - 9.58	0.307 (0.224 - 0.420)	96.7	0.29	1.890	<LOQ - 17.36	0.833 (0.624-1.111)	0.83	5.28	0.115 - 44.33
2017	0.695 (0.534 - 0.904)	100	0.70	5.78	0.100 - 11.16	0.200 (0.147 - 0.274)	86.7	0.21	1.73	<LOQ - 6.89	0.331 (0.244 - 0.448)	95.0	0.31	3.350	<LOQ - 6.62	0.910 (0.696-1.191)	0.92	7.48	0.125 - 18.05

grey: second measurement campaign; LOQ: limit of quantification; GM: geometric mean; P50: median; P95: 95th percentile; * semi-quantitative

(the first year we could derive a median concentration for OH-MINCH) we observe a rapid increase from 0.15 µg/L to twice the concentration in 2011 (0.31 µg/L) and further increasing median concentrations in 2013 (0.37 µg/L), 2015 (0.59 µg/L) and 2017 (0.70 µg/L). Similar increases, albeit at lower concentration levels, can be observed for the other two metabolites.

Interestingly, and in spite of the steadily increasing medians, maximum metabolite concentrations in this study population were peaking in the years 2011 and 2012 with the highest 95th percentile for OH-MINCH determined in 2011 (9.55 µg/L) and the highest overall maximum determined in 2012 (236 µg/L), confirmed by the other metabolites.

Similar time trends were detected for the creatinine-adjusted metabolite concentrations (Table S1). Median creatinine-adjusted concentrations of OH-MINCH increased from 0.22 µg/g in 2010 to 0.93 µg/g in 2017. Highest exposures at the 95th percentile and maximum were seen in 2011 (8.97 µg/g and 189 µg/g). As for the volume-related concentrations, the other metabolite concentrations also increased but at lower levels, detectable since 2011.

Linear correlation analyses between the logarithmically transformed metabolite concentration of OH-MINCH and the sampling years indicated a statistical significant increase over the sampling years (Fig. 3, red regression line). Compared with the linear regression analysis (red regression line) the results of the distance-weighted least square correlation analyses reflect the time trend of exposure more clearly because outliers will get lower weights than values within the normal distribution and the results are smoothed correlation curves (green regression line). This analysis demonstrates the strongest correlation between the metabolite concentrations and the years of sampling within the years 2006 and 2012. Thereafter, the slope of the green regression curve decreases. Still, from 2012 to 2017, there is a 80% increase in OH-MINCH median levels, and from 2015 to 2017 there is a 20% increase. This increasing time trend of exposure was also confirmed with the Kruskal-Wallis and Jonckheere-Terpstra tests ($p \leq 0.001$).

3.2. Exposure and risk assessment

For risk assessment, urinary DINCH metabolite levels can be directly compared to the human biomonitoring value (HBM-I) for DINCH derived by the German Human Biomonitoring Commission. This value represents urinary biomarker concentration(s) equalling a steady state exposure at the TDI (Angerer et al., 2011; Apel et al., 2017). For DINCH this HBM-I value is 4,500 µg/L for adults and 3,000 µg/L for children (calculated as the sum of concentrations of the metabolites OH-MINCH and cx-MINCH). Therefore, in Table 4 and Fig. 2d we also present metabolite data for the sum of OH-MINCH and cx-MINCH. In 2017, the year of the highest median concentration (ΣOH-MINCH + cx-MINCH = 0.92 µg/L) this concentration was a factor of 4,891 times below the HBM-I value. The highest individual concentration (ΣOH-MINCH + cx-MINCH) determined so far in this study population (in 2012; 334 µg/L) was more than a factor of 10 below.

The daily DINCH intake (DI), calculated from the urinary concentration of the metabolites OH-MINCH and cx-MINCH, their known urinary excretion fractions, the individual 24-h urine volume and the individual body weight of each volunteer are depicted in Table 5. Similar to the urinary metabolite levels, the median DIs indicate continuously increasing DINCH exposures. Compared to the TDI of 1 mg/kg bw/d the median DI in the year 2017 (0.23 µg/kg bw/d) was a factor of 4,310-times lower. The maximum DI (calculated for the year 2012, 42.6 µg/kg bw/d) was lower by a factor of more than 20.

4. Discussion

4.1. Time trends and comparison with other populations

The results of the second measurement campaign on ESB 24-h urine samples from 2010 to 2017 fit well with the results of the first measurement campaign on samples from 1999 to 2012 (Schütze et al., 2014) and impressively prove the rapid increase of urinary DINCH metabolites both in terms of detection rates and concentrations. With the sensitive analytical methodology applied (LOQs of 0.05 µg/L for all three oxidized DINCH metabolites investigated) we are able to report reliable median concentrations for the major metabolite OH-MINCH

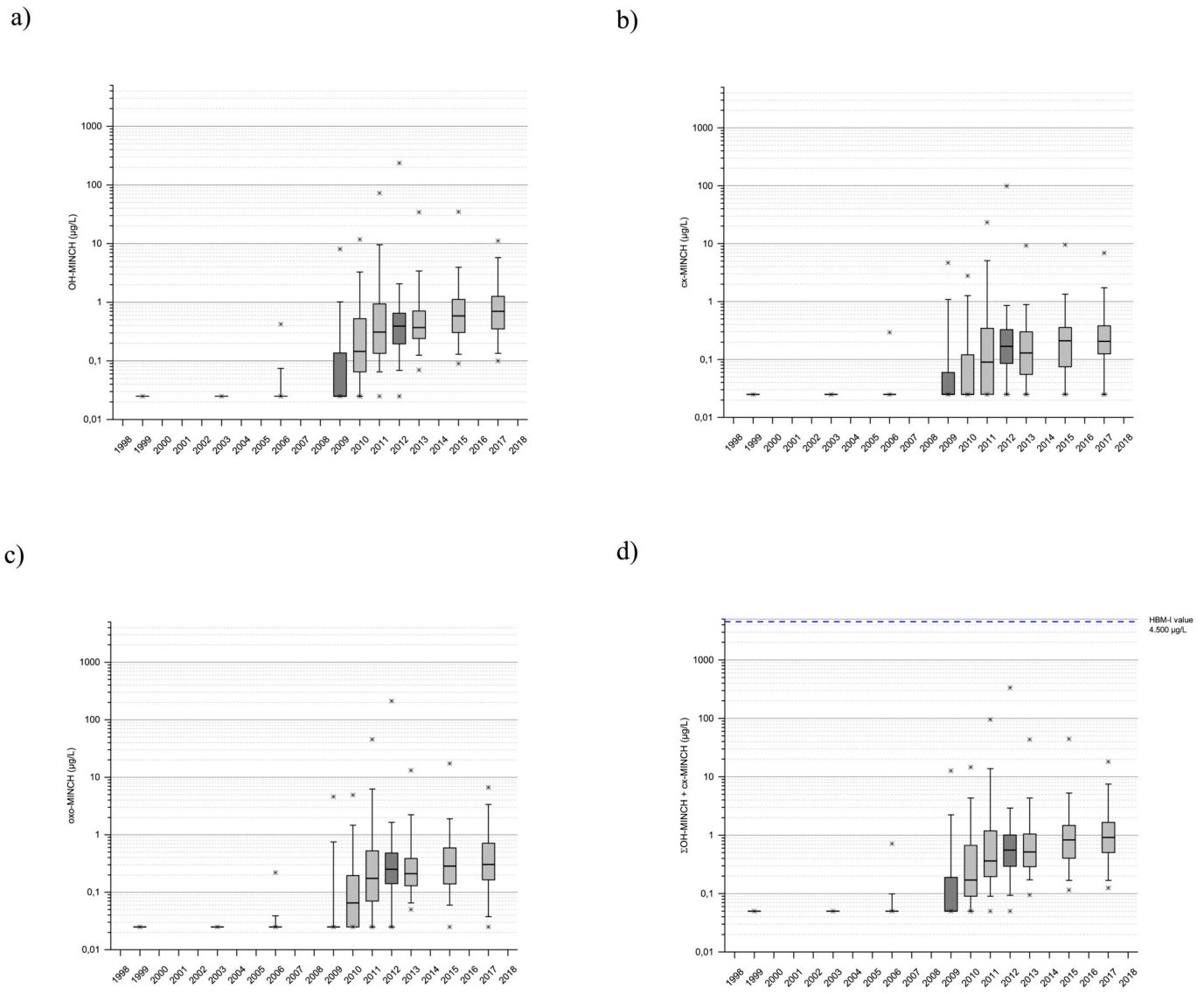

Fig. 2. DINCH metabolites over all individual sampling years (1999–2017) in µg/L: (a) OH-MINCH, (b) cx-MINCH, (c) oxo-MINCH and (d) ΣOH-MINCH + cx-MINCH, presented as box-plots. Boxes represent the interquartile range (25th to 75th percentile). The median is represented by the horizontal line, the whiskers represent the 5th and the 95th percentile; min and max values are represented by an x. Boxes of the recent measurement campaign in light grey.

starting from the year 2010 and the other two metabolites starting from the year 2011. Starting from the year 2013 we are able to detect OH-MINCH in each and every of the ESB 24-h urine samples analyzed. Somewhat lower concentrations of the other two metabolites (cx-MINCH and oxo-MINCH) are in line with the knowledge on human metabolism and urinary excretion fractions reported previously (Koch et al., 2013; Schütze et al., 2017; Völkel et al., 2016). However, the strong correlations among all three metabolites underline the ruggedness of the analytical method and the general quality of the urinary DINCH metabolites as exposure biomarkers.

We detected slightly, but statistically significant higher urinary DINCH metabolite concentrations in women compared to men. The U.S. National Health and Nutrition Examination Survey (NHANES) also detected higher concentrations in women compared to men at the median and P95 levels (e.g. OH-MINCH median: women 0.76 vs. men 0.57 µg/L; P95: women 7.32 vs men 5.75 µg/L) (CDC, 2019). We are not aware of any female characteristic sources of DINCH exposure. For the phthalates DINCH is used as a substitute (e.g. DEHP) we have not observed such significant effects (Koch et al., 2017). In their metabolism study (oral DINCH dose to three women and three men), Völkel et al. (2016) reported slightly higher excretions of oxidized DINCH metabolites in women compared to men (e.g. in women 16.0% of the DINCH dose was excreted as OH-MINCH, in men only 12.9%). Therefore, the differences observed in our study and in NHANES might be related to some slight differences in quantitative metabolism and excretion between women and men.

A linear extrapolation of the increasing metabolite concentrations (see Figs. 2 and 3) points to median OH-MINCH concentrations to exceed 1 µg/L within the next few years, however, there are also indications that the rapid increase observed over the last decade is slowing down or levelling off to median OH-MINCH levels in the low µg/L range, accompanied by the other metabolites. In the end, such predictions are unreliable and can only be confirmed or refuted by the continuation of actual population measurements. As has been shown for phthalates or other substitutes, changes can be rather rapid depending on plasticizer market changes, commercial and marketing aspects, regional peculiarities and the regulatory environment in the EU and other parts of the world (Koch et al., 2017).

The rapid increase in DINCH exposure in the German ESB population of young adults is mirrored by other studies in Europe and the U.S. Increasing trends for DINCH exposure were detected in primiparous mothers in a Swedish study performed between 2009 and 2014 (30

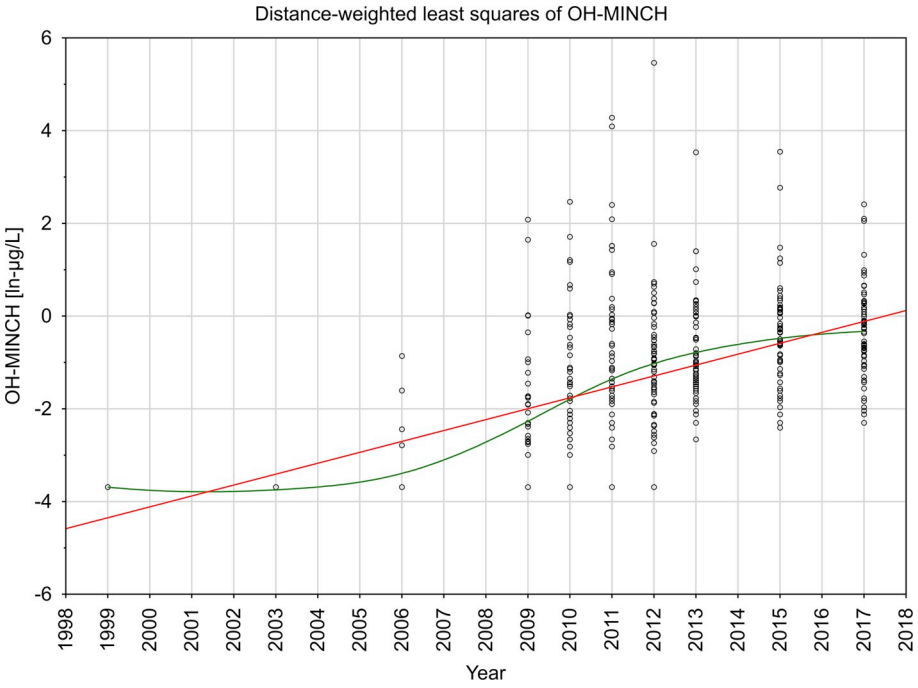

Fig. 3. Distance-weighted least square regression analyses of OH-MINCH (ln-transformed concentrations).

mothers per year). In this study, oxo-MINCH metabolite levels (the only DINCH metabolite analyzed there) increased by 20% per year (Gyllenhammar et al., 2017). Year-matched oxo-MINCH levels were roughly comparable to levels determined in our study. In a convenience group of anonymous U.S. adult volunteers Silva et al. (2013) measured the same three oxidized DINCH metabolites as in our study in 527 spot urine samples collected between 2000 and 2012. Comparable to our findings they detected no DINCH metabolites in samples of the early years (2000/2001) but reported steadily increasing detections from 2007 to 2012, reaching detection rates between 16 and 21% for the three metabolites in 2012. For the same year, detection rates in our study were considerably higher (85 %–98%). This, however, is mostly related to the lower detection limit in our study (0.05 µg/L vs. 0.4 µg/L). 95th Percentiles for 2012 reported by Silva et al. (1.0–2.4 µg/L) were highly comparable to 95th percentiles determined by us for the same year (0.85–2.06 µg/L). Recently available NHANES data from 2011 to 2016 (CDC, 2019) further confirms the increasing trend of DINCH exposure in spot urine samples in the U.S. For the adult (20 + years) population a median of 0.50 µg/L and a 95th percentile of 7.20 µg/L is reported for OH-MINCH for the survey years 2015/2016. These data, again, are in good agreement with our data for 2015 where we reported a median of 0.585 µg/L and a 95th percentile of 3.94 µg/L.

Without investigating time trends the ubiquitous presence of urinary DINCH metabolites has recently been reported for selected populations in Israel (Machtinger et al. 2018a, 2018b), Portugal (Correia-Sa et al., 2017), Australia (Gomez Ramos et al., 2016), Sweden (Shu et al., 2018), Norway (Giovanoulis et al., 2016) and Germany (Fromme et al., 2016). For a detailed presentation of these data see Supplementary Table S2. The overall view of these data suggests that children might have higher exposure to DINCH than adults. 208 children, aged 27–80 months tested in German daycare centers between 2011/2012 had median levels for the three DINCH metabolites between 1.14 and 1.66 µg/L. These levels are approximately 5 fold higher compared to median levels of 0.168–0.393 µg/L determined for 2012 in our study. Metabolite levels of 112 children (4–18 years old) from Portugal, sampled in 2014/15 were between 1.08 and 2.14 µg/L and

Table 5
Daily DINCH intakes (DI) for ΣOH-MINCH + cx-MINCH (µg/kg bw/d), calculated for individual sampling years 1999–2017.

Sampling year	GM	95th conf. interval	P50	P95	Max
1999	N.A.	N.A.	N.A.	N.A.	N.A.
2003	N.A.	N.A.	N.A.	N.A.	N.A.
2006	N.A.	N.A.	N.A.	N.A.	0.19
2009	N.A.	N.A.	N.A.	0.58	5.15
2010	0.07	0.05 - 0.10	0.05	1.33	3.60
2011	0.14	0.09 - 0.21	0.09	3.13	29.15
2012	0.18	0.13 - 0.24	0.17	1.19	42.60
2013	0.16	0.12 - 0.21	0.15	0.84	19.45
2015	0.23	0.17 - 0.32	0.23	1.87	29.33
2017	0.26	0.20 - 0.33	0.23	2.01	6.32

GM: geometric mean; P50: median; P95: 95th percentile; grey: second measurement campaign. DIs at GM, P50 and P95 are only presented if a sufficient number of samples had OH-MINCH levels above the LOQ (> 60% for GM and median; > 10% for 95th percentile). In all other cases, DI values were set to N.A. (not applicable).

again approximately four to five fold higher than levels determined in our study in the year 2015 (0.210–0.585 µg/L). Likewise for the U.S., NHANES data suggests that children have higher DINCH exposures than adults. Higher exposures to phthalate plasticizers in children compared to adults have been reported in several previous studies (Kasper-Sonnenberg et al., 2012; Koch et al., 2007; Hartmann et al., 2015) and probably also apply to their substitutes. Reasons for higher exposures of children to DINCH can probably be found in their higher food intake in relation to their body weight, the increased use of DINCH especially in children's toys, in child specific behaviour such as mouthing, increased uptake of dust due to playing near the ground, and due to their higher proportion of skin surface to body volume (Wittassek et al., 2007; Koch et al., 2007; BfR and UBA, 2001; Wittassek et al., 2011).

4.2. Risk assessment

The comparison of our data either directly with biomarker based guidance values HBM-I; 4,500 µg/L ΣOH-MINCH + cx-MINCH (Apel et al., 2017) or back calculated DIs with the TDI (1 mg/kg bw/d (EFSA, 2006) or RfD (0.7 mg/kg bw/d (Bhat et al., 2014) revealed that for the ESB samples (and the years of highest exposures) median exposures are more than a factor of 3,000 (RfD),and more than a factor of 4,000 (TDI, HBM-I) lower than these guidance values and even maximum exposures are at least more than 100- to 200 fold lower. For instance, the DI in 2017 at the median concentration (0.23 µg/kg bw/d) reflects only 0.02% of the TDI and 0.03% of the RfD. At the 95th percentile (2.01 µg/kg bw/d) the DI represents 0.2% (TDI) and 0.29% (RfD) of these values. All of this taken together, no negative health effects of DINCH exposure are to be expected for young adults at this point in time. However, as explained above, the likely increase of DINCH exposure needs to be closely followed in the future and potentially higher exposed (sub-) populations, such as children, deserve special attention.

5. Conclusion

The increasing detection of DINCH exposure in the general German population over the last decade (since the market introduction of DINCH in 2002) has in the meantime reached the level of ubiquitous exposure with DINCH metabolites detectable in every urine sample analysed from 2013 on. Urinary metabolite levels are still increasing, not only in Germany but also in many other parts of the world, as a sign of the ongoing substitution of phthalate plasticizers with alternatives. Current levels of DINCH exposure, however, based on existing (health based) guidance/limit values (HBM-I, TDI, RfD) seem to be consistently below any level of concern.

Nevertheless, the ongoing increase in DINCH exposure needs to be closely monitored in the future, including populations with potentially higher DINCH exposures such as children. One such population in Germany, complementing the ESB population of young adults, is the national representative children sampling of the German Environmental Survey for Children (GerES V) for which human biomonitoring data on DINCH will be available soon, covering the years 2015–2017.

These and other contemporary biomonitoring data (e.g. HBM exposure data currently collected in the EU-wide HBM4EU program; www.hbm4eu.eu) can inform regulatory or policy decisions if (sub-) population exposures exceed the level of no concern. The data can also safeguard that the substitution process of critical phthalates with alternative plasticizers has an overall positive effect on reducing population exposures to potentially endocrine disrupting and reprotoxic chemicals.

Declarations of interest

None.

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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.2019.07.011.

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